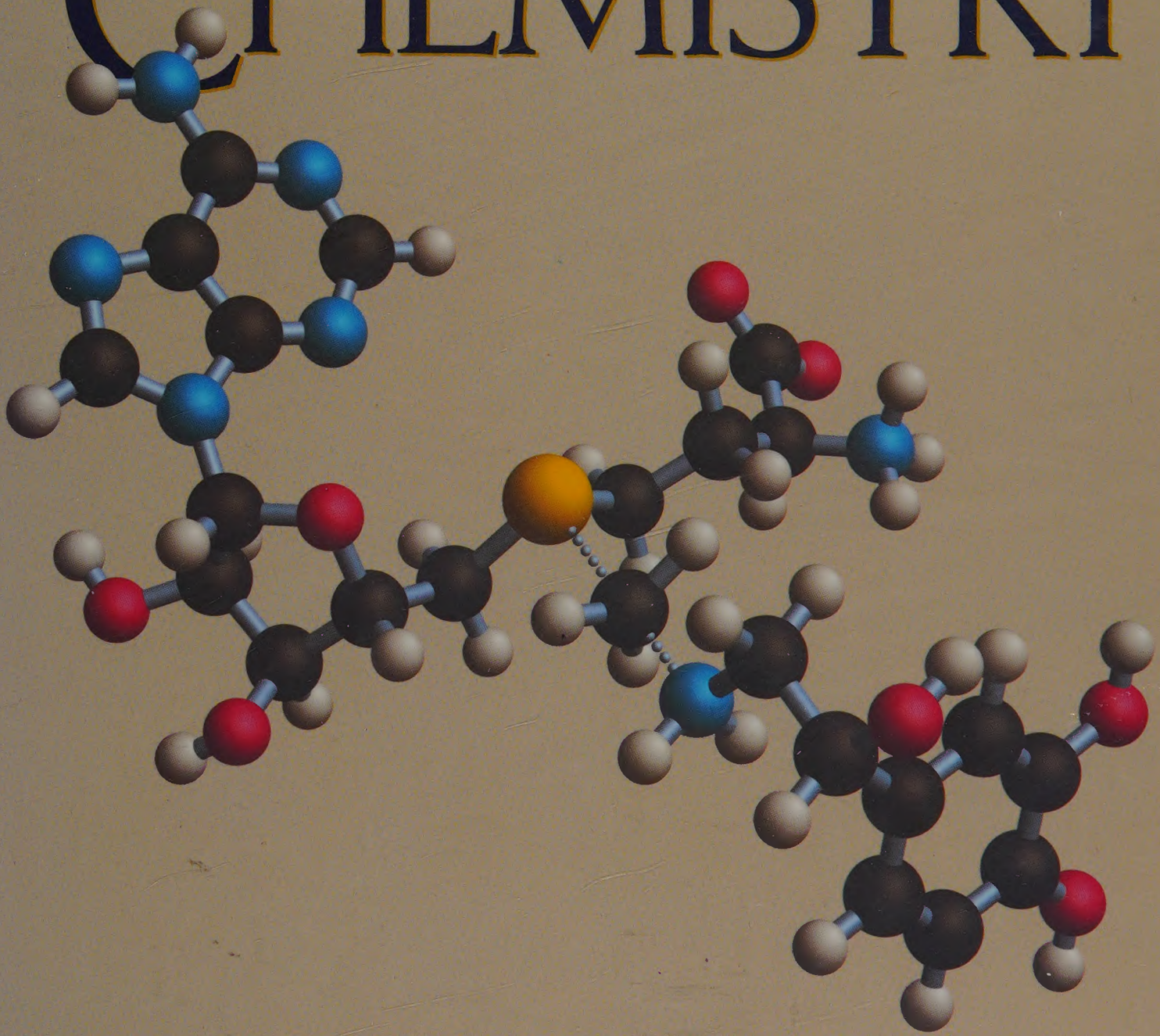
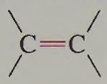
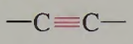
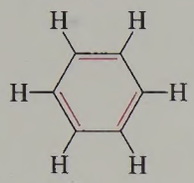
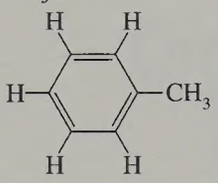
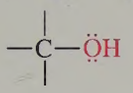
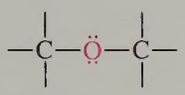
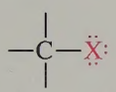
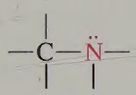
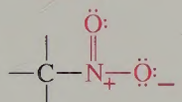
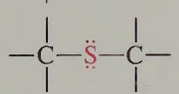
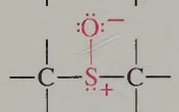
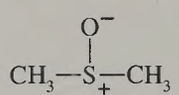
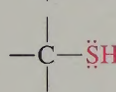
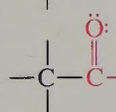
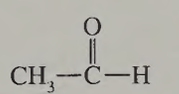
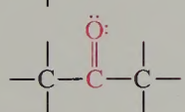
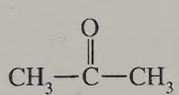
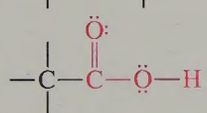
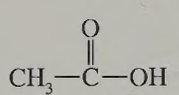
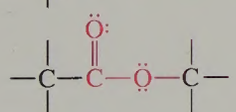
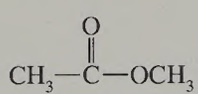
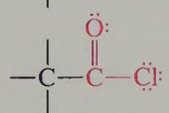
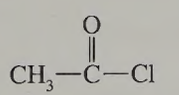
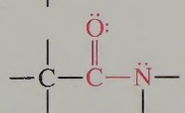
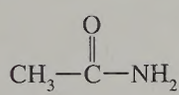
ORGANIC CHEMISTRY



ROBERT J. OUELLETTE
J. DAVID RAWN

Essays

Common Functional Groups

Class	*Functional group structure*	*IUPAC prefix or suffix*	*Example*	*Name*
Alkane	C—H and C—C single bonds	-ane	$CH_3—CH_3$	ethane
Alkene		-ene	$CH_2=CHCH_3$	propene
Alkyne		-yne	$CH_3C\equiv CH$	propyne
Arene		none		toluene
Alcohol		-ol	$CH_3CH_2—OH$	ethanol
Ether		ether	$CH_3—O—CH_3$	dimethyl ether
Halide		halo-	$CH_3—Br$	bromoethane
Amine		-amine	$CH_3CH_2—NH_2$	ethylamine
Nitrile		-nitrile	$CH_3C\equiv N$	ethanenitrile
Nitro		nitro-	$CH_3—NO_2$	nitromethane
Sulfide		sulfide	$CH_3—S—CH_3$	dimethyl sulfide
Sulfoxide		sulfoxide		dimethyl sulfoxide
Thiol		-thiol	$CH_3CH_2—SH$	ethanethiol
Aldehyde		-al		ethanal
Ketone		-one		propanone
Carboxylic acid		-oic acid		ethanoic acid
Ester		-oate		methyl ethanoate
Acid chloride		-oyl chloride		ethanoyl chloride
Amide		-amide		ethanamide

Organic Chemistry

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Brief Contents

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Preface

In 1835, Friederich Wöhler, a protean figure in the early days of organic chemistry, wrote a letter to another distinguished scientist, Jöns Jacob Berzelius, in which he remarked, "Organic chemistry just now is enough to drive one mad. It gives me an impression of a primeval tropical forest, full of the most remarkable things, a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter." We wrote this book to tame "the monstrous and boundless thicket"; more than that: to make of it a garden, in which the paths are clearly marked, and the most remarkable things are laid out with crystalline clarity. This clarity emerges in part because organic compounds can be divided into classes called "functional groups." Also, their reactions can be divided into similar classes that share common pathways, or mechanisms. This close interplay between the "class of compound" and the "class of reaction" provides an overall unity to the subject. We have extended these common themes a step further, and have carefully, systematically, and consistently integrated a discussion of energy changes into our treatment of organic reactions. The unifying principles that govern energy changes in organic reactions gives us a single "key" that unlocks many doors. If functional groups are the "anatomy" of organic chemistry; reaction mechanisms and their associated energy changes constitute its "physiology."

To this unity of structure in the form of functional groups and function in the form of reaction mechanisms and energy changes, we have introduced a set of essays that provide many biological applications of organic chemistry. These essays show again and again, in chapter after chapter, from one end of the book to the other, how the basic principles of organic chemistry provide an understanding of a huge range of biological phenomena. In fact, we will often find that the chemical reactions of living cells are a straightforward extension of organic chemistry. "Grey is all theory, green grows the golden tree of life."

In the previous paragraph we noted that we have incorporated an analysis of "energy changes" into our treatment of organic chemistry. This is another way of saying we use "thermodynamics." Thermodynamics allows us to analyze the energy changes that occur in a chemical reaction (or any physical process). Since every process occurs with an energy change of some sort, the importance of ther-

modynamics cannot easily be exaggerated. For example, a thermodynamic analysis tells us how much energy is released or absorbed in a reaction, and this knowledge tells us about the relative stabilities of the reactants and products. Thermodynamics also leads us from the concentrations of reactants and products in an organic reaction to the equilibrium constant for the reaction, and from the quilibrium constant we can determine the magnitude of the "force" that "drives" the reaction to equilibrium. Thermodynamics also reveals how this force (the free energy) is partitioned between a potential energy changes (the enthalpy) and a change in the molecular order (the entropy) of the system. We will use (and review!) the thermodynamics you learned in general chemistry. Thermodynamics allows us to understand many aspects of organic chemistry without resorting to dubious "hand waving"—that is, without making up long-winded explanations of phenomena that are easily understood in terms of energy changes.

You won't have to memorize for this course. On the other hand, there are a lot of things that you'll have to remember! These slightly contradictory assertions summarize an essential part of learning any subject, especially one as complex as organic chemistry. It's tempting to seek refuge from intellectual difficulty by attempting to blindly memorize an infinite number of facts. You might think that "If I learn all the facts, I'll know the subject and do well in it." However, even if it were possible to memorize all the known facts of organic chemistry (it isn't), that fear would avail nothing unless the facts were understood in terms so underlying general principles: observations without concepts are blind. So, perhaps you would like to say "It's a waste of time to learn all these empty facts. Instead, I'll save time and learn the concepts. Then I'll be able to reason my way to the solution of any given problems." Perhaps you'll not be surprised to learn that this isn't a great idea either: concepts without observations are empty. This leaves a third "way": learn the basic facts, organize them in terms of fundamental principles, and then learn to apply this knowledge in a new framework. "But how," you exclaim, "am I going to do that?" The answer is really very simple: work the exercises! There are a couple of thousand or so to keep you busy. We have also provided some help. First, at the end of each section, after you have had time to digest a coherent block of material, you will find worked-out examples. These are accompanied by several similar problems. Work your way through each chapter in the following way: read a section, study the solved problems, and solve the companion exercises. By the time you have finished a chapter, you will have a firm grasp of it. To convince yourself that you have learned this material, work some of the exercises at the end of each chapter. They are divided by topic. Since there are so many exercises, work one in each section. When you've reached the end, you will have reviewed the entire chapter. Go through each topic, then go back to the beginning and start again. One more bit of advice: don't study as if you were a boa constrictor have a monthly meal (followed by a month of indigestion). Work an hour or so, systematically, every day. If you do this, you can be confident of prospering in organic chemistry.

Organic chemistry is fun. You'll discover that it's the best course you've ever taken!

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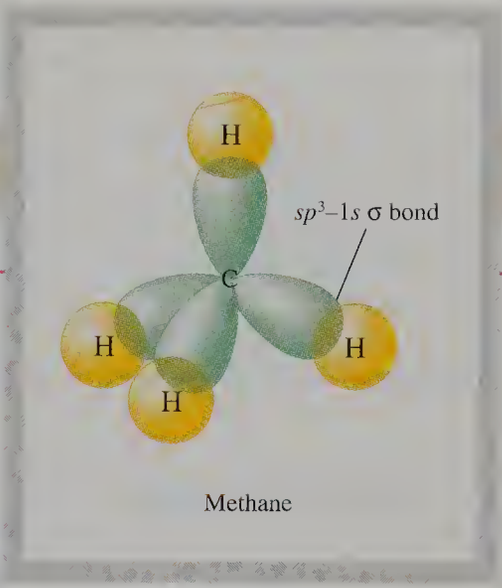
The authors are indebted to Mary Bailey for her reading of the first draft of the manuscript as well as her contribution in the preparation of the Solutions Manual. She provided the eyes of a non-organic chemist and served in the role of a student to find subject areas and explanations that might be difficult for a student to comprehend. Her dedicated efforts have improved the text.

The authors are grateful that Elisabeth Belfer was assigned as Senior Project Manager. Her many years of experience in the production area as well as her knowledge of chemistry were invaluable for such a difficult project. For one of us (RJO), this is the sixth time that we have worked together. As in the past, her carefully phrased questions about inconsistency in style as well as actual chemical content helped the author focus on the options for resolution of problems which she also provided. Both authors are grateful for her tenacious attention to detail in the incredibly complex task of producing an organic chemistry text.

1

Atoms, Molecules, and Bonding



Methane

1.1 Inorganic and Organic Compounds

In the late eighteenth century, chemists divided substances into two classes, called inorganic and organic compounds. Inorganic compounds came from mineral sources. Organic compounds could only be obtained from plants or animals. Thus, chemists assumed that organic compounds could only be produced by living organisms, which contained a "vital force". Organic compounds were more difficult to study in the laboratory because they decomposed more easily than inorganic compounds. But by the middle of the nineteenth century, chemists had learned how to work with organic compounds in the laboratory and could also synthesize them. As a result, the concept of a vital force disappeared.

The distinction between organic and inorganic compounds now rests on chemical composition. An inorganic compound can contain any of the elements. In contrast, organic compounds always contain carbon and a few other elements such as hydrogen, oxygen, and nitrogen. Most organic compounds contain many more atoms than inorganic compounds, and they have more complex structures. Common examples include table sugar, or sucrose ($C_{12}H_{22}O_{11}$), vitamin B_2 ($C_{17}H_{20}N_4O_6$), cholesterol ($C_{27}H_{46}O$), and the fat glycerol tripalmitate ($C_{51}H_{98}O_6$). Some biological compounds are gigantic molecules. DNA, which stores genetic information in all living species, has molecular weights that range from 5 to 15 million amu.

Inorganic and organic compounds have different physical properties. Inorganic compounds generally have high melting points, but organic compounds are most commonly gases, liquids, or low-melting solids. Inorganic and organic compounds also have different solubilities. Many inorganic compounds dissolve in water, but organic compounds generally do not.

Inorganic and organic compounds also have different electrical conductivities. Many inorganic compounds exist as ions when dissolved in water, and the solutions can conduct electric current. In contrast, the organic compounds that dissolve in water, such as ethanol (alcohol) and sucrose (table sugar), usually do not produce ions. Their solutions do not conduct electricity. Some organic compounds,

such as acetic acid, dissolve in water to give some ions, and their solutions weakly conduct electricity.

Based on the physical characteristics of compounds, chemists have proposed that the atoms of the elements are bonded in compounds in two principal ways—ionic bonds and covalent bonds. Both types of bonds result from a change in the electronic structure of atoms when the atoms associate with each other. The number and type of bonds formed, and the shape of the molecule, depend on the electron configuration of the atoms.

1.2 Atomic Structure

An atom has a small, dense nucleus containing protons and neutrons. Electrons are around the nucleus. Protons have a +1 charge; electrons have a −1 charge. Each element contains a unique number of subatomic particles. The number of protons, which determines an atom's identity, is given as its **atomic number**. Since the number of protons in the nucleus equals the number of electrons in the neutral atom, the atomic number also indicates the number of electrons in an atom.

Atomic Orbitals

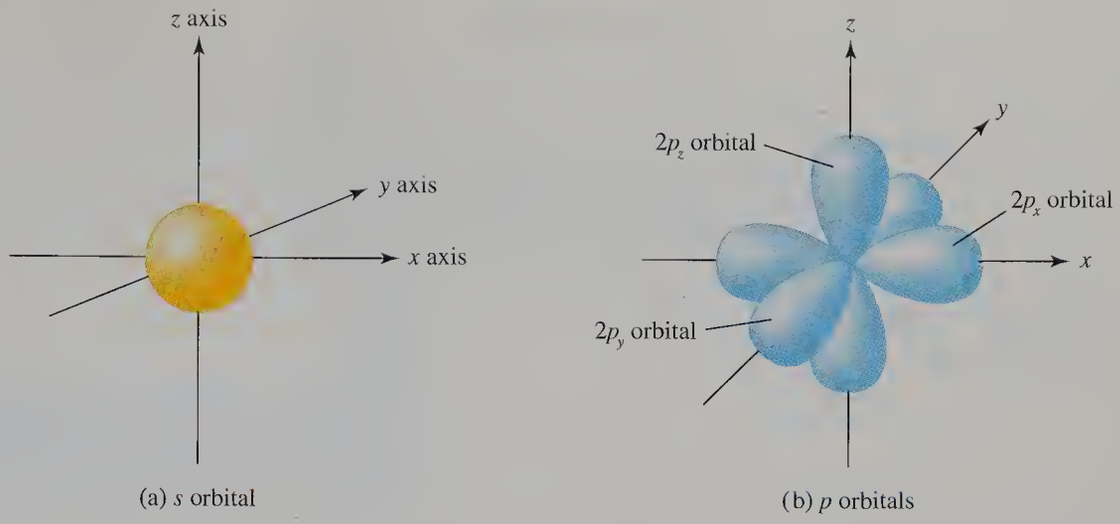
The electrons in an atom occupy **atomic orbitals,** which are designated by the letters *s, p, d* and *f*. Each orbital can contain a maximum of two electrons. All orbitals describe a probability for the distribution of electron density in space. Electrons within each specific orbital also have a characteristic energy.

Orbitals are grouped in shells of increasing energy, designated by the integers 1, 2, 3, 4, . . . , *n*. These integers are called **principal quantum numbers**. Each shell contains a unique number and type of orbitals. The first shell contains a 1*s* orbital. The second shell contains one 2*s* orbital and three 2*p* orbitals. Each kind of orbital can contain no more than two electrons, and they must have opposite spin. We need consider only the orbitals of the first three shells for the elements commonly found in organic compounds.

An *s* orbital, whatever the principal quantum number, is spherically symmetrical (Figure 1.1a). The 2*s* orbital is larger than the 1*s* orbital. Its electrons are farther from the nucleus, and it has a higher energy than a 1*s* orbital. The three p orbitals in a shell are not spherically symmetrical. Electron density in each *p* orbital is concentrated in two regions, or lobes—one on each side of the nucleus. The two lobes together are the orbital. The shapes of the p orbitals are shown in Figure 1.1b. The *p* orbitals are often designated p_x, p_y, and p_z to emphasize that they are mutually perpendicular to one another and that they are aligned along the *x, y,* and *z* axes in space. Although the orientations of the p_x, p_y, and p_z orbitals differ, the electrons in each *p* orbital have equal energies.

Orbitals of the same type within a shell constitute a group called a **subshell**. For example, an *s* subshell contains one orbital and can contain only two electrons. In contrast, a *p* subshell contains three orbitals and can contain a total of six electrons.

Electrons are distributed in the subshells of an atom to give an **electron configuration** that has the lowest energy. The order of increasing energy of subshells is $1s < 2s < 2p < 3s < 3p$ for elements of atomic number less than 18. For any subshell, the lowest energy state is the arrangement that maximizes the number of electrons with the same spin. This means that electrons first occupy orbitals singly within subshells before pairing in a common orbital. The atomic number and electron configurations for the first 10 elements are given in Table 1.1.



(a) *s* orbital (b) *p* orbitals

FIGURE 1.1 Shapes of *s* and *p* Orbitals
(a) Boundary surface enclosing a volume where electrons in an *s* orbital may be located.
(b) Boundary surfaces of the three mutually perpendicular $2p$ orbitals. Each orbital may be occupied by a maximum of two electrons.

TABLE 1.1
Electron Configuration

Element	*Atomic number*	1*s*	2*s*	2*p*			*Electron configuration*
H	1	↑					$1s^1$
He	2	↑↓					$1s^2$
Li	3	↑↓	↑				$1s^2 2s^1$
Be	4	↑↓	↑↓				$1s^2 2s^2$
B	5	↑↓	↑↓	↑	—	—	$1s^2 2s^2 2p^1$
C	6	↑↓	↑↓	↑	↑	—	$1s^2 2s^2 2p^2$
N	7	↑↓	↑↓	↑	↑	↑	$1s^2 2s^2 2p^3$
O	8	↑↓	↑↓	↑↓	↑	↑	$1s^2 2s^2 2p^4$
F	9	↑↓	↑↓	↑↓	↑↓	↑	$1s^2 2s^2 2p^5$
Ne	10	↑↓	↑↓	↑↓	↑↓	↑↓	$1s^2 2s^2 2p^6$

Valence-Shell Electrons

Electrons in filled lower energy shells of atoms do not participate in chemical reactions. Only the higher energy electrons, located in the outermost shell—called the **valence shell**—participate in chemical reactions. These electrons are called **valence electrons**. For example, the single electron of the hydrogen atom is a valence electron. The numbers of valence electrons for the common atoms of organic molecules are given by their group number in the periodic table. Carbon, nitrogen, and oxygen have four, five, and six valence electrons, respectively.

Problem 1.1

Some important biological molecules contain sulfur or phosphorus. How many electrons does each of these elements have in the valence shell? Write the electron configurations for these elements.

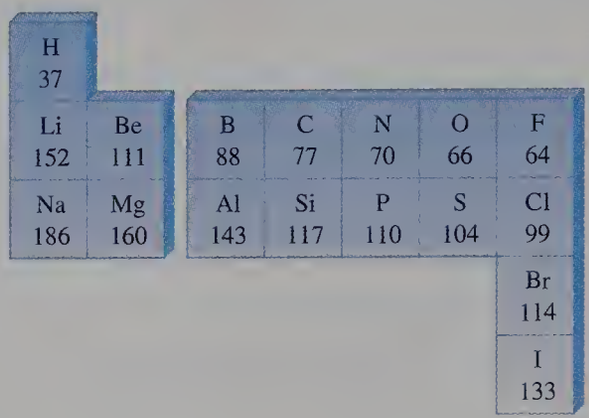
1.3 Atomic Properties

The periodic table of the elements is arranged by atomic number. The elements are arranged in horizontal rows called **periods** and vertical columns called **groups**. The physical and chemical properties of an element may be estimated from its position in the periodic table. Two properties that help us explain the properties of organic compounds are the atomic radius and electronegativity.

Atomic Radius

An atom is usually pictured as a sphere with a specific radius. However, the electron density distribution does not stop abruptly at that distance. The distance selected defines a volume in which there is a high probability (for example, 95%) of locating the electrons of the atom (Figure 1.2). The size of an atom is expressed as an **atomic radius**, given in picometers (pm) or angstroms (1 angstrom, Å = 10^2 pm).

FIGURE 1.2 Atomic Radii (in picometers)



Atomic radii increase from top to bottom in a group of the periodic table. Each successive member of a group has one more shell, whose electrons are located at a larger distance from the nucleus. Therefore, the atomic radius of sulfur is greater than that of oxygen, and the radii of the halogens increase in the order F < Cl < Br < I.

The atomic radius decreases from left to right across a period. The electrons of these atoms are in the *s* and *p* orbitals in the same energy level, but the nuclear charge increases from left to right within a period. As a consequence, the nucleus draws the electrons inward and the atomic radius decreases. The radii of the common elements in organic compounds decrease in the order C > N > O.

Electronegativity

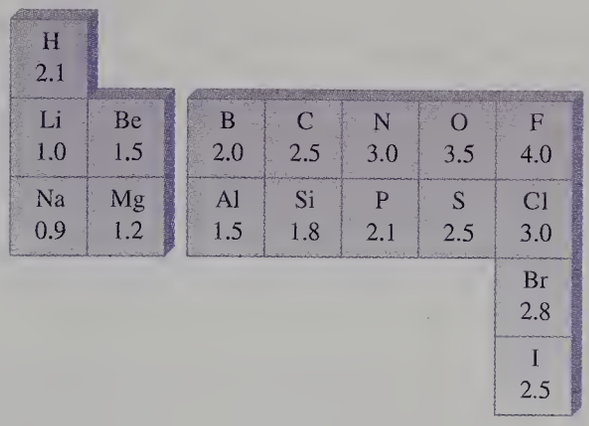
Electronegativity is a measure of the tendency of an atom in a molecule to attract electrons to itself. Linus Pauling placed electronegativity on a scale that ranges from slightly less than 1 for the alkali metals to a maximum of 4 for fluorine. Large electronegativity values indicate a stronger attraction for electrons than small electronegativity values.

Electronegativity values increase from left to right across the periodic table (Figure 1.3). Elements in Groups I and II of the periodic table have low electronegativities and are **electropositive**. Electronegativity increases in period 2 in the order C < N < O < F. Electronegativity values decrease from top to bottom within a group of elements. For example, the electronegativity values of the halogens decrease in the order F > Cl > Br > I. We will use these trends to interpret the chemical and physical properties of organic compounds.

Problem 1.2

A few proteins contain selenocysteine, which contains a selenium atom in place of the sulfur atom of cysteine. Which of the two elements, sulfur or selenium, is the more electronegative?

FIGURE 1.3
Electronegativity



1.4 Energy and Bond Formation

Atoms combine to form molecules because of changes in their chemical energy, a form of potential energy. **Chemical energy** results from attractive and repulsive forces between electrons and nuclei of atoms and also between atoms of molecules. The absolute chemical energy of an atom or molecule cannot be determined. Instead, we describe the difference between the energy of one set of atomic or molecular states and the energy of a second set of states. If one system has a relatively high chemical energy, and a second system has a lower chemical energy, the second system has an arrangement of atoms that is more stable than the first.

The chemical energies of atoms and molecules are expressed by their enthalpies, symbolized by H. A system with a high chemical energy has a high enthalpy (Greek *enthalpein*, to warm in; German *enthalten*, to contain.) The **enthalpy** of a substance is established relative to a reference whose enthalpy is defined as zero. (Enthalpy is not the only quantity defined this way. Altitude is defined similarly. The altitude of Denver, Colorado, is based on its height above sea level, set at zero.)

A system with a high chemical energy compared to a reference system has a high enthalpy. If a collection of atoms or molecules in one arrangement is converted into another one, as in a chemical reaction, the difference in enthalpy is expressed as $\Delta H°$, where the Δ means difference, and the superscript $°$ indicates that the difference is measured under some defined standard conditions. Processes that occur from a state of high enthalpy to a state of low enthalpy release energy.

By convention we express $\Delta H°$ for a process as the difference between the enthalpy of the final state of a system (such as products) and the enthalpy of the initial state (such as reactants).

$$\Delta H° = H°_{\text{final}} - H°_{\text{initial}}$$

The heat energy absorbed or released at one atmosphere and 298 K for a process is $\Delta H°$. If heat energy flows out of the system into the surroundings, the process is called **exothermic**. If heat flows from the surroundings into the system, the process is called **endothermic**. An exothermic process has a negative $\Delta H°$ and an endothermic process has a positive $\Delta H°$.

Enthalpy is a state function. This means that $\Delta H°$ for a conversion from an initial state to a final state is independent of the pathway. Thus, regardless of whether the process occurs in a single step or in a series of steps, the $\Delta H°$ difference between two defined states is the same. (Using altitude as an analogy, the net difference in altitude that we would experience in going from sea level to Denver is the same regardless of how we make the trip.)

The fact that enthalpy changes are independent of path forms the basis for **Hess's law**, which states that the overall $\Delta H°$ for a multistep process—such as a series of chemical reactions—equals the sum of the $\Delta H°$ values for each step. Therefore, we can calculate the $\Delta H°$ for a process of interest, such as the conversion of A to C, if we know the $\Delta H°$ for processes converting A to B and B to C.

Step 1	$A \longrightarrow B$	ΔH_1°
Step 2	$B \longrightarrow C$	ΔH_2°
Sum	$A \longrightarrow C$	$\Delta H_3^\circ = \Delta H_1^\circ + \Delta H_2^\circ$

Hess's law also provides us with a way to evaluate the factors that contribute to a chemical reaction. We can separate a process into two or more hypothetical steps. Although the actual reaction does not occur by this path, we may know the energy required for each hypothetical step. We can then evaluate the relative importance of specific atomic or molecular properties that determine the energy associated with the actual reaction.

Problem 1.3

Hydrogenation is a reaction of a compound with hydrogen. The $\Delta H°$ for the hydrogenation of acetylene to yield ethane, which requires two moles of hydrogen, is -310 kJ mole^{-1}. The $\Delta H°$ for the hydrogenation of ethylene to yield ethane, which requires one mole of hydrogen, is -136 kJ mole^{-1}. What is the $\Delta H°$ for the hydrogenation of acetylene with one mole of hydrogen to yield ethylene?

Sample Solution

Even though you may not recognize the names of the substances or the term hydrogenation, we nevertheless can use Hess's law to do the calculation. We know how much energy is released in converting both acetylene and ethylene to the same compound—ethane. As in the case of knowing the mileage between several cities or the altitudes of those cities, we can either add or subtract the numbers appropriately. The energy released in the hydrogenation of acetylene is greater than the energy released in the hydrogenation of ethylene. Thus the difference between these two numbers is the energy released in the hydrogenation of acetylene to ethylene. The $\Delta H°$ is -174 kJ mole^{-1}. This result is also obtained by combination of the appropriate equations.

acetylene + $2\,H_2 \longrightarrow$ ethane	$\Delta H° = -310$ kJ mole^{-1}
ethane $\longrightarrow$ ethylene + H_2	$\Delta H° = +136$ kJ mole^{-1}
acetylene + $H_2 \longrightarrow$ ethylene	$\Delta H° = -174$ kJ mole^{-1}

The second equation is the reverse of the equation for the stated reaction for the hydrogenation of ethylene. Accordingly, the sign of $\Delta H°$ for the reaction is changed to a positive value.

1.5 Types of Bonds

In 1916, the American chemist G. N. Lewis proposed that elements react to obtain the electron configurations of the inert gases. This hypothesis is summarized in the **Lewis octet rule**: Atoms tend to combine and form bonds by transferring or sharing electrons until each atom contains eight electrons in its valence shell. Note that hydrogen requires only two electrons to complete its valence shell because it has only a 1*s* orbital.

Ionic Bonds

Ionic bonds form between two or more atoms by the transfer of one or more electrons between atoms. Electron transfer produces negative ions, called **anions**, and positive ions, called **cations**. These ions attract each other. In general, ionic compounds result from combinations of metallic elements, located on the left side of the periodic table, with nonmetals, located on the upper right side of the periodic table. Such reactions are strongly exothermic. Polyatomic ions contain several bonded atoms. They can be positively or negatively charged. We will encounter many of these ions—including cyanide (CN^-), hydroxide (OH^-), nitrate (NO_3^-), sulfate (SO_4^{2-}), phosphate (PO_4^{3-}), hydronium (H_3O^+), and ammonium (NH_4^+)—in our study of organic chemistry.

Let us consider the ionic bond in sodium chloride. A sodium atom, which has 11 protons and 11 electrons, has a single valence electron in its 3*s* subshell. A chlorine atom, which has 17 protons and 17 electrons, has seven valence electrons in its third shell (designated $3s^23p^5$). When the electropositive sodium atom forms an ionic bond, it loses its valence electron to a chlorine atom. The resulting sodium ion has a +1 charge and the same electron configuration as neon ($1s^22s^22p^6$). The chlorine atom, which has a high electronegativity, gains an electron and is converted into a chloride ion. The chloride ion has a −1 charge and has the same electron configuration as argon ($1s^22s^22p^63s^23p^6$).

The formation of sodium chloride from the sodium and chlorine atoms is shown using Lewis structures. **Lewis structures** represent only the valence electrons, with pairs of valence electrons shown as pairs of dots. By convention, the complete octet is shown for anions formed from electronegative elements. However, the filled outer shell of cations resulting from loss of electrons from electropositive elements is not shown.

$$Na\cdot + :\ddot{\underset{\cdot\cdot}{Cl}}\cdot \longrightarrow Na^+ + :\ddot{\underset{\cdot\cdot}{Cl}}:^-$$

Now let's consider why the reaction of a metal and a nonmetal is exothermic. For simplicity we imagine a series of gas phase (g) reactions of atoms. Removing an electron from Na(g) to form $Na^+(g)$ requires 496 kJ $mole^{-1}$. Adding an electron to Cl(g) to form $Cl^-(g)$ releases 349 kJ $mole^{-1}$. Thus, if the transfer of an electron from sodium to chlorine were the only factor in the formation of sodium chloride, the reaction would be endothermic.

$$\begin{array}{rll} Na(g) \longrightarrow Na^+(g) + e^- & \Delta H^\circ = & 496 \text{ kJ mole}^{-1} \\ Cl(g) + e^- \longrightarrow Cl^-(g) & \Delta H^\circ = & -349 \text{ kJ mole}^{-1} \\ \hline Na(g) + Cl(g) \longrightarrow Na^+(g) + Cl^-(g) & \Delta H^\circ = & 147 \text{ kJ mole}^{-1} \end{array}$$

The reaction is actually exothermic because there is an attraction between ions of opposite charge. When the ions draw together to form an ion pair in the gas phase, 504 kJ $mole^{-1}$ is released.

$$Na^+(g) + Cl^-(g) \longrightarrow Na^+Cl^-(g) \qquad \Delta H^\circ = -504 \text{ kJ mole}^{-1}$$

This quantity exceeds the 147 kJ $mole^{-1}$ associated with the net transfer of an electron from sodium to chlorine and makes the overall formation of an ion pair of sodium chloride exothermic by approximately 357 kJ $mole^{-1}$.

$$\begin{array}{ll} Na(g) + Cl(g) \longrightarrow Na^+(g) + Cl^-(g) & \Delta H^\circ = \ \ 147 \text{ kJ mole}^{-1} \\ Na^+(g) + Cl^-(g)^- \longrightarrow Na^+Cl^-(g) & \Delta H^\circ = -504 \text{ kJ mole}^{-1} \\ \hline Na(g) + Cl(g) \longrightarrow Na^+Cl^-(g) & \Delta H^\circ = -357 \text{ kJ mole}^{-1} \end{array}$$

Covalent Bonds

Covalent bonds are much more common in organic chemistry than ionic bonds. A **covalent bond** consists of the simultaneous attraction of one or more pairs of electrons by two atomic nuclei. Shared electrons located between the two nuclei are **bonding electrons**. Covalent bonds occur between like atoms or between different atoms whose difference in electronegativity is insufficient to allow transfer of electrons to form ions.

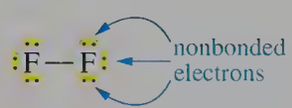
Let's consider the covalent bond in the hydrogen molecule. A hydrogen molecule forms from two hydrogen atoms, each with one electron in a 1*s* orbital. The two hydrogen atoms share the two electrons in the covalent bond, and each acquires a helium-like electron configuration.

$$H\cdot + \cdot H \longrightarrow H{:}H$$

Energy is released as the electrons associated with the two hydrogen atoms form a covalent bond. The process has $\Delta H^\circ = -435$ kJ mole^{-1} (-104 kcal mole^{-1}), which indicates that the hydrogen molecule is more stable than the two hydrogen atoms. The reverse process, pulling the two bonded hydrogen atoms apart, requires 435 kJ mole^{-1} (104 kcal mole^{-1}), a measurement called the **bond strength** of the H—H bond.

The two hydrogen nuclei are separated by a distance called the **bond length**. This distance results from a balance between attractive and repulsive forces. There is an attraction between the nuclei and the bonding electrons, but there is also a repulsion between the two nuclei as well as between the two electrons (Figure 1.4).

A covalent bond also occurs in F_2. In the fluorine molecule, the two fluorine atoms are attracted to the same pair of electrons. Each fluorine atom has seven valence electrons in the second energy level, and requires one more electron to form a neon-like electron configuration. Each fluorine atom contributes one electron to the bonded pair shared by the two atoms. The remaining six valence electrons of each fluorine atom are not involved in bonding, and are concentrated around their respective atoms. They are variously called **nonbonding electrons**, **lone pair electrons**, or **unshared electron pairs**.



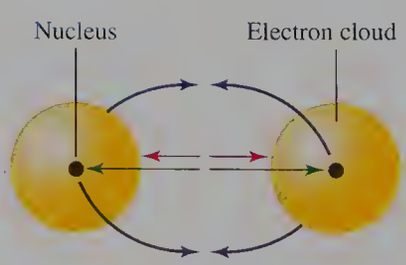
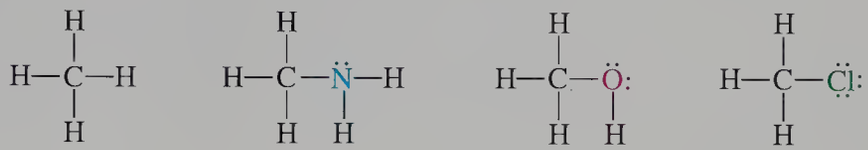


FIGURE 1.4 Bonding Forces in the Hydrogen Molecule
The sum of attractive forces between the electron of one atom and the proton in the nucleus of the other hydrogen atom is greater than the sum of the electron–electron repulsive forces and the proton–proton repulsive forces.

A covalent bond is drawn as a dash in a Lewis structure to distinguish the bonded pair from the lone pair electrons. Lewis structures show the nonbonded electrons as pairs of dots located around the atomic symbols for the atoms. The Lewis structures of four simple organic compounds—methane, methylamine, methanol, and chloromethane—are drawn below to show both bonded and nonbonded electrons. In these compounds, carbon, nitrogen, oxygen, and chlorine have 4, 3, 2, and 1 bonds, respectively.



methane methylamine methanol chloromethane

TABLE 1.2
Valences of Common Elements

Atom	*Valence**
hydrogen	1
fluorine	1
chlorine	1
iodine	1
oxygen	2
sulfur	2
nitrogen	3
carbon	4

* The valence is the usual number of bonds formed by the atom. It is not the number of attached atoms because there may be more than one bond to an attached atom.

The hydrogen atom and the halogen atoms form only one covalent bond to other atoms in stable neutral compounds. However, the carbon, oxygen, and nitrogen atoms can bond to more than one atom. The number of covalent bonds an atom can form is called the **valence** of the atom. The valence of a given atom is the same in most stable neutral organic compounds. The valences of some common elements contained in organic compounds are listed in Table 1.2.

Structural Formulas

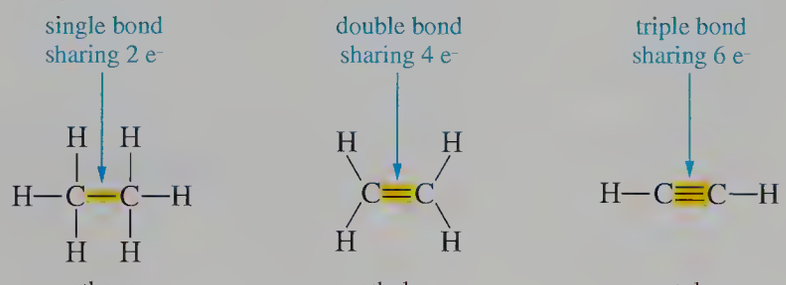
A molecular formula gives only the composition of a molecule. A **structural formula** shows the arrangement of atoms and bonds in a molecule. The structural formulas for methane, methylamine, methanol, and chloromethane show all of the bonds connecting the constituent atoms. Structural formulas are often drawn in abbreviated or condensed versions to save time and space. **Condensed structural formulas** show only specific bonds; other bonds are implied, but not shown. The degree of condensation depends on which bonds are shown and which are only implied. For example, because hydrogen forms only a single bond to carbon, the C—H bond need not be shown in the condensed structure. Similarly, the two nitrogen–hydrogen bonds in methylamine and the oxygen–hydrogen bond in methanol need not be shown. Condensed structural formulas showing only the bond from carbon to atoms other than hydrogen are written as follows.

$$CH_4 \qquad CH_3—NH_2 \qquad CH_3—OH \qquad CH_3—Cl$$

Note that the pairs of nonbonded electrons are usually not indicated in condensed structural formulas. However, they do contribute to the physical and chemical properties of compounds that contain halogen, nitrogen, and oxygen atoms.

Multiple Covalent Bonds

A carbon atom forms four bonds in stable organic compounds such as ethane, ethylene, and acetylene.

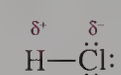


ethane ethylene acetylene

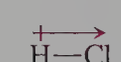
Each carbon atom in ethane forms four single bonds, one to each of three hydrogen atoms and one to the neighboring carbon atom. However, in some organic molecules, a carbon atom shares two or three pairs of electrons with another bonded atom. If two electron pairs are shared, a **double bond** exists. For example, a carbon–carbon double bond is present in ethylene. Each carbon atom in ethylene forms two single bonds to hydrogen atoms and one double bond to the neighboring carbon atom. If two bonded atoms share three electron pairs, a **triple bond** exists. For example, each carbon atom in acetylene forms a single bond to a hydrogen atom, and the two carbon atoms share a triple bond. This triple bond contains six electrons. In ethane, ethylene, and acetylene, each carbon atom makes a total of four bonds.

Polar Covalent Bonds

When the atoms in a covalent bond have different electronegativities, the bond is **polar**. For example, a polar covalent bond is present in an HCl molecule. In HCl, each atom requires one more electron to form an inert gas electron configuration. Chlorine is more electronegative than hydrogen, but the chlorine atom does not attract electrons strongly enough to remove an electron from hydrogen. Even though the shared electron pair is associated to a larger extent with chlorine than with hydrogen, the molecule is represented by the conventional Lewis structure. Because the bonded pair is shared unequally, there is a partial negative charge on the chlorine atom and a partial positive charge on the hydrogen atom. These fractional charges are denoted by the symbol δ (Greek lowercase delta).



The hydrogen chloride molecule has a **dipole** (two poles), which consists of a pair of opposite charges separated from each other. The dipole is shown by an arrow with a cross at one end. A cross is near the partially positive end of the molecule, and the arrowhead is near the partially negative end of the molecule.



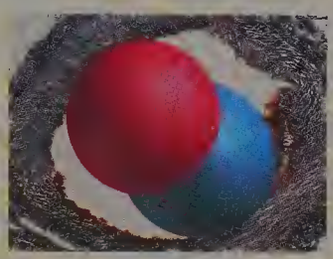
Unlike the polar bond in HCl, single or multiple bonds between carbon atoms are nonpolar. Hydrogen and carbon have similar electronegativity values, and the C—H bond is not normally considered a polar covalent bond. Ethane, ethylene, and acetylene have nonpolar covalent bonds, and the compounds are nonpolar.

The polarity of a bond depends upon the difference in the electronegativities of the bonded atoms. As the difference between the electronegativities of the bonded atoms increases, the bond polarity also increases. Hence, the direction of the polarity of common bonds found in organic molecules is easily predicted. The common nonmetals are more electronegative than carbon. Therefore, when a carbon atom is bonded to common nonmetal atoms, it has a partial positive charge.

Hydrogen is less electronegative than the common nonmetals. Therefore, when a hydrogen atom is bonded to a common nonmetal, the resulting polar bond has a partial positive charge on the hydrogen atom.

Nitric Oxide—An Unlikely Biologically Active Molecule

Nitric oxide is one of those rare examples of a simple substance that does not have a Lewis octet about each atom. A single unpaired electron on the nitrogen atom is responsible for the high reactivity of this toxic molecule. In air, this colorless substance reacts rapidly with oxygen to give nitrogen dioxide, also a highly toxic molecule. Nitric oxide is a by-product of the combustion of fossil fuels and contributes to both acid rain and photochemical smog. Thus, it was never thought that nitric oxide, which is so incompatible with life and the environment, could ever be a subject of interest for beneficial biochemical reactions.



Nitric oxide molecule superimposed over a micrograph of human artery.

In the mid-1980s scientists began to discover that nitric oxide plays an astonishing role in a range of physiological activities in mammals. It is formed in small amounts in chemical reactions in a variety of tissues and, in concert with other more complex molecules, plays many diverse roles. To date, nitric oxide is known to affect blood pressure, blood clotting, neurotransmission, and the immune system. Release of nitric oxide in the endothelial cells of the inner walls of blood vessels stimulates the release of endothelium-derived relaxing factor (EDRF), which in turn is responsible for the relaxation of vascular smooth muscles. EDRF controls the diameter of the blood vessels and hence the blood pressure. This information now tells us why nitroglycerin tablets, which have been used for almost a century, are effective in the treatment of angina associated with cardiovascular disease. In the body, chemical reactions of nitroglycerin release nitric oxide, which starts a series of reactions that give relief from the angina attack.

Although the chemistry is complex, nitric oxide has also been implicated in neurotransmission. It may play a role in long-term depression as well as in memory processes. Substantial research is in progress to learn how this simple molecule is involved in such complex processes.

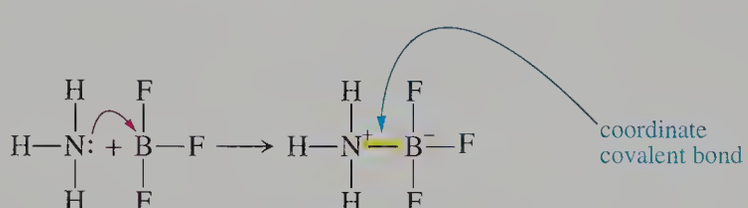
Nitric oxide is also produced by macrophages, structures that are part of the immune system. The nitric oxide inhibits an enzyme that converts ribonucleotides to the deoxyribonucleotides required for DNA synthesis. Thus nitric oxide may be indirectly responsible for inhibiting the growth of tumor cells.

Some pharmaceutical research now targets the development of nitric oxide–releasing drugs that may replace older drugs. Because nitric oxide is important to many physiological functions, it may make possible the development of dramatically new therapies for a variety of ailments.

·N=O:
nitric oxide

Coordinate Covalent Bonds

A **coordinate covalent bond** exists when both electrons of a bonded pair are provided by one atom. For example, a coordinate covalent bond forms in the reaction of ammonia with boron trifluoride,



In ammonia, the nitrogen atom shares three of its five valence electrons with three hydrogen atoms. The remaining two valence electrons are an unshared pair that forms a coordinate covalent bond with the electron-deficient boron atom of BF_3. In BF_3, boron has only six electrons in its valence shell. It needs the two electrons provided by the nitrogen atom to form a covalent bond.

Problem 1.4

Magnesium forms ionic compounds. What is the electron configuration of the magnesium ion? What are the chemical formulas for magnesium hydroxide (milk of magnesia) and magnesium sulfate (Epsom salts)?

Problem 1.5

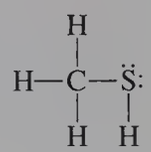
Potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$) are two oxidizing agents used in organic chemistry. What are the charges of the permanganate and dichromate ions?

Problem 1.6

Unlike methanol, which is a nearly odorless liquid, methanethiol (CH_3SH) is a gas with an appalling odor reminiscent of skunks. It is one of the compounds added to natural gas as a warning for gas leaks. Write the Lewis structure of methanethiol.

Sample Solution

Note that the molecular formula for methanol (CH_3OH) resembles that of methanethiol. When we locate sulfur in the periodic table in the same family as oxygen, we understand why. Both oxygen and sulfur have the same number of valence electrons and can form the same number and type of bonds. Thus we write a structure similar to methanol and simply substitute sulfur for oxygen. The structure is

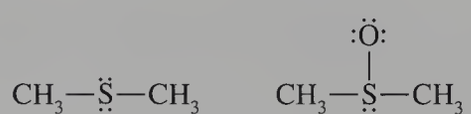


Problem 1.7

Chloroethane (CH_3CH_2Cl) is a topical anesthetic that boils at 12 °C. It is used to numb the skin by releasing the liquid from a pressurized spray can. Describe the bonding in this compound. (Refer to the structure of ethane.)

Problem 1.8

Dimethyl sulfoxide is a liquid that is readily absorbed through the skin. It was once considered as a possible solvent to deliver drugs by direct application to the skin, but turned out to be too toxic for this use. Compare its structure to dimethyl sulfide, and describe the sulfur–oxygen bond.



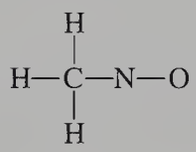
1.6 Strategy for Writing Lewis Structures

When we write Lewis structures of molecules, we show all valence electrons. Hydrogen shares two electrons in a covalent bond. The second-row elements carbon through fluorine have octets of electrons either as nonbonded or bonded pairs. The electrons may participate in single, double, or triple bonds. We can use the following strategy to write Lewis structures.

1. Determine the total number of valence electrons by adding the valence electrons in the constituent atoms.
2. Write a skeletal structure linking the necessary atoms with single covalent bonds. This structure has the minimum number of bonding electrons.

3. For each bond, subtract two electrons from the total number of valence electrons to give the number of electrons that can exist as nonbonded electrons or form multiple bonds.
4. Determine the number of electrons required to complete the octet around each atom (except hydrogen, which only requires two electrons). If this number equals the number calculated in step 3, place the electrons as nonbonded electron pairs around the appropriate atoms to complete the structure.
5. If the number of electrons determined in step 3 does not provide all atoms with octets, we must use multiple bonds. If the deficiency is 2, a double bond must be used. If the deficiency is 4, either two double bonds or a triple bond must be used.
6. Modify the structure with the appropriate number of multiple bonds. The remaining electrons are nonbonded electrons that satisfy the individual electronic requirements of each atom.

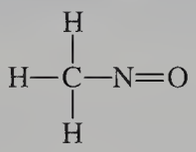
Let's apply these rules to nitrosomethane (CH_3NO), which has the following arrangement of atoms.



The total number of valence electrons is $3(1) + 4 + 5 + 6 = 18$ for the hydrogen, carbon, nitrogen, and oxygen atoms. A total of 10 electrons is depicted in the skeletal structure. The number of "unused" electrons is $18 - 10 = 8$. Now find out the number of electrons needed by each atom to complete its octet (remember, hydrogen needs only two).

Atom	*Electrons present*	*Electrons needed*
hydrogen	2 in each case	0
carbon	$4 \times 2 = 8$	0
nitrogen	$2 \times 2 = 4$	4
oxygen	2	6

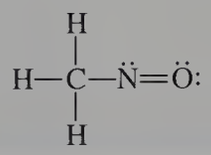
Because the 10 electrons required to form octets exceed the 8 electrons available after forming the single bonds, we need a double bond in the structure. The carbon atom has its required octet, so the double bond can be placed only between nitrogen and oxygen atoms.



Based on this structure, calculate the number of electrons needed by each atom.

Atom	*Electrons present*	*Electrons needed*
hydrogen	2 in each case	0
carbon	$4 \times 2 = 8$	0
nitrogen	$2 + 4 = 6$	2
oxygen	4	4

The number of electrons present in the structure is now 12, and 6 more electrons are required to complete the necessary octets. Six electrons remain available after using 8 for single bonds and 4 for a double bond. The 2 electrons required by nitrogen are added as a lone pair, the 4 needed by oxygen are added as two lone pairs. Thus, the structure is



Problem 1.9

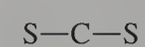
Sodium borohydride ($NaBH_4$) is a reducing agent used in organic chemistry. This ionic compound contains the borohydride ion BH_4^-. Write its Lewis structure.

Problem 1.10

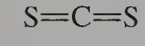
Write the Lewis structure for carbon disulfide (CS_2), a solvent used in some organic reactions. The sulfur atoms are bonded to the central carbon atom but not to each other.

Sample Solution

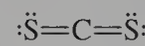
First write the connection of atoms in a molecular framework using only single covalent bonds between atoms.



Now calculate the total number of valence electrons for one carbon atom and two sulfur atoms, which is 4 + 2(6) = 16. Four electrons are placed in the two covalent bonds, leaving 12 electrons to complete octets around each atom using either lone pairs or multiple bonds. Each sulfur atom requires an additional 6 electrons and carbon requires 4 electrons. The total of 16 electrons is 4 more than are available. This deficiency is made up by using two double bonds—one between each sulfur atom and the central carbon atom.

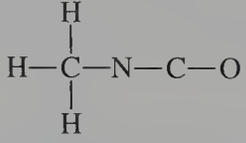


Now we have used 8 electrons of the original 16 valence electrons to form the molecular framework. Each sulfur atom now requires 4 more electrons, and carbon does not require any because it already has an octet of electrons. The remaining 8 electrons are distributed as two lone pairs of electrons on each sulfur atom, giving each an octet.



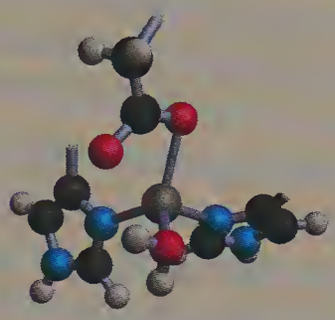
Problem 1.11

Methyl isocyanate is an important industrial intermediate used to synthesize compounds such as Sevin, an insecticide. A massive leak of this compound occurred in Bhopal, India, in 1984 and caused the death of at least 2000 people. Using the following molecular framework, write a Lewis structure for methyl isocyanate.



Coordinate Covalent Bonds of Metal Ions in Biochemistry

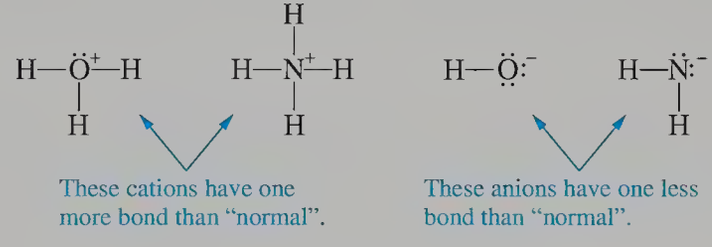
It may seem incongruous to start our discussion of organic chemistry by considering coordinate covalent bonds of metal ions. However, essential metals such as cobalt, copper, iron, magnesium, and zinc are involved in a host of biochemical reactions. The activity of many biomolecules is only possible because a metal ion such as Zn^{2+} forms coordinate covalent bonds with the lone pair electrons of nitrogen and oxygen atoms in these large molecules. The metal ions serve two roles. In some cases, the metal ion coordinates with several sites to determine the overall shape of the biomolecule. The unique shape of the molecule determines the specificity of chemical reactions such as the hydrolysis of a peptide into its component amino acids. In other cases, the metal ion is directly involved in the reaction because it also coordinates to the reactant and brings the reactant into an environment suitable for reaction. For example, zinc is an essential constituent of carboxypeptidase, an enzyme that catalyzes the hydrolysis of peptides. The zinc ion coordinates two nitrogen atoms and one oxygen atom located at three sites that would be widely separated if they weren't pulled together by the zinc. In the absence of a suitable reactant, the zinc is also coordinated to water.



When the hydrolysis of a peptide is required by the organism, this water molecule is easily displaced by an oxygen atom of a peptide. This coordination at oxygen polarizes the carbon–oxygen bond and makes the carbon atom more susceptible to attack by a water molecule, which is necessary for hydrolysis of the peptide.

1.7 Formal Charge

Although most organic molecules are represented by Lewis structures containing the "normal" number of bonds, some organic ions—and even molecules—contain less than or more than the customary number of bonds. First, let's recall the structures of some "inorganic" ions. The valence of the oxygen atom is two: it normally forms two bonds. However, oxygen has one bond in the hydroxide ion and three in the hydronium ion. Similarly, the nitrogen atom, whose valence is three, has two bonds in an amide ion and four bonds in an ammonium ion.



Two questions arise when atoms in polyatomic ions contain more or fewer bonds than expected from the valence of the central atom. First, what is the net charge of the ion? Second, what atom bears that charge? We answer these questions by assigning to each atom a formal charge determined by a bookkeeping method. The method is also used for neutral molecules that have unusual numbers of bonds. In such cases, centers of both positive and negative charge are located at specific atoms.

The **formal charge** of an atom equals the number of its valence electrons as a free atom minus the number of electrons that it "owns" in the Lewis structure.

$$\text{formal charge} = \begin{matrix}\text{number of valence}\\ \text{electrons in free}\\ \text{atom}\end{matrix} - \begin{matrix}\text{number of valence}\\ \text{electrons in bonded}\\ \text{atom}\end{matrix}$$

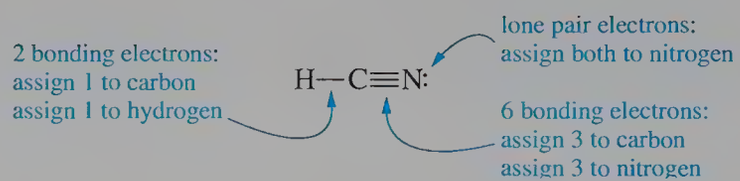
Two simple rules decide the question of "ownership".

1. Unshared electrons belong exclusively to the parent atom.
2. One half of the bonded electrons between a pair of atoms is assigned to each atom.

Thus, the total number of electrons "owned" by an atom in the Lewis structure equals the number of nonbonded electrons plus half the number of bonded electrons. Therefore, we may write

$$\text{formal charge} = \begin{matrix}\text{number of}\\ \text{valence}\\ \text{electrons}\end{matrix} - \begin{matrix}\text{number of}\\ \text{nonbonded}\\ \text{electrons}\end{matrix} - \tfrac{1}{2}\begin{pmatrix}\text{number of}\\ \text{bonded}\\ \text{electrons}\end{pmatrix}$$

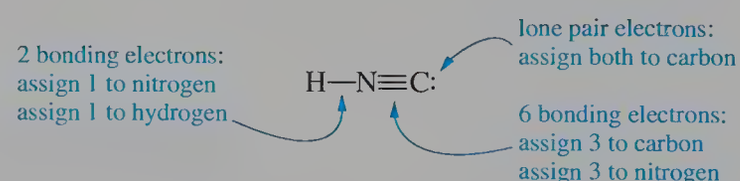
The formal charge of an atom may be zero, negative, or positive. The sum of the formal charges of each atom in a molecule equals zero. The sum of the formal charges of each atom in an ion equals the charge of the ion. Let's consider HCN and determine the formal charge of each atom.



The formal charge of each atom is calculated by substitution into the formula.

$$\begin{aligned}\text{formal charge of hydrogen} &= 1 - 0 - \tfrac{1}{2}(2) = 0\\ \text{formal charge of carbon} &= 4 - 0 - \tfrac{1}{2}(8) = 0\\ \text{formal charge of nitrogen} &= 5 - 2 - \tfrac{1}{2}(6) = 0\end{aligned}$$

The formal charge of each atom is zero—the usual case in most organic molecules. Now let's consider the molecule HNC.



The formal charge of each atom is calculated by substitution into the formula.

$$\begin{aligned}\text{formal charge of hydrogen} &= 1 - 0 - \tfrac{1}{2}(2) = 0\\ \text{formal charge of carbon} &= 4 - 2 - \tfrac{1}{2}(6) = -1\\ \text{formal charge of nitrogen} &= 5 - 0 - \tfrac{1}{2}(8) = +1\end{aligned}$$

The formal charges of two atoms are not zero. However, note that the sum of the formal charges of the atoms equals the net charge of the species, which in this case is zero. When we show formal charges of a structure in this text, they may be placed within parentheses over or beside the appropriate atoms.

Problem 1.12

Consider the structure of dimethyl sulfoxide given in Problem 1.8, and calculate the formal charges of the sulfur and oxygen atoms.

Problem 1.13

The acylium ion is an intermediate in one of the substitution reactions of aromatic compounds (Chapter 14). Calculate the formal charges of the carbon and oxygen atoms connected by a triple bond in the following structure. What is the charge of the ion?

$$CH_3—C{\equiv}O:$$

1.8 Molecular Geometry

Until now we have shown organic compounds as two-dimensional structures. But molecules are, of course, three-dimensional. The three-dimensional structure of a molecule is defined by its bond lengths—the distance between the nuclei of two bonded atoms—and bond angles—the angle between two bonds to the same atom.

Bond Lengths

The length of a bond depends on the bonded atoms. Some representative bond lengths are given in Table 1.3. The following generalizations are based on these data.

TABLE 1.3
Average Bond Lengths

Structural unit	*Bond length (pm)*
H—C	110
H—N	98
H—O	94
H—F	92
H—S	132
H—Cl	127
H—Br	142
H—I	161
C—C	154
C—N	147
C—O	143
C—F	141
C—Cl	176
C—Br	191
C—I	210
C=C	134
C=O	122
C≡C	121
C≡N	115

1. Bond lengths increase as the sizes of the bonded atoms increase. For example, chlorine is larger than fluorine, and the C—Cl bond is longer than the C—F bond.
2. Bond lengths between a given atom and a series of other atoms decrease from left to right within a period of the periodic table. For example, the C—F bond is shorter than the C—C bond. Part of the decrease of the bond length results from the smaller size of atoms toward the right in a period. However, the decrease is also partly due to the greater attraction for the bonding electrons, which are "pulled" closer by these electronegative atoms.
3. Bond lengths between atoms of the same element decrease as the number of bonds increase. For example, the bond lengths for carbon–carbon bonds decrease in the order C—C > C=C > C≡C. We will explain the reasons for this trend in Section 1.19.

Drawing Structures

Chemists use the following conventions to show the three-dimensionality of molecules and their bonds.

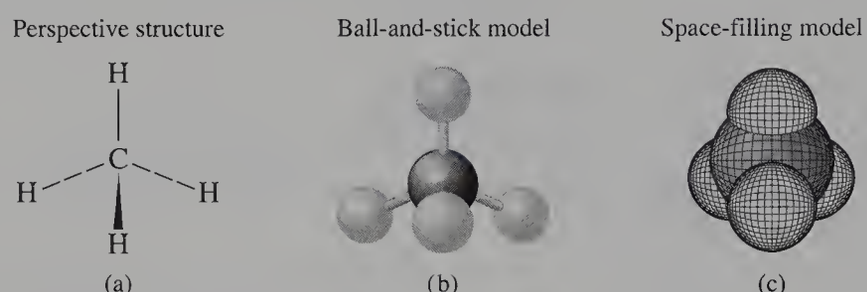
1. Solid lines represent bonds in the plane of the page.
2. Wedge-shaped lines represent bonds projecting forward out of the plane of the page.
3. Dashed lines represent bonds projecting back out of the plane of the page.

Let's apply these conventions to the structure of methane (CH_4). The four hydrogen atoms in methane are located at the corners of a regular tetrahedron with the carbon atom in the center of the tetrahedron and in the plane of the page (Figure 1.5a). Each H—C—H bond angle is 109.5°, the "tetrahedral" angle. One hydrogen atom is also in the plane of the page. Its bond is shown with a solid line. Two hydrogen atoms, shown with dashed bond lines, lie behind the plane of the page, and one hydrogen atom, shown with a wedge-shaped bond line, lies in front of the plane.

Because structure is so important to understanding chemical reactions, chemists construct three-dimensional models of molecules that can be viewed from a variety of angles. You will find it useful to purchase a molecular model kit to help you understand the structures of organic molecules.

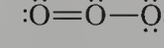
Two types of molecular models are ball-and-stick models and space-filling models. Each has certain advantages and disadvantages. Ball-and-stick models show the molecular framework and bond angles: the balls represent the atoms; the sticks represent bonds (Figure 1.5b). Ball-and-stick models do not show the actual volume occupied by the molecule, however. Space-filling models represent the volume occupied by the electrons surrounding each atom, but the carbon skeleton and its bond angles are obscured (Figure 1.5c).

FIGURE 1.5 Perspective Structural Formula and Molecular Models



1.9 Resonance Theory

In the Lewis structures for the molecules we have shown to this point, valence electrons have been pictured as either between two nuclei or associated with a specific atom. These are localized electrons. However, a single Lewis structure does not adequately represent the electronic structures of some molecules. For example, the Lewis structure of ozone (O_3) shows one double bond and one single bond.



A double bond is shorter than a single bond, so the Lewis structure shown above implies that there is one "long" O—O bond and a "short" O=O bond in ozone. However, the measured oxygen–oxygen bond lengths in the ozone molecule are both 128 picometers (pm). Hence the bonds are identical, and the terminal oxygen atoms are structurally equivalent. Therefore, a Lewis structure with single and double bonds does not accurately describe the ozone molecule. To give the information that a Lewis structure cannot represent, we use the concept of resonance. A molecule is resonance stabilized if it can be represented by two or more Lewis structures that have identical arrangements of atoms, but different arrangements of electrons. Ozone is such a molecule. The real structure of ozone is a hybrid of two Lewis structures, neither of which is completely correct.

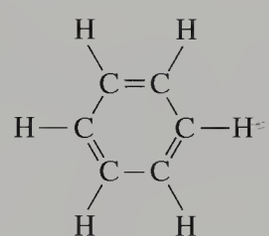
The double-headed arrow between the two Lewis structures says that the actual structure lies somewhere between the two simple structures. The individual Lewis structures are called contributing structures, or resonance structures. Each resonance structure for ozone has one O=O bond and one O—O bond. The arrangements of the atoms are the same, but the arrangements of electrons are different.

When we write resonance structures, we use curved arrows to keep track of the electrons. The tail of the arrow is located near the bonded or nonbonded pair of electrons to be "moved" or "pushed", and the arrowhead shows the final destination of the electron pair.

structure 1 structure 2

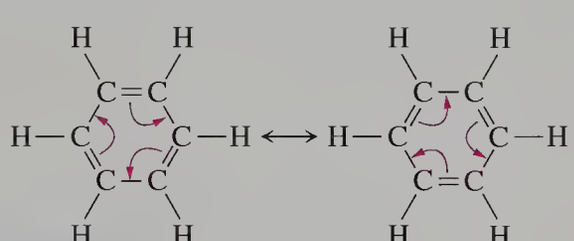
In resonance structure 1, the nonbonded pair of electrons on the right-hand oxygen atom is moved to form a double bond with the central oxygen atom. One of the bonded pairs of electrons between the central oxygen atom and the oxygen atom on the left is also moved to form a nonbonded pair of electrons on the left oxygen atom. The result is resonance structure 2. This procedure of "pushing" electrons from one position to another is only a bookkeeping formalism. Electrons do not really move this way! The actual ozone molecule has **delocalized** electrons around all three atoms. A single Lewis structure cannot show this phenomenon.

Electrons can be delocalized over many atoms. For example, benzene (C_6H_6) consists of six equivalent carbon atoms contained in a ring in which all carbon–carbon bonds are identical. Each carbon atom is bonded to a hydrogen atom. A single Lewis structure containing alternating single and double bonds can be written to satisfy the Lewis octet requirements.



Lewis structure of benzene

Single and double bonds have different bond lengths, but all carbon–carbon bonds in benzene are the same length. Like ozone, benzene is represented by two contributing resonance structures separated by a double-headed arrow. The positions of the alternating single and double bonds are interchanged in the two resonance structures.



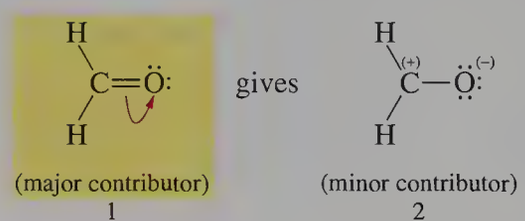
Six of the electrons in benzene are delocalized over the six carbon atoms in the ring. This means that there is an equal probability of finding any given electron near any given carbon atom. There are no true single or double carbon–carbon bonds in benzene. They are of an intermediate type that cannot be represented with a single structure.

Nonequivalent Resonance Structures

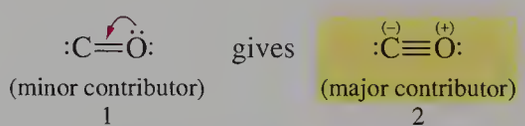
The resonance structures for molecules such as O_3 and benzene are equivalent and contribute equally to the structure of the molecule. However, many molecules have nonequivalent resonance structures that don't contribute equally to the structure of the actual molecule. To decide which resonance form is the more important, we can use the following four guidelines. The rules are applied with priority 1 > 2 > 3 > 4.

1. Lewis structures with the maximum number of Lewis octets are the most stable.
2. Avoid charge separation if possible. Charges are located on atoms with the most appropriate electronegativity characteristics (e.g., negative charges are placed on electronegative elements).
3. Opposite charges are located on atoms with the minimum separation.
4. Charges can be separated if Lewis octets result.

Let's apply these rules to two electronic structures of formaldehyde (CH_2O). Structure 1, with the carbon–oxygen double bond, has Lewis octets for both the carbon atom and the oxygen atom. Structure 2 has a Lewis octet for the oxygen atom, but not the carbon atom. Therefore, structure 1 is preferred over structure 2 (rule 1). Structure 2 also has a formal negative charge on the oxygen atom and a positive charge on the carbon atom. We want to avoid charge separation if possible (rule 2).

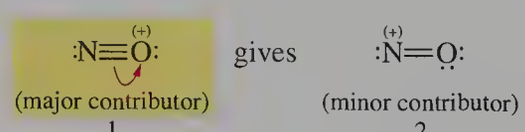


Consider two resonance structures for carbon monoxide (CO). The formal charges are placed above the appropriate atoms.



Structure 2, on the right, is more stable than structure 1. It is the major contributor to carbon monoxide because it has a Lewis octet for both the carbon atom and the oxygen atom. Note that the Lewis octet is formed even though there is a formal positive charge on the electronegative oxygen atom! Rule 4 allows this.

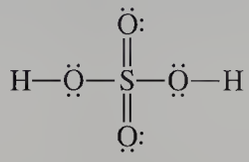
Now consider the resonance structures for NO^+.



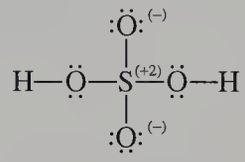
Structure 1, on the left, is more stable than structure 2. Structure 1 is the major contributor to NO^+ because the nitrogen and oxygen atoms each have a Lewis octet. Because the oxygen atom is more electronegative than the nitrogen atom, the positive charge is better tolerated on the nitrogen atom of structure 2 than on the oxygen atom of structure 1. However, structure 2 does not have a Lewis octet on the nitrogen atom and is less stable.

Exceptions to the Lewis Rule

Some organic molecules contain atoms found beyond the second period such as sulfur and phosphorus. These atoms can have more than eight bonded and nonbonded electrons shown in structural formulas. However, Lewis structures can also be drawn with only eight electrons in the valence shell for sulfur and phosphorus. The sulfur atom in sulfuric acid is an example.



1



2

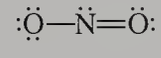
These two representations are contributing resonance forms. Note that structure 2 has a +2 formal charge on sulfur and a −1 formal charge on oxygen atoms.

Problem 1.14

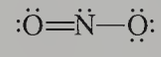
Nitrites (NO_2^-) are added as antioxidants in some processed meats and occasionally at salad bars. Write resonance structures for the nitrite ion.

Sample Solution

Using the procedure for drawing Lewis structures outlined in Section 1.6, we find that there must be one double bond between the nitrogen atom and one of the oxygen atoms.



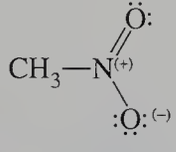
However, the choice of location of the double bond is arbitrary. The positions of the nitrogen–oxygen single and double bonds can be interchanged as long as the lone pair electrons are located appropriately on each oxygen atom.



Thus, the compound can be represented by two equivalent resonance contributors. Note that the nitrogen atom has no formal charge in either structure. The single-bonded oxygen atom in each case has a formal minus charge.

Problem 1.15

Consider the structure of nitromethane, a compound used to increase the power in some specialized race car engines. A nitrogen–oxygen single bond length is 136 pm; a nitrogen–oxygen double bond length is 114 pm. The nitrogen–oxygen bonds in nitromethane are equal and are 122 pm. Explain the data in terms of the electronic structure of nitromethane.



Problem 1.16

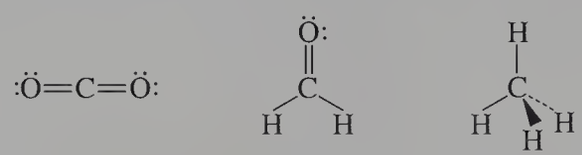
Write two structures that represent phosphoric acid (H_3PO_4). The molecule consists of a central phosphorus atom with four oxygen atoms bonded to it. The hydrogen atoms are bonded to oxygen atoms.

1.10 Valence-Shell Electron-Pair Repulsion Theory

We can predict the geometry of simple molecules using **valence-shell electron-pair repulsion** (VSEPR) theory. This theory is based on the idea that bonded and nonbonded electron pairs around a central atom repel one another. Hence, they are arranged in a geometry that provides maximum separation in space and therefore minimum electron repulsion. Two electron pairs should be arranged at 180° to each other and three pairs at 120° in a common plane; four electron pairs should have a tetrahedral arrangement, with angles of 109.5°.

two pairs of electrons | three pairs of electrons | four pairs of electrons

To illustrate VSEPR theory, let's consider the geometry of three simple molecules. Carbon dioxide is a linear molecule; formaldehyde (CH_2O) is a trigonal planar molecule, and methane (CH_4) is a tetrahedral molecule. All of the valence electrons around the central carbon atom in these molecules participate in bonds. The electrons in single, double or triple bonds of the molecules repel each other. VSEPR theory considers electrons in multiple bonds the same as those in single bonds.



carbon dioxide | formaldehyde | methane

Carbon dioxide has two equivalent double bonds: each lies as far as possible from the other double bond, forming a 180° angle between the bonds. Formaldehyde has a double bond and two single bonds to the central carbon atom. These bonds correspond to three regions in space that contain electrons separated by the maximum distance in a trigonal planar arrangement. However, the actual H—C=O bond angle is 121.7°, slightly larger than the predicted 120°. The H—C—H bond angle is slightly smaller than 120°. These deviations from the predicted structure arise because the various bonding electrons are not equivalent. Methane has four bonded electron pairs in single bonds, and they are located in a tetrahedral arrangement. Each H—C—H bond angle is predicted to be 109.5°, which agrees with the experimental value.

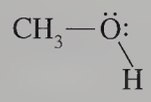
Now let's consider molecules that have both bonded and nonbonded pairs of electrons in the valence shell of the central atom. Water and ammonia have four electron pairs around the central atom. Some of the electron pairs in water and ammonia are bonded to hydrogen atoms, but the central atom also has unshared electron pairs. VSEPR theory describes the distribution of bonded and nonbonded electron pairs. However, molecular structure is defined by the positions of the nuclei. The four pairs of electrons in both water and ammonia are tetrahedrally arranged around the central atom. Water, with only three atoms, is angular, and ammonia, with four atoms, is pyramidal (Figure 1.6).

The H—C—H, H—N—H, and H—O—H bond angles are 109.5°, 107°, and 104.5°, respectively. We can explain these differences by considering electron pair repulsions. The decrease in bond angle suggests that the nonbonded electron pair is more spread out than the bonding electron pairs . The nonbonded electrons push the bonded electron pairs, and hence the bonded atoms, closer together. As a consequence, electron pair repulsion decreases as follows.

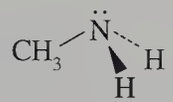
lone pair–lone pair > lone pair–bonded pair > bonded pair–bonded pair

In methane, the four bonded pairs are equivalent, arranged around the carbon atom at the tetrahedral angle, 109.5°. In ammonia, the lone pair electrons repel the bonded pairs, and contract the H—N—H angle to 107°. In water, the two sets of lone pair electrons repel each other and the bonded pairs. Hence, the bonded pairs are forced even closer together than in ammonia.

The arrangements of bonds to the oxygen atom of methyl alcohol and the nitrogen atom of methylamine are similar to those in water and ammonia, respectively. The groups bonded to the oxygen atom of methyl alcohol form an angular molecule. The groups bonded to the nitrogen atom of methylamine are arranged in a pyramid.



methanol



methylamine

Problem 1.17

Use the structure of the nitrite ion given in Problem 1.14 to determine its geometry.

Sample Solution

There is one lone pair of electrons, one single bond, and one double bond in either resonance contributor. Thus there are three regions containing electrons about the nitrogen atom. According to VSEPR theory these three regions should separate by 120° and lie in a plane. The exact O—N—O angle may not be 120° because the electron densities of the three regions are not equal.

Problem 1.18

The electronic structure of allyl isothiocyanate, a flavor ingredient in horseradish, is shown below. What are the C—N=C and N=C=S bond angles?

allyl isothiocyanate

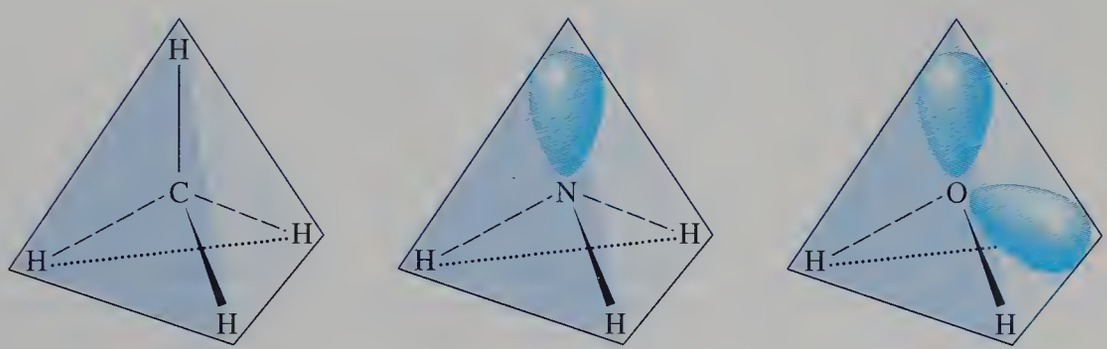


FIGURE 1.6 VSEPR Model to Predict Geometry About Central Atom
All electron pairs in methane, ammonia, and water are directed to the corners of a tetrahedron. However, the ammonia molecule is described as trigonal pyramidal; the water molecule is angular.

1.11 Dipole Moments

The measure of the polarity of a bond is the **bond moment**, μ. It is the product of the absolute value of the charge, q, and the distance between the charges, r.

$$\mu = |q|r$$

For diatomic molecules, the bond moment is equal to the **dipole moment** of the molecule. The dipole moment is expressed in Debye units (D). A dipole moment of 1 D equals the bond moment that results when opposite charges of 1×10^{-10} esu (electrostatic unit) are separated by one angstrom; 1 D equals 1×10^{-10} esu Å.

Determining Charge Separation

The dipole moment gives us an idea about the amount of charge separation in a bond. The dipole moment of hydrogen chloride (HCl), for example, is 1.08 D. The bond length of HCl is 1.27 Å. Solving for q, the charge is 0.85×10^{-10} esu. The charge of an electron is 4.8×10^{-10} esu. Thus, the partial charge on the chlorine atom in HCl is 0.18 that of an electron.

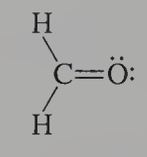
$$\frac{0.85 \times 10^{-10}\ \text{esu}}{4.8 \times 10^{-10}\ \text{esu/electron}} = 0.18\ \text{electron}$$

TABLE 1.4
Average Bond Moments (Debye)

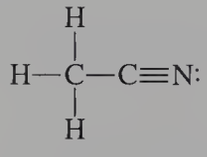
*Structural unit**	*Bond moment (D)*
H—C	0.4
H—N	1.3
H—O	1.5
H—F	1.7
H—S	0.7
H—Cl	1.1
H—Br	0.8
H—I	0.4
C—C	0.0
C—N	0.2
C—O	0.7
C—F	1.4
C—Cl	1.5
C—Br	1.4
C—I	1.2
C=O	2.3
C≡N	3.5

* The more electronegative part of the unit is to the right of the bond.

The bond moments of some bonds in Debye units are given in Table 1.4. The bond moment of a specific bond is relatively constant from compound to compound. The C—H bond moment, for example, is small because the hydrogen and carbon atoms have similar electronegativity values. Therefore, the C—H bond is not a polar covalent bond. In contrast, the bond moment of the C—Cl bond in molecules such as chloromethane is large. Carbon has an electronegativity of 2.5. Chlorine has an electronegativity of 3.0. Because chlorine is more electronegative than carbon, the bonded electrons are pulled toward the chlorine atom. Note that the bond moments of multiple bonds between carbon and oxygen, and between carbon and nitrogen, are quite large. Hence, the C=O bond in formaldehyde and the C≡N bond in acetonitrile (CH_3—C≡N) are both very polar.



formaldehyde



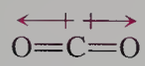
acetonitrile

Polarity and Molecular Geometry

Some molecules have polar bonds but no dipole moment. The polarity of molecules depends on the polarity of the bonds and the geometry of the molecule. The molecular dipole moment equals the vector sum of the individual bond moments.

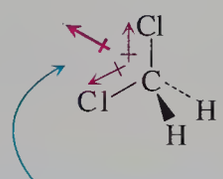
To illustrate the relationship between molecular geometries and dipole moments, let's first consider carbon dioxide (CO_2). The C=O bonds are polar, with the polarity directed from the carbon atom toward the more electronegative oxygen atoms. The two bonds are located along a common line in this linear molecule. As

a result, the bond moments of the C=O bonds cancel each other, and the molecule has no net dipole moment.



Now consider carbon tetrachloride (CCl_4) and dichloromethane (CH_2Cl_2). Both molecules have polar C—Cl bonds with the negative ends of the bond moments toward the chlorine atoms.

The bond moments cancel and there is no net polarity.



The bond moments do not cancel and a net polarity results.

However, CCl_4 has no dipole moment because the vector sum of the symmetrically arranged bonds is zero. In contrast, dichloromethane has a dipole moment of 1.62 D. The vector sum of the two C—Cl bonds is located at an angle bisecting the Cl—C—Cl bond angle. The C—Cl bonds are largely responsible for the observed dipole moment. The resultant of the two smaller C—H bond moments is in the same direction as the net resultant of the two C—Cl bond moments. The small resultant of the two C—H bond moments therefore reinforces the C—Cl bond moments.

Problem 1.19

The bond moment of C=O in compounds such as formaldehyde is 2.3 D. The bond length is 1.22 Å. Determine the partial charge of the oxygen atom.

1.12 Molecular Orbital Theory

In Section 1.4, we represented the electronic structures of molecules as Lewis structures. Lewis structures enable us to "explain" the order of connectivity of atoms, the most fundamental feature of molecular structure. We then used valence-shell electron-pair repulsion (VSEPR) theory to "explain" molecular geometry. Lewis structures and VSEPR theory, however, are somewhat naive because they do not describe molecular structure in terms of atomic and molecular orbitals. In this section we will "explain" covalent bonding and molecular structure in greater depth using molecular orbital theory.

When we introduce any theory of bonding and structure, we discover that the theories are mathematical. However, we are in luck. We can leap right over the mathematical treatment of bonding and structure and use qualitative results predicted by the theory without serious harm to our understanding. We will summarize the theory of structure and bonding with pictures instead of mathematical equations. So, not only is "a picture worth a thousand words", it is also a worthy substitute for a thousand equations.

Atomic Orbitals

Although you may be accustomed to thinking of electrons as particles, many of the properties of electrons can only be interpreted in terms of wave-like phenomena. An electron in an orbital can be described by a wave equation whose solutions corre-

spond to the energy states of the electron. We call these solutions orbitals. The orbital solutions to the wave equations have the familiar names: 1*s*, 2*s*, 2*p*, and so forth. The wave function for an electron tells us only about the energy of the electron. However, the square of the wave function tells us the probability of finding an electron in a certain region of space. The square of the wave function gives us the "shape" of the orbital. For example, a 1*s* orbital is spherical, as shown in Figure 1.7a.

The 1*s* orbital is spherical because the value of the square of the wave function at a given distance from the nucleus is the same in all directions. The value of the function changes with distance from the nucleus, but the sign does not change. We place a plus sign within a sphere that represents the 1*s* orbital (Figure 1.7a). Do not confuse the *sign* of the wave function with the positive or negative *charges* of the electron, the proton, or ions!

A 2*p* orbital has two lobes. It is not spherical, but is symmetrical around an axis through its two lobes. The sign of the wave function within one lobe is opposite to the sign of the wave function within the other, so we place a plus sign in one lobe and a minus sign in the other lobe (Figure 1.7b). The value of the wave function is zero at a node located between the two lobes of the 2*p* orbital. The 2*p* orbital is perpendicular to a plane containing the node.

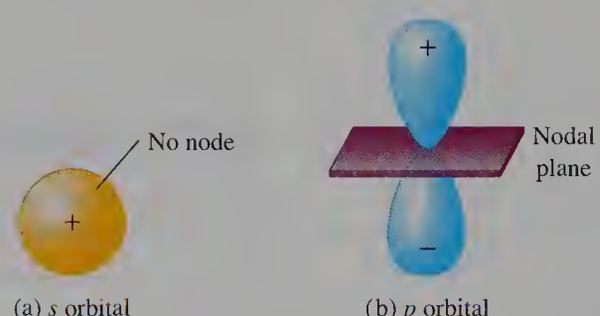


FIGURE 1.7 Signs of Wave Functions of Atomic Orbitals
(a) The wave function of an *s* orbital is spherically symmetrical. The sign of the wave function does not change within the orbital.
(b) The sign of the wave function for a 2*p* orbital is different in each lobe. A node exists at a point between the lobes of the orbital.

Molecular Orbitals

Atomic orbitals describe the probability of finding a given electron of an atom in space. We can combine atomic orbitals of atoms in molecules to form orbitals called **molecular orbitals** (MOs). The molecular orbitals result from adding or subtracting atomic orbitals to give a **linear combination of atomic orbitals** (LCAO). The number of molecular orbitals is conserved. For example, adding two atomic orbitals represented by A_1 and A_2 produces two wave functions M_1 and M_2, described by the following equations.

$$M_1 = c_1A_1 + c_2A_2$$
$$M_2 = c_1A_1 - c_2A_2$$

The coefficients c_1 and c_2 are weighting factors that indicate the degree to which the atomic orbitals contribute to the molecular orbital. The coefficients are equal for diatomic molecules containing identical atoms.

Like an atomic orbital, a molecular orbital can hold a maximum of two electrons with opposite spins. The shapes of molecular orbitals obtained by merging two atomic orbitals resemble the shapes of the atomic orbitals. When the atomic

orbitals merge to give a molecular orbital, they overlap in a region of space common to the bonded nuclei. First, consider the merger of two 1*s* orbitals. Partial overlap of the spheres yields an egg-shaped molecular orbital (Figure 1.8a). The orbital is symmetrical around an axis through both nuclei. Rotation around this axis does not change the appearance of the orbital. Orbitals that have this characteristic are called **sigma** (σ) molecular orbitals.

Now let's consider a combination of atomic orbitals that results in a molecular orbital with different symmetry. When two parallel 2*p* orbitals overlap, the area of overlap occurs above and below the internuclear axis and is not cylindrically symmetrical (Figure 1.8b). A molecular orbital that results from sideways overlap of atomic orbitals is a **pi** (π) molecular orbital. A π molecular orbital can hold a maximum of two electrons, and these electrons must have opposite spins.

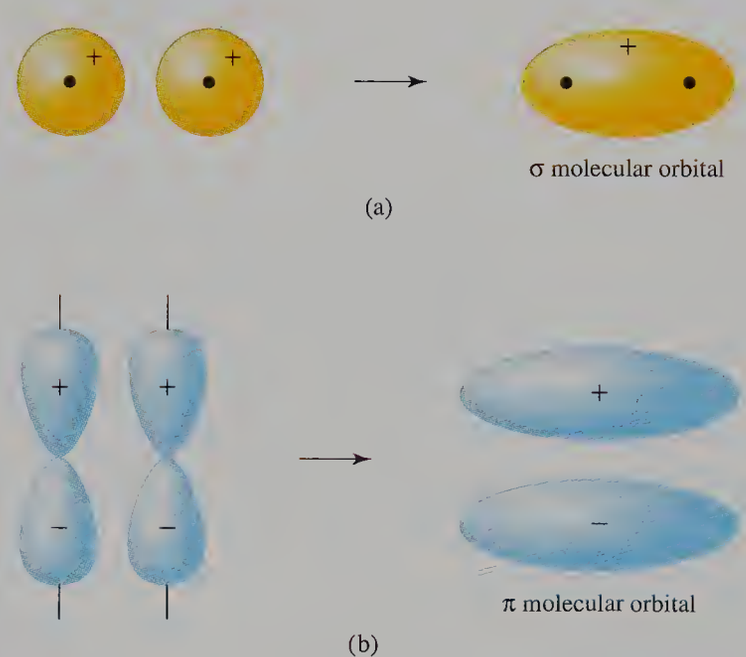


FIGURE 1.8 Linear Combination of Atomic Orbitals
(a) When the 1*s* atomic orbitals of hydrogen atoms overlap, they may do so with reinforcement of the wave functions. The constructive interaction—that is, the addition of wave functions—gives a sigma (σ) molecular orbital. The electron density between two nuclei is located in this cylindrically symmetrical region.
(b) When two 2*p* orbitals overlap sideways, they may do so with reinforcement of the wave functions. The constructive interaction—that is, the addition of wave functions—results in a pi (π) molecular orbital.

1.13 The Hydrogen Molecule

The molecular orbital containing the bonding electrons in H_2 results from the overlap of two 1*s* atomic orbitals. The molecular orbital of the hydrogen molecule encompasses both nuclei. They are separated by an optimum distance, the bond length, which results from a balance between attractive and repulsive forces. The nuclei attract the bonding electrons, but repel each other. As two atoms move closer together, the resulting increase in the electron density between the two atoms causes an attraction that lowers the potential energy (Figure 1.9). However, as the nuclei move still closer, the repulsion between the two nuclei eventually balances the effect of the electrons, and the potential energy increases. The internuclear distance corresponding to the minimum energy is the bond length.

Thus far, we've added wave functions. What happens when we "subtract" wave functions? Because subtraction is mathematically equivalent to the addition of a positive and a negative quantity, we can consider the addition of wave functions of opposite signs (Figure 1.10) the same as subtraction. When the two 1*s* orbitals of hydrogen atoms with wave functions of opposite sign interact, the

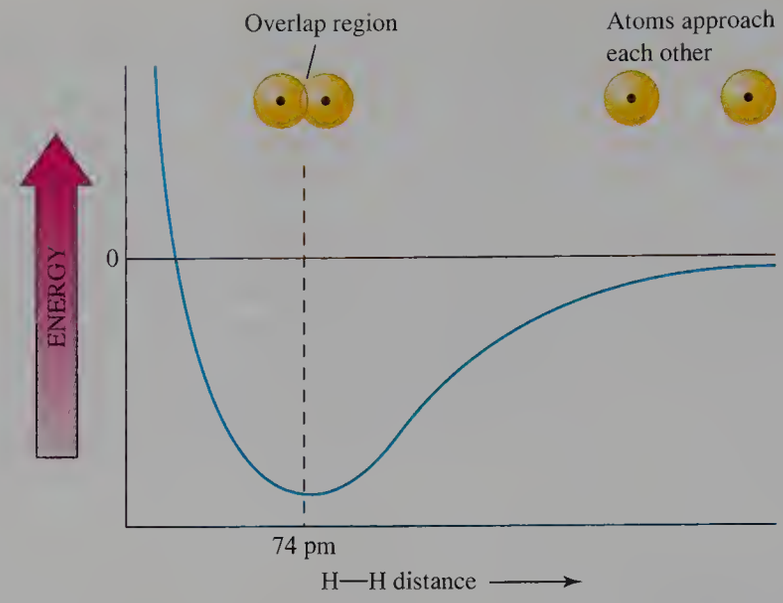


FIGURE 1.9 Bond Formation in the Hydrogen Atom
An energy minimum for the interaction of two hydrogen atoms occurs when they are 74 pm apart. This minimum corresponds to bond formation between the two atoms. If the nuclei move closer, the energy increases because the two positively charged nuclei repel each other more.

resulting molecular orbital corresponds to a destructive interaction in which the wave functions cancel out where the orbitals overlap. The resulting molecular orbital is called an **antibonding** orbital. The antibonding molecular orbital has a nodal plane between the two atoms. It has the same symmetry as the bonding molecular orbital and is symbolized by σ^*.

Figure 1.10 shows the energy of the σ and σ^* molecular orbitals relative to the energy of the 1*s* orbitals of the hydrogen atoms. As noted above, the energy of the bonding molecular orbital is lower than the combined energies of the atomic orbitals. Thus, energy is released as bonding occurs. The antibonding molecular orbital is at higher energy than the atomic orbitals.

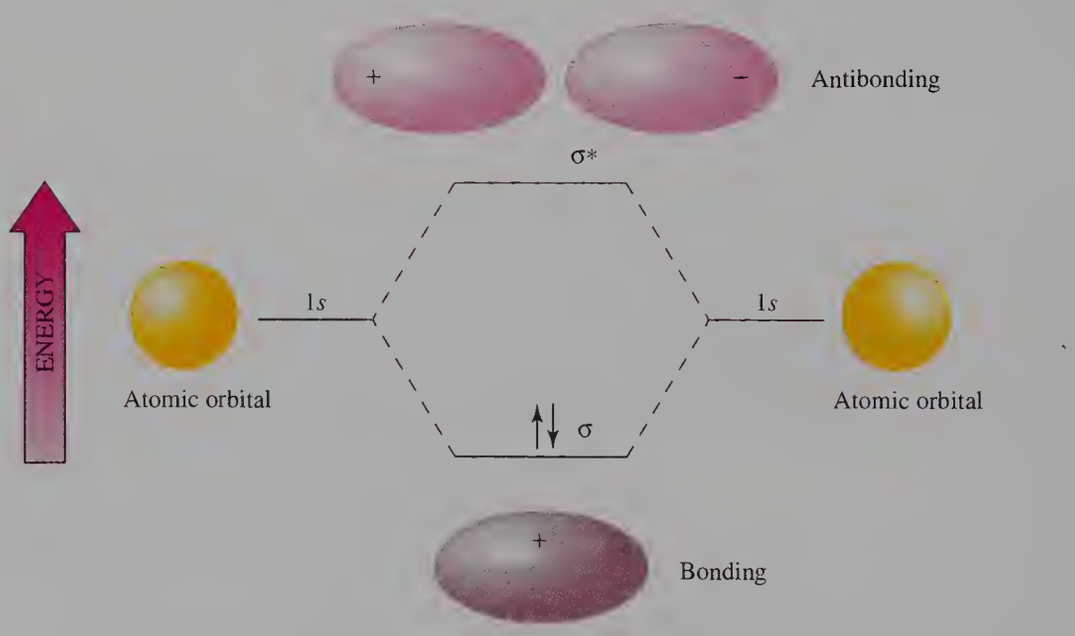


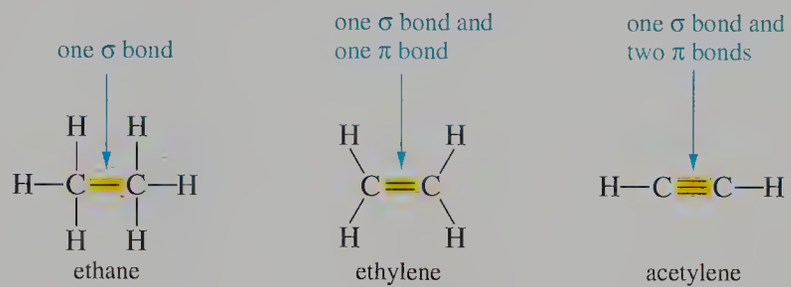
FIGURE 1.10 Energy of Bonding and Antibonding Molecular Orbitals
Two molecular orbitals are formed by combining two 1*s* hydrogen orbitals. The bonding molecular orbital is lower in energy that the antibonding molecular orbital. When the signs of the 1*s* wave functions differ, the resulting molecular orbital also has cylindrical symmetry, but there is no electron density between the two nuclei.

Because there is no electron density between the nuclei in the antibonding molecular orbital, there is no attractive force to compensate for nuclear repulsion. Hence the σ^* orbital is less stable than the bonding molecular orbital, and even less stable than the isolated atoms.

1.14 Bonding in Carbon Compounds

Many years ago, Linus Pauling suggested that the strongest bonds form when two orbitals achieve maximum overlap, which occurs when two orbitals point directly toward each other. The σ bonds between carbon atoms and other atoms, such as the hydrogen atom, result from overlap of orbitals along the internuclear axis. As a consequence, σ bonds have high bond energies. Because the overlap of orbitals in a π bond is less than that of a σ bond, π bonds are weaker than σ bonds.

A single bond in an organic molecule is always a σ bond. A double bond consists of a σ bond and a π bond. A triple bond consists of a σ bond and two π bonds.



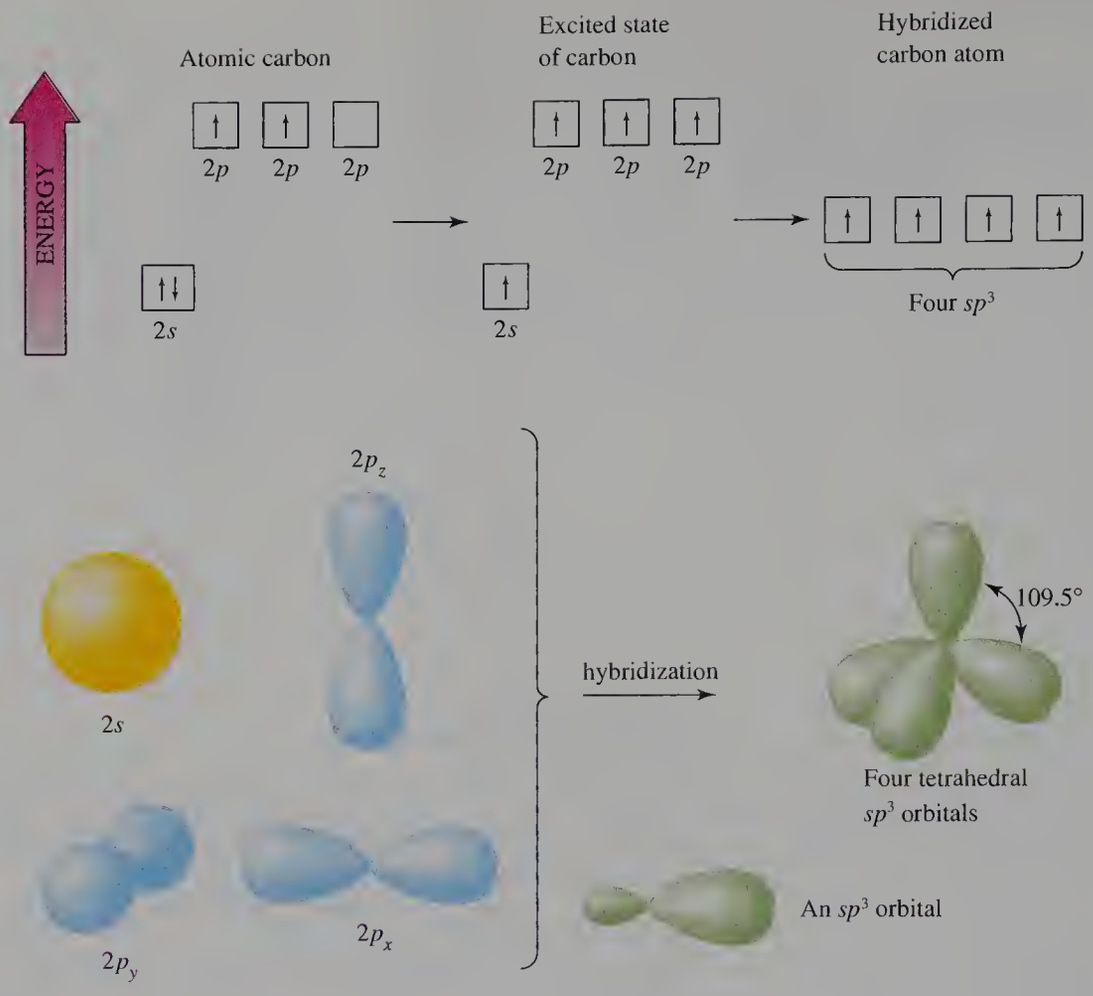
Orbital Hybridization

In Lewis structures of ethane, ethylene, and acetylene, all carbon atoms have four bonds. In this section we will consider the atomic and molecular orbitals from which bonds to carbon are made. Carbon has the electron configuration $1s^2 2s^2 2p^2$. We know that the 1*s* electrons do not participate in bonding and that carbon bonds with its 2*s* and 2*p* electrons. However, because the 2*s* orbital is filled and the 2*p* electrons are distributed between $2p_x$ and $2p_y$ orbitals, the ground state electron configuration does not appear to permit the formation of four bonds. Linus Pauling proposed that the original, ground state orbitals of carbon are mixed, or **hybridized**, to give a new set of atomic orbitals used to make σ and π bonds. The Pauling orbital hybridization process is designed to generate the molecular geometry predicted by VSEPR theory. In the following sections, we will consider the molecular geometries and orbital hybridization of carbon when it forms four σ bonds, three σ bonds and one π bond, and two σ bonds and two π bonds. We will also consider the hybridization of oxygen and nitrogen because these atoms are present in many organic compounds. The Pauling orbital hybridization model is universally accepted because of its enormous predictive power, but we shouldn't forget that it is purely a theoretical construct that does not correspond to an actual physical process.

1.15 sp^3 Hybridization of Carbon in Methane

The tetrahedral geometry of methane can be explained by imagining that the 2*s* orbital and the three 2*p* orbitals of carbon hybridize to form four identical hybrid orbitals (Figure 1.11). We can divide the hybridization process into two steps. First, an electron in the 2*s* orbital is "promoted" to a vacant 2*p* orbital to produce an excited state of carbon. Then the half-filled 2*s* orbital and the three half-filled 2*p* orbitals mix to form new sp^3 hybrid orbitals (pronounced "s-p-three," not "sp cubed"). These orbitals are so named because they result from the combination of one *s* and three *p* orbitals. Each hybrid orbital has 25% *s* character and 75% *p* character. The four sp^3 hybrid orbitals have the same energy. Each orbital has two lobes of unequal volume. The signs of the wave functions in the two lobes are opposite. The larger volume corresponds to a region of higher electron density. We usually consider only

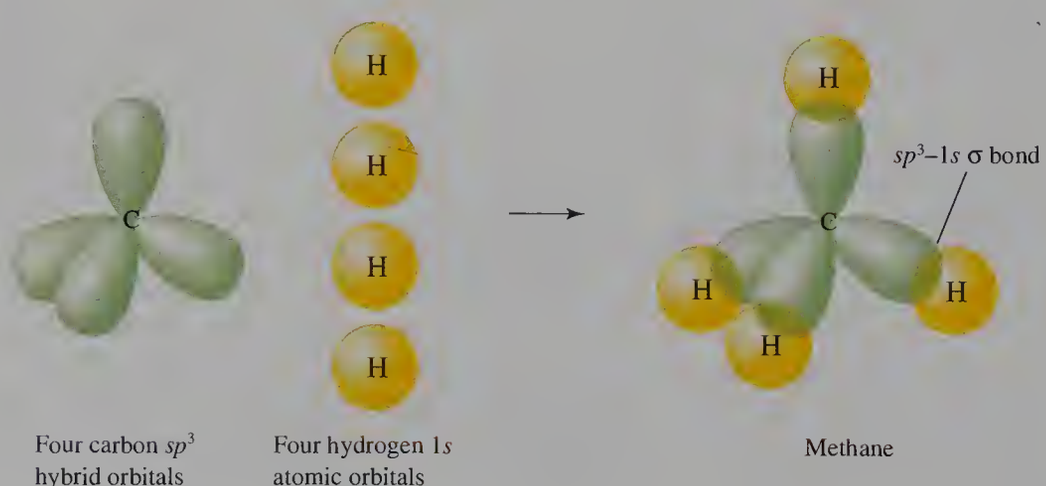
FIGURE 1.11
sp^3-Hybridized Carbon Atom



the larger lobe when showing bonds made with sp^3 hybrid orbitals. For purposes of clarity, the smaller lobes of each sp^3 hybrid orbital are usually omitted from structures showing bonding of atoms.

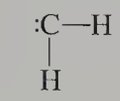
The four single bonds and the tetrahedral shape of CH_4 are explained by using sp^3 hybrid orbitals, each of which contains one electron. The sp^3 orbitals extend toward the corners of a tetrahedron, achieving maximum separation of the electrons. The large lobe of each sp^3 hybrid orbital overlaps the 1*s* orbital of a hydrogen atom. Hence, the carbon atom forms four σ bonds (Figure 1.12).

FIGURE 1.12 Bonding and Structure of Methane



Energy Changes in Hybridization and Bonding

Let's consider the energy changes that accompany hybridization and bonding to form methane, as compared to the formation of the hypothetical molecule CH_2. The Lewis structure of CH_2 would be



In this structure, the two $2p$ orbitals, which have one electron each, form two σ bonds with the $1s$ orbitals of hydrogen atoms. When bonds form, energy is released (a negative $\Delta H°$). Let's use Hess's law to compare the energy released when CH_4 is formed compared to the energy that would be released in the formation of CH_2. Formation of a C—H bond releases about 420 kJ mole^{-1} (100 kcal mole^{-1}). Thus, more energy would be released when four bonds form in CH_4. The σ_{sp^3-1s} bonds are also stronger than the σ_{2p-1s} bonds that would form in CH_2. The 25% s character of the sp^3 hybrid orbital makes it more electron attracting because a $2s$ orbital is closer to the nucleus than a $2p$ orbital. However, energy is required to change carbon from its $1s^2 2s^2 2p^2$ electron configuration to an sp^3-hybridized atom. This energy requirement is about 400 kJ mole^{-1} (96 kcal mole^{-1}). That is, $\Delta H° = +400$ kJ mole^{-1}. But this energy requirement is more than offset by the 1670 kJ mole^{-1} (400 kcal mole^{-1}) released ($\Delta H° = -1670$ kJ mole^{-1}) when four C—H bonds form. The net release of about 1250 kJ mole^{-1} is larger than the approximately 670 kJ mole^{-1} that would be released for the formation of two weaker C—H bonds of "unhybridized" carbon in CH_2.

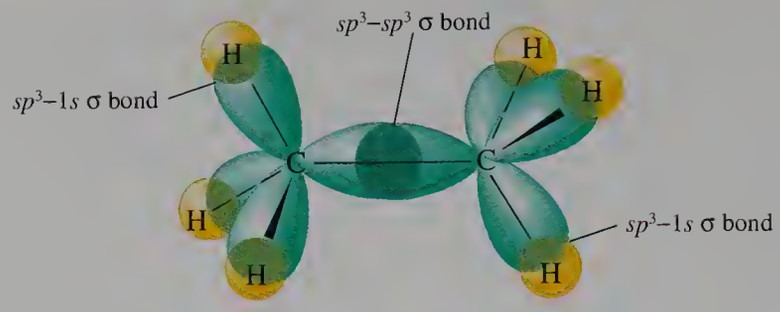
1.16 sp^3 Hybridization of Carbon in Ethane

The orbital hybridization model of bonding in methane also accounts for the carbon–carbon bonds in more complex organic compounds. Ethane ($CH_3—CH_3$) can be thought of as two CH_3 (methyl) groups—obtained by removing one hydrogen atom from each of two methanes—joined by a carbon–carbon bond (Figure 1.13). These units are sp^3 hybridized. Three of the sp^3 orbitals of each carbon atom overlap with $1s$ atomic orbitals of hydrogen to form the CH_3 units. These C—H bonds are similar to the σ_{sp^3-1s} bonds in methane. The C—H bond in ethane (111 pm) is slightly longer than the C—H bond in methane (109 pm). The bond energies of the C—H bonds of ethane and methane are 422 and 438 kJ mole^{-1}, respectively.

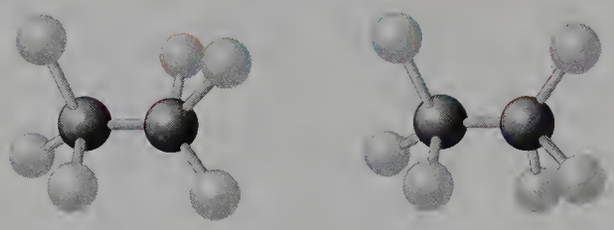
The carbon atoms in ethane are linked by a $\sigma_{sp^3-sp^3}$ bond. The C—C bond length is 154 pm; the C—C bond energy of ethane is 368 kJ mole^{-1} (88 kcal mole^{-1}). Each CH_3 unit can be rotated around the C—C internuclear axis. That is, the positions of the hydrogen atoms of each carbon atom with respect to each other can change. Two such orientations, called **conformations**, are shown in Figure 1.13. In these two conformations, as well as any others resulting from different angles of rotation around the C—C bond, the σ bond remains unaffected because the overlap of the sp^3 orbitals of the bonded carbon atoms does not change.

Which of the conformations represents ethane? They all do. Rotation around the carbon–carbon σ bond occurs constantly in ethane. However, this rotation does not alter the connectivity of the carbon–carbon or carbon–hydrogen bonds. The motion is like the twisting and turning of your body while dancing. You may look different, but the parts of your body are still connected in all the normal ways. Only the orientation of your limbs is changing. Conformations of ethane and other hydrocarbons—compounds of carbon and hydrogen—will be discussed in more detail in Chapter 4.

FIGURE 1.13
Hybridization in Ethane and Conformations
(a) The bonding molecular orbital of the C—C bond in ethane is cylindrically symmetrical.
(b) Rotation of the two methyl groups about the bond axis maintains the bond but changes the relative positions of the C—H bonds.



(a)

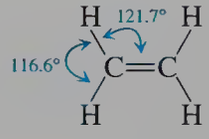


Two conformations of ethane

(b)

1.17 sp^2 Hybridization of Carbon in Ethylene

Now let us consider the bonding electrons in the double bond of ethylene, in which each carbon atom is bonded to three atoms. All six nuclei lie in a plane, and all the bond angles are close to 120°.

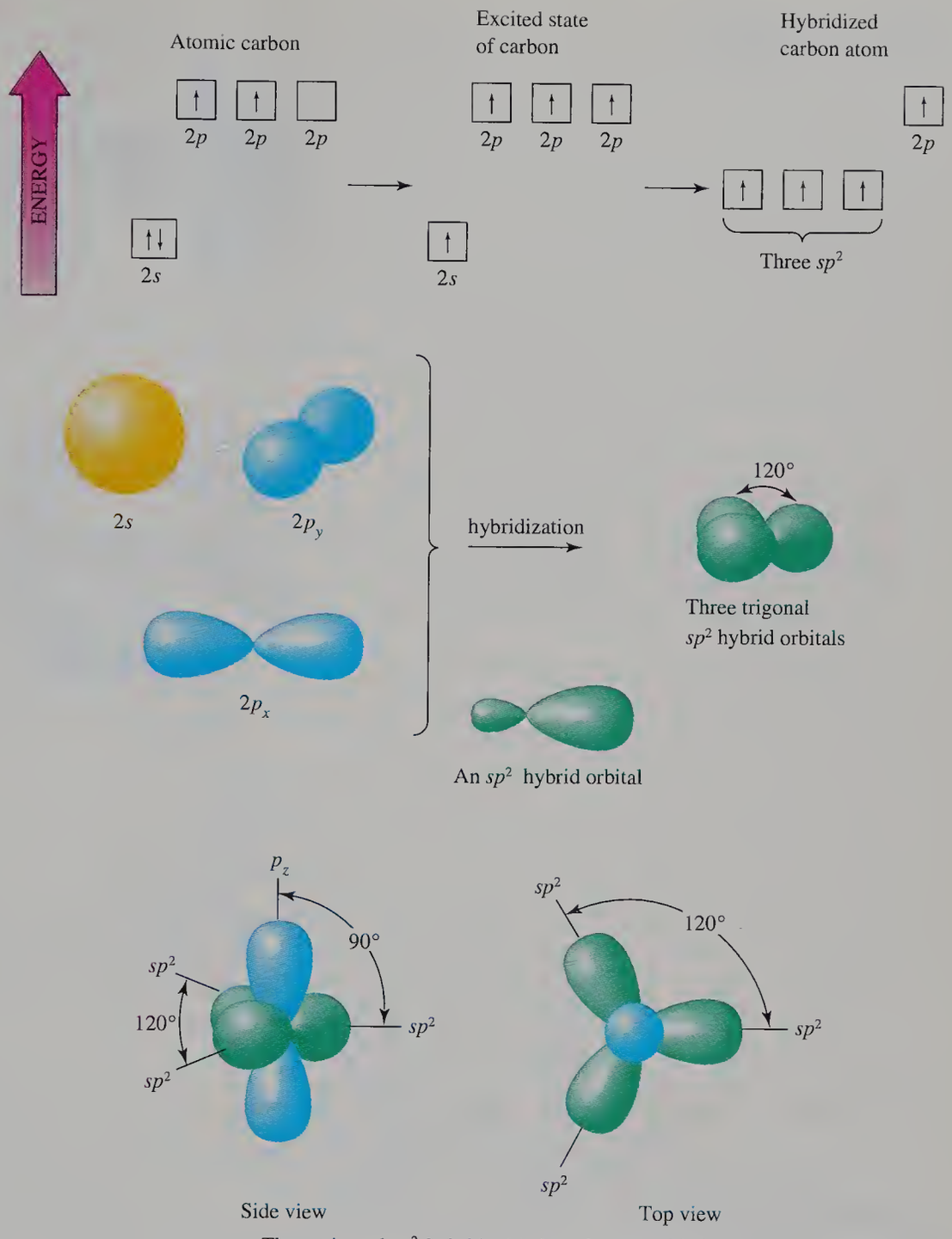


Since each carbon atom in ethylene is bonded to three other atoms, we need three σ bonds. We hybridize carbon by "mixing" a 2s orbital and two 2p orbitals to obtain three ***sp*² hybrid orbitals** (pronounced "s p two"). The third 2p orbital remains unchanged. The three sp^2 hybrid orbitals have the same shapes and energies. The orbitals differ only in their position in space. They lie in a plane and are directed to the corners of an equilateral triangle (therefore separated by 120°) to achieve maximum separation of the electrons. The four valence electrons are distributed as indicated in Figure 1.14.

Two of the sp^2 orbitals, containing one electron each, form σ bonds with hydrogen. The third sp^2 orbital, which also contains one electron, forms a σ bond with the other carbon atom in ethylene (Figure 1.15). A second carbon–carbon bond in ethylene is a π bond resulting from lateral overlap of the 2p orbitals of each carbon atom. Each p orbital stands perpendicular to the plane containing the sp^2 orbitals. The 2p orbital of each atom provides one electron to the electron pair for the second bond.

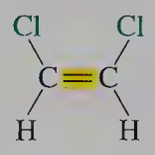
In contrast to the rotation that occurs around the C—C bond of ethane, no rotation occurs around the C=C bond of ethylene. Rotation around the C=C internuclear axis would not disrupt the sp^2–sp^2 σ bond. However, this motion would separate the two 2p orbitals and break the π bond. A large amount of energy—approximately 250 kJ mole^{-1} (60 kcal mole^{-1})—is required to break the π bond.

FIGURE 1.14
sp^2-Hybridized Carbon Atom

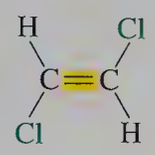


Three trigonal sp^2 hybrid orbitals and one p orbital

The three-dimensional relationship between the two methylene (CH_2) units of ethylene is rigidly fixed by the π bond. As a consequence, two different compounds, called isomers, can exist in certain substituted ethylene compounds. For example, consider the isomeric structures with one chlorine atom bonded to each sp^2-hybridized carbon atom of ethylene.

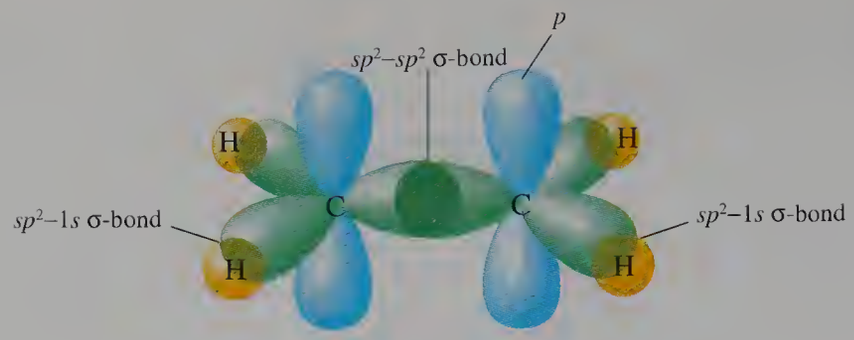


cis-1,2-dichloroethene

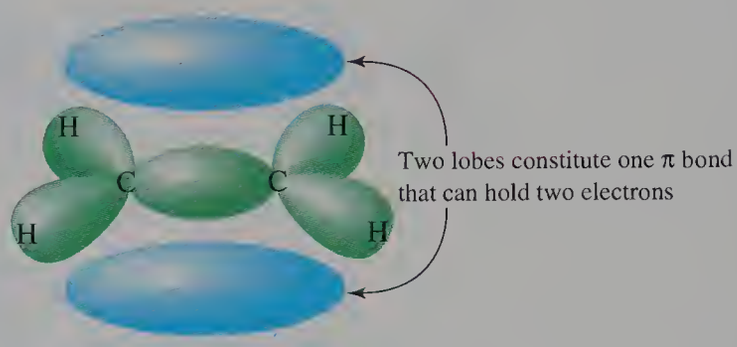


trans-1,2-dichloroethene

FIGURE 1.15 Bonding and Structure of Ethylene



Formation of C — C and C — H σ bonds using sp^2 hybrid orbitals



Formation of π bond by overlap of 2*p* orbitals

The two chlorine atoms are on the same "side" of the double bond in the cis isomer and on the opposite "sides" of the double bond in the trans isomer. These isomers have different physical properties. We will discuss isomerism in more detail in Chapter 2.

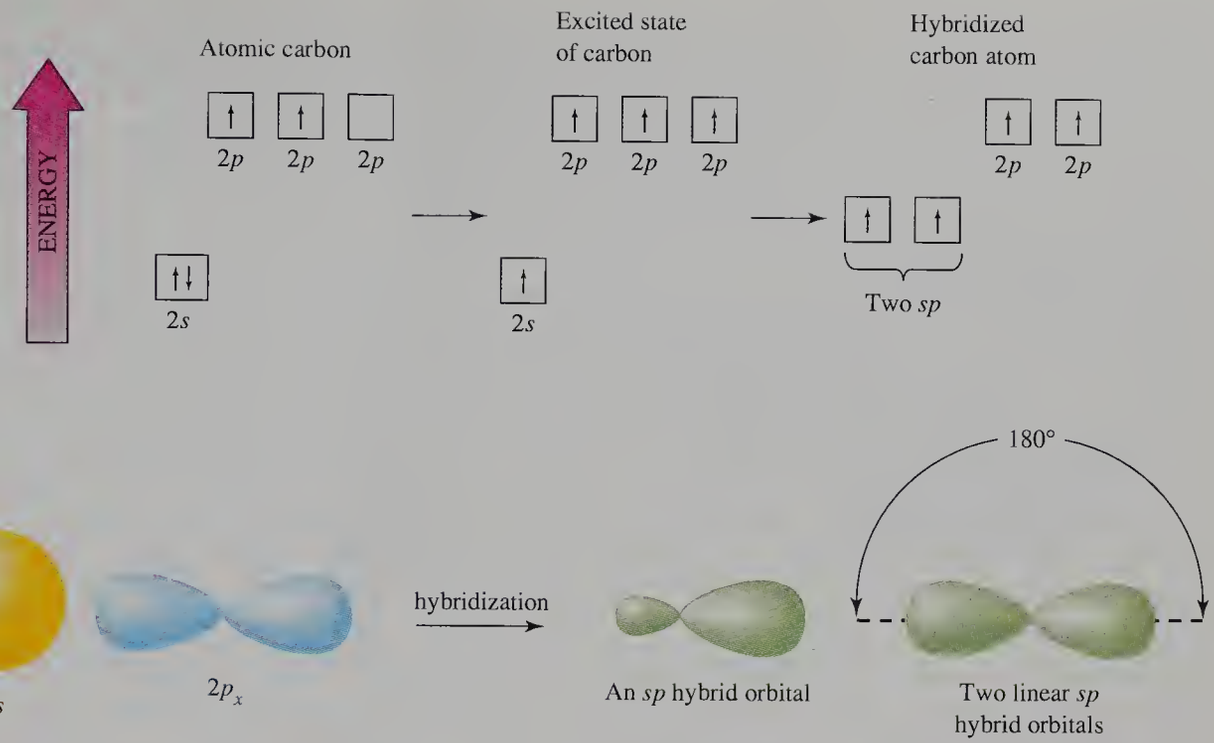
1.18 *sp* Hybridization of Carbon in Acetylene

We next consider the bonding in acetylene, a molecule in which each carbon atom is bonded to two atoms by σ bonds. Let's suppose that acetylene is composed of two methine (CH) units. Since each carbon atom of acetylene is connected to two other atoms—a carbon atom and a hydrogen atom—each methine unit requires two σ bonds. We obtain these two bonds as follows.

1. Promote an electron from a filled 2*s* orbital to a vacant 2*p* orbital.
2. Mix one 2*s* orbital with one 2*p* orbital to form two identical ***sp* hybrid orbitals** of equal energy. Two half-filled 2*p* orbitals remain (Figure 1.16).

The *sp* hybrid orbitals differ only in their position in space. They lie at a 180° angle, which provides for maximum separation of the electrons. The *sp* hybrid orbitals can form σ bonds. One *sp* hybrid orbital on each carbon atom forms a bond with hydrogen; the other *sp* hybrid orbital forms a σ bond with the second carbon atom. Hence, all four atoms of acetylene lie on a straight line (Figure 1.17).

FIGURE 1.16
***sp*-Hybridized Carbon Atom**



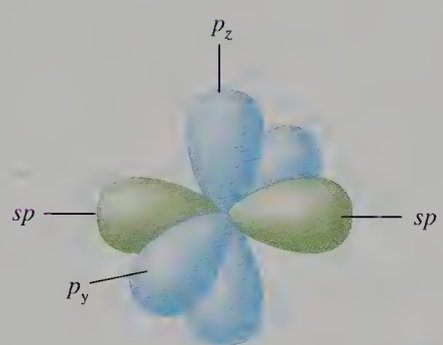
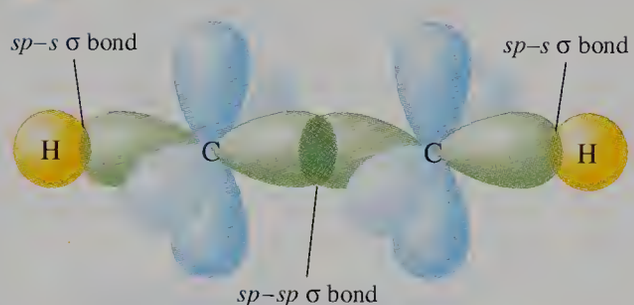
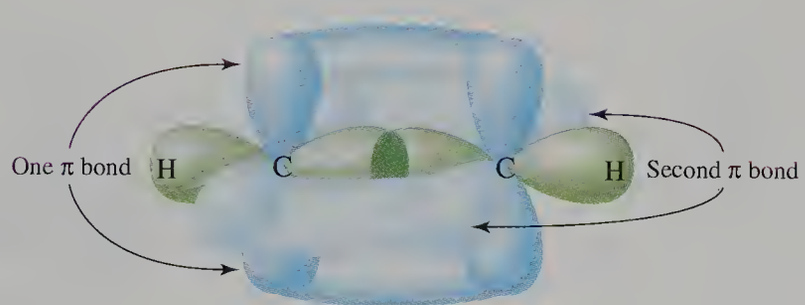


FIGURE 1.17 Bonding and Structure of Acetylene



Formation of C—C and C—H σ bonds using *sp* hybrid orbitals



Formation of two π bonds by overlap of 2*p* orbitals

After each carbon atom has formed two σ bonds, each still has two half-filled 2*p* orbitals. The half-filled 2*p* orbitals overlap side by side to give two π bonds. One set of 2*p* orbitals overlaps in "front" and "back" of the molecule to form one π bond. The second set of 2*p* orbitals overlaps "above" and "below" the molecule to form the second π bond. Thus, the carbon atoms in acetylene are linked by one σ bond and two π bonds to give a triple bond.

1.19 Effect of Hybridization on Bond Length

An sp^2 hybrid orbital of carbon has approximately the same shape as an sp^3 hybrid orbital. However, an sp^2 hybrid orbital has 33% *s* character compared to 25% *s* character for an sp^3 hybrid orbital. As the percent *s* character of hybrid orbitals increases, the electrons in the hybrid orbitals are closer to the nucleus. Therefore, the electrons in an sp^2 hybrid orbital are closer to the nucleus than the electrons in an sp^3 hybrid orbital. Increasing the percent *s* character of a hybrid orbital effectively increases the electronegativity of the carbon atom.

Orbital hybridization strongly affects physical properties such as bond lengths and bond energies. The length of a bond between carbon and another atom is shorter for a carbon atom with sp^2 hybrid orbitals than for a carbon atom with sp^3 hybrid orbitals. For example, we find that the C—H bond length in ethylene is 107 pm, whereas in ethane the C—H bond length is 109 pm. The bonds of sp^2-hybridized atoms also have larger bond energies than bonds of sp^3-hybridized atoms. For example, the C—H bond energy of ethylene is 452 kJ mole^{-1} (108 kcal mole^{-1}) compared to 422 kJ mole^{-1} (101 kcal mole^{-1}) for the C—H bond energy of ethane.

The trend toward shorter bond lengths and stronger bonds prevails when we compare *sp* hybrid orbitals with sp^2 and sp^3 hybrid orbitals. The C—H bond length of acetylene is about 105 pm, and the C—H bond energy is 523 kJ mole^{-1} (125 kcal mole^{-1}). Carbon–carbon bond lengths also decrease in the order $sp^3 > sp^2 > sp$. The carbon–carbon bond lengths of ethane, ethylene, and acetylene are 154, 133, and 120 pm, respectively. These bond lengths decrease partly because the electrons in the hybrid orbitals used to form the σ bonds are progressively closer to the nucleus as the percent *s* character increases. However, the decrease in the carbon–carbon bond length also results from the increased number of bonds joining the carbon atoms. Two shared pairs of electrons (one σ and one π) draw the carbon nuclei closer together than a single bond. Three shared pairs (one σ and two π) pull the carbon atoms still closer.

Problem 1.20

What type of overlap is present in the carbon–carbon single bond of propene? What is the C—C=C bond angle?

$CH_3—CH=CH_2$
propene

Problem 1.21

The carbon–carbon single bond length of propyne is 146 pm. Why is this value different from the carbon–carbon single bond length of ethane (154 pm)?

$CH_3—C\equiv C—H$
propyne

1.20 Hybridization of Nitrogen

A nitrogen atom forms hybrid orbitals in much the same way as carbon. The only difference in the hybridization scheme is that nitrogen has one more electron than carbon to distribute in its hybridized orbitals (Figure 1.18). The four orbitals around nitrogen form a tetrahedron. One sp^3 orbital of nitrogen contains a pair of electrons. The other three orbitals each contain a single electron. Each electron can form a σ bond to another atom such as hydrogen in ammonia or carbon in trimethylamine. In trimethylamine, the three methyl (CH_3) groups are bonded to the central nitrogen atom to form a trigonal pyramidal molecule with C—N—C bond angles of 108°. The value differs slightly from the tetrahedral angle, 109.5°, because lone pair electrons occupy more volume than bonding electrons. The nonbonded electrons repel the bonding electrons, compressing the C—N—C bond angle.

In contrast to carbon, nitrogen could form three single bonds to hydrogen or other atoms to achieve a Lewis octet without hybridizing the atomic orbitals. However, the sp^3 hybrid orbital has 25% *s* character, and the overlap of the hybrid orbital with the 1*s* orbital of the hydrogen atom is more efficient than the overlap of a 2*p* orbital of nitrogen with a 1*s* orbital of hydrogen. Again, the percent *s* character of the sp^3 hybrid orbital results in a stronger bond and a more stable molecule.

The five valence electrons of nitrogen can also be distributed in three sp^2 hybrid orbitals (Figure 1.19). The three orbitals around nitrogen lie in the same plane (they are coplanar). One sp^2 orbital contains a pair of electrons. The other two orbitals have a single electron. Each electron forms a σ bond to another atom, such as hydrogen or carbon. The single electron in the remaining 2*p* orbital forms a π bond with the 2*p* orbital of another atom, such as carbon.

The five valence electrons of nitrogen can also be distributed in two *sp* hybrid orbitals (Figure 1.20). The two *sp* orbitals around nitrogen are collinear. One of the *sp* orbitals contains a pair of electrons. The other *sp* orbital contains a single electron, which forms a σ bond to an atom such as carbon. The single electrons in each of the two 2*p* orbitals form π bonds with the electrons in 2*p* orbitals of another atom such as carbon.

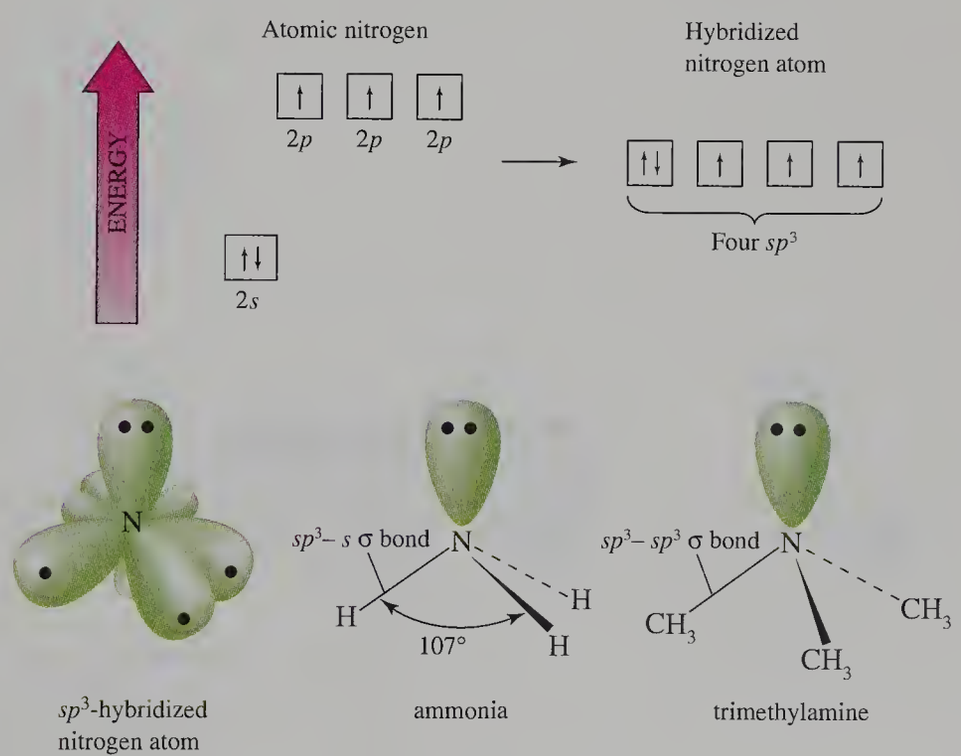


FIGURE 1.18
sp^3-Hybridized Nitrogen Atom

FIGURE 1.19
sp^2-Hybridized Nitrogen Atom

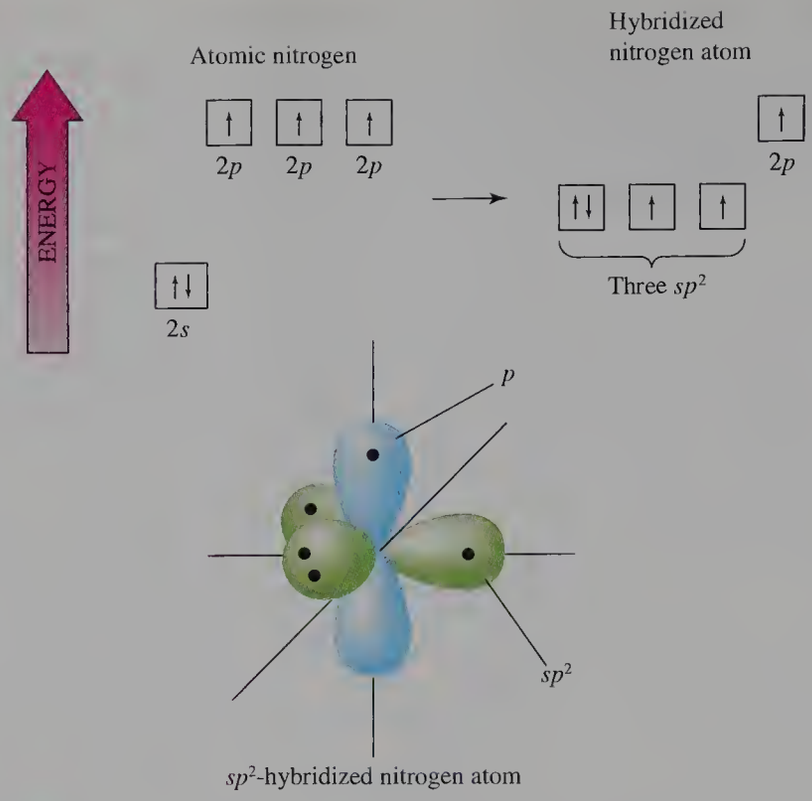
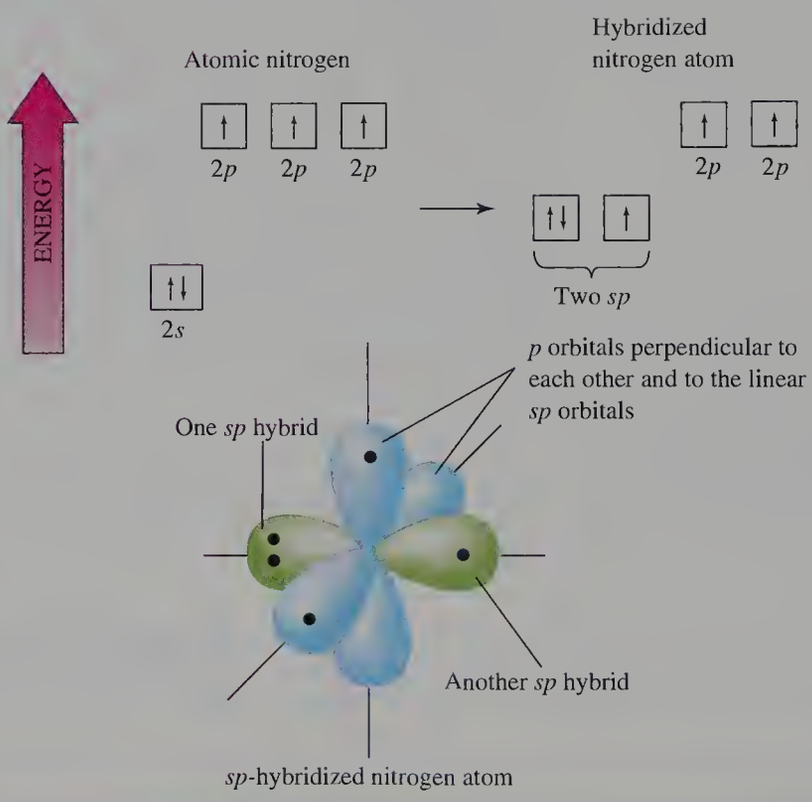


FIGURE 1.20
sp-Hybridized Nitrogen Atom



Problem 1.22

Compare the structures of ethylene and a simple compound with a C=N bond. What similarities and differences do you see between these two molecules? Where are the lone pair electrons of nitrogen located?

Problem 1.23

Compare the structures of propyne and acetonitrile, a compound with a C≡N bond. What similarities and differences do you see between these two molecules? Where are the lone pair electrons of nitrogen located?

$CH_3—C\equiv C—H$ propyne

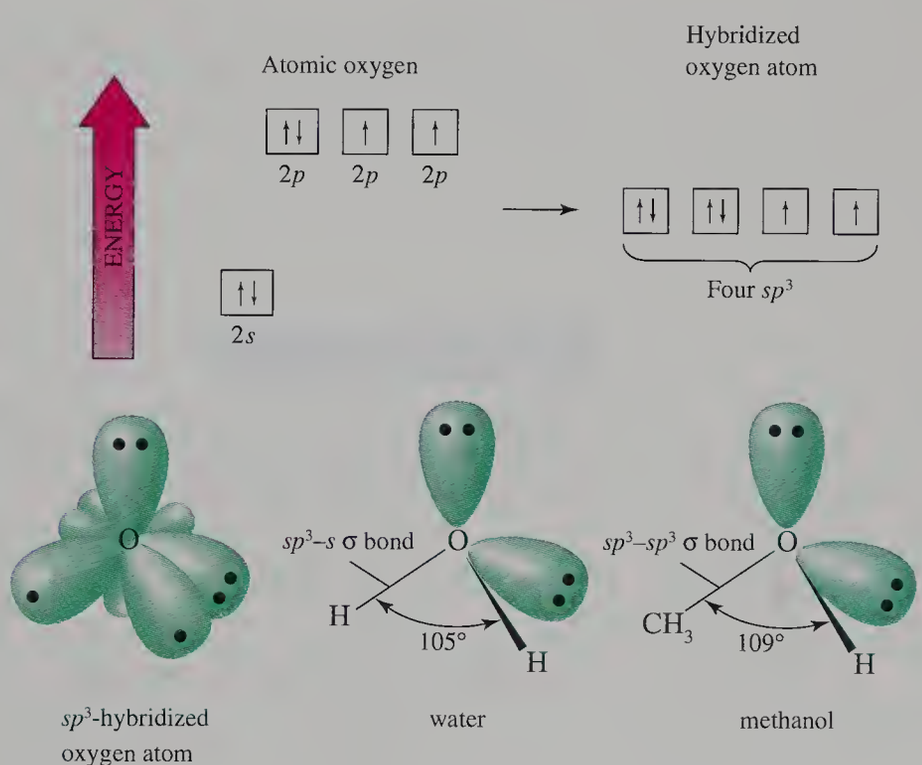
$CH_3—C\equiv N:$ acetonitrile

1.21 Hybridization of Oxygen

An oxygen atom forms hybrid orbitals in much the same way as carbon. The only difference in the hybridization scheme is that oxygen has two more electrons than carbon to distribute in its hybridized orbitals. Oxygen has six valence electrons to distribute in four sp^3 hybrid orbitals (Figure 1.21). The four orbitals around oxygen form a tetrahedron. Two of the sp^3 hybrid orbitals contain pairs of electrons. The other two hybrid orbitals contain a single electron, which can form a σ bond to an atom such as hydrogen or carbon. For example, the oxygen atom in water bonds to two hydrogen atoms through sp^3-hybridized orbitals to form an angular molecule with an H—O—H bond angle of 104.5°. This angle is somewhat smaller than the 109.5° tetrahedral angle because, as in the case of nitrogen, lone pair electrons occupy more volume than bonding electrons. The nonbonded electrons repel the bonding electrons, compressing the H—O—H bond angle.

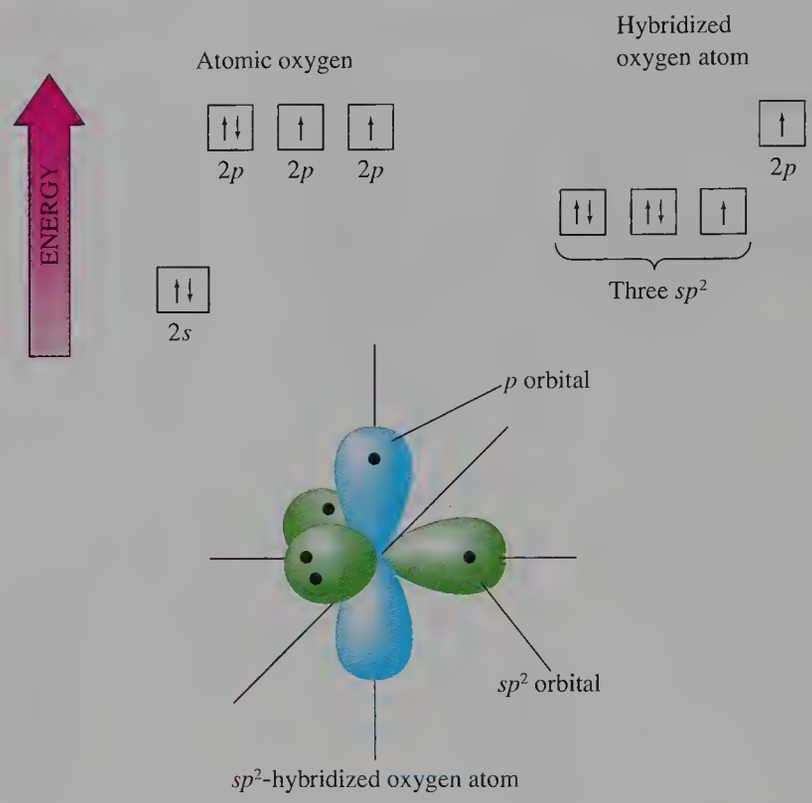
Oxygen could form two bonds to hydrogen to achieve a Lewis octet without hybridized orbitals. However, the overlap of a 2*p* orbital of oxygen with a 1*s* orbital of hydrogen would not form as strong a bond as overlap of an sp^3 hybrid orbital with a 1*s* orbital. As we saw for ammonia, the percent *s* character of the sp^3 hybrid results in a stronger bond and a more stable molecule.

FIGURE 1.21
sp^3-Hybridized Oxygen Atom

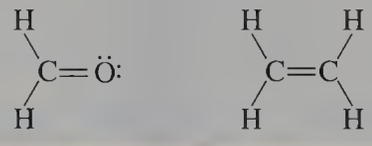


The six valence electrons of oxygen can also be distributed in three sp^2 hybrid orbitals (Figure 1.22). The three sp^2 orbitals are coplanar and are separated by 120° in a trigonal planar arrangement. Two of the sp^2 orbitals contain a pair of electrons. The other sp^2 orbital contains a single electron, which can form a σ bond to an atom such as carbon. The single electron in the remaining $2p$ orbital forms a π bond with the $2p$ orbital of another atom such as carbon.

FIGURE 1.22
sp^2-Hybridized Oxygen

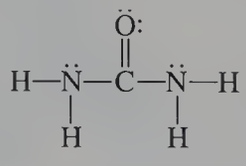


Formaldehyde (H_2CO) has an sp^2-hybridized oxygen atom. The sp^2 lone pair electrons lie in the same plane as the carbon and hydrogen atoms. Formaldehyde structurally resembles ethylene.



Problem 1.24

Urea, which contains carbon in its highest positive oxidation state, is a metabolic product excreted in urine. Based on the following Lewis structure, predict the hybridization of both the carbon and oxygen atoms.



EXERCISES

Atomic Properties

1.1 How many valence electrons are in each of the following elements?

(a) N **(b)** F **(c)** C **(d)** O **(e)** Cl **(f)** Br **(g)** S **(h)** P

1.2 Which atom in each of the following has the larger electronegativity? Which has the larger atomic radius?

(a) Cl or Br **(b)** O or S **(c)** C or N **(d)** N or O

(e) I or Br **(f)** C or F **(g)** C or O **(h)** O or I

Ions and Ionic Compounds

1.3 The formula of the dihydrogen phosphate ion, an ion eliminated in urine to control pH of cellular fluids, is $H_2PO_4^-$. What is the formula of calcium dihydrogen phosphate?

1.4 Ionic arsenic compounds contain ions such as arsenite (AsO_3^{3-}) that react with thiol groups of proteins. What is the formula of magnesium arsenite?

1.5 Write a Lewis structure for each of the following ions.

(a) OH^- **(b)** CN^- **(c)** H_3O^+ **(d)** NH_4^+ **(e)** NO_3^-

1.6 Write a Lewis structure for each of the following ions.

(a) NO_2^- **(b)** SO_3^{2-} **(c)** SO_4^{2-} **(d)** NH_2^- **(e)** CO_3^{2-}

Lewis Structures of Covalent Compounds

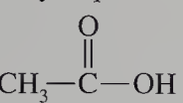
1.7 Write a Lewis structure for each of the following compounds.

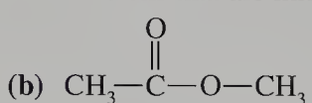
(a) NH_2OH **(b)** CH_3CH_3 **(c)** CH_3OH **(d)** CH_3NH_2 **(e)** CH_3Cl **(f)** CH_3SH

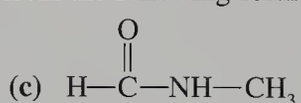
1.8 Write a Lewis structure for each of the following compounds.

(a) HCN **(b)** HNNH **(c)** CH_2NH **(d)** CH_3NO **(e)** CH_2NOH **(f)** CH_2NNH_2

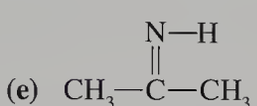
1.9 Place any required unshared pairs of electrons that are missing from the following formulas.

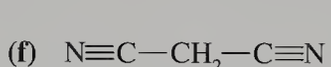
(a) 

(b) 

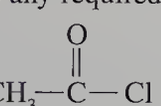
(c) 

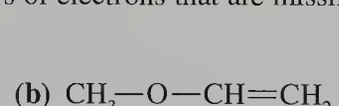
(d) 

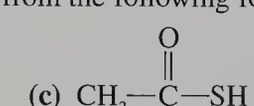
(e) 

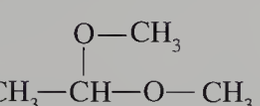
(f) 

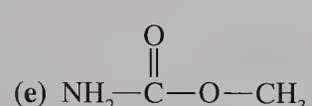
1.10 Place any required unshared pairs of electrons that are missing from the following formulas.

(a) 

(b) 

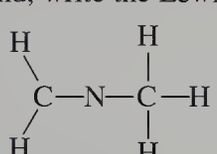
(c) 

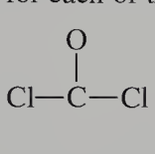
(d) 

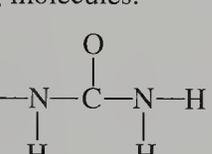
(e) 

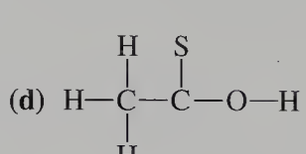
(f) 

1.11 Using the number of valence electrons in the constituent atoms and the given arrangement of atoms in the compound, write the Lewis structure for each of the following molecules.

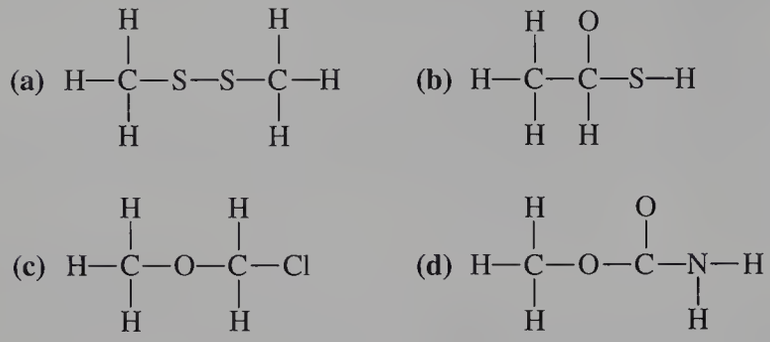
(a) 

(b) 

(c) 

(d) 

1.12 Using the number of valence electrons in the constituent atoms and the given arrangement of atoms in the compound, write the Lewis structure for each of the following molecules.

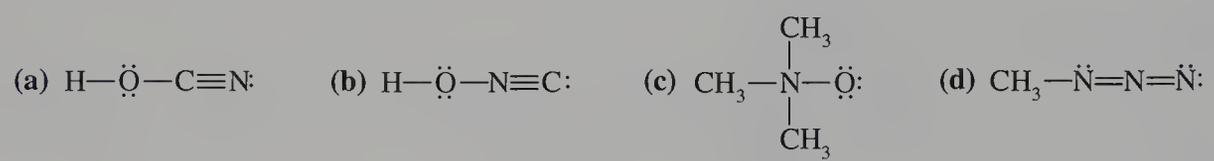


1.13 Two compounds used as dry cleaning agents have the molecular formulas C_2Cl_4 and C_2HCl_3. Write the Lewis structures for each compound.

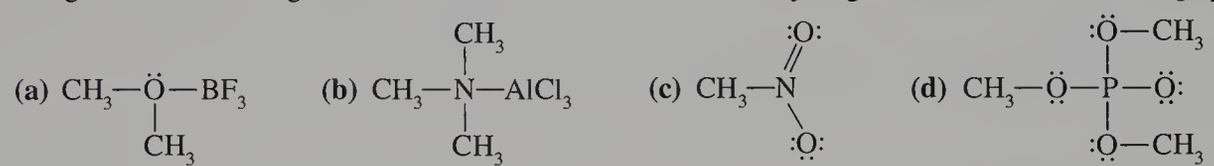
1.14 Acrylonitrile, a compound used to produce fibers for rugs, is represented by the formula CH_2CHCN. Write the Lewis structure for the compound.

Formal Charge

1.15 Assign the formal charges for the atoms other than hydrogen in each of the following species.



1.16 Assign the formal charges for the atoms other than carbon and hydrogen in each of the following species.



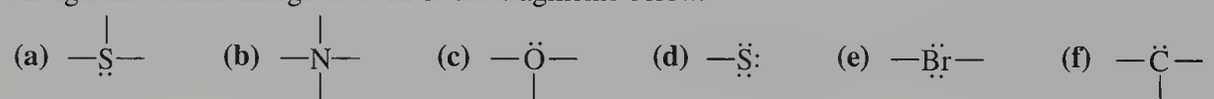
1.17 All of the following species are isoelectronic, that is, they have the same number of electrons bonding the same number of atoms. Determine which atoms have a formal charge. Calculate the net charge for each species.

(a) :C≡O: **(b)** :N≡O: **(c)** :C≡N: **(d)** :C≡C:

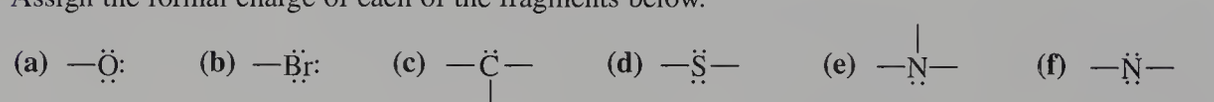
1.18 The following species are isoelectronic. Determine which atoms have a formal charge. Calculate the net charge for each species.

(a) :N̈=N=N̈: **(b)** :Ö=N=Ö:

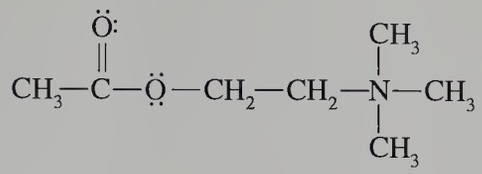
1.19 Assign the formal charge of each of the fragments below.



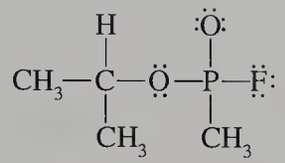
1.20 Assign the formal charge of each of the fragments below.



1.21 Acetylcholine, a compound involved in the transfer of nerve impulses, has the following structure. What is the formal charge on the nitrogen atom? What is the net charge of the species?



1.22 Sarin, a nerve gas, has the following structure. What is the formal charge of the phosphorus atom?



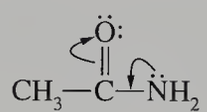
Resonance

1.23 The small amounts of cyanide ion contained in the seeds of some fruits are eliminated from the body as SCN^-. Draw two possible resonance forms for the ion. Which atom has the formal negative charge in each form?

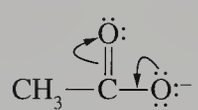
1.24 Are the following pairs contributing resonance forms of a single species? Explain.

(a) $:\ddot{N}—N\equiv N:$ and $:\ddot{N}=N=\ddot{N}:$ **(b)** $H—C\equiv N—\ddot{O}:$ and $H—\ddot{C}=N=\ddot{O}:$

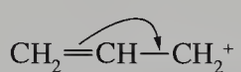
1.25 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for the following amide. Calculate any formal charges that result.



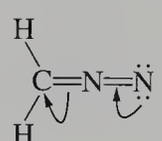
1.26 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for the acetate ion. Calculate any formal charges that result.



1.27 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrow for the following electron-deficient ion. To what extent do each of the two resonance forms contribute to the structure of the ion?



1.28 Write the resonance structure that results when electrons are moved in the direction indicated by the curved arrows for the following compound. Do each of the two resonance forms contribute equally to the structure of the ion?



Molecular Shapes

1.29 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?

(a) C—C—N in $CH_3—C{\equiv}N$ **(b)** C—O—C in $CH_3—O—CH_3$ **(c)** C—N—C in $CH_3—NH—CH_3$

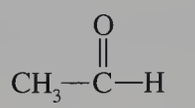
(d) C—C—C in $CH_2{=}C{=}CH_2$ **(e)** C—C—C in $CH_3—C{\equiv}C—H$

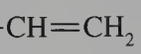
1.30 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?

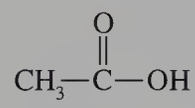
(a) C—O—H in $CH_3—OH_2^+$ **(b)** C—N—H in $CH_3—NH_3^+$

(c) C—N—C in $(CH_3)_2NH_2^+$ **(d)** C—O—C in $(CH_3)_2OH^+$

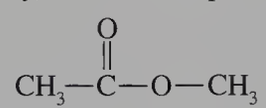
1.31 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?

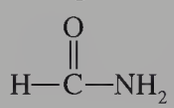
(a) C—C—O in 

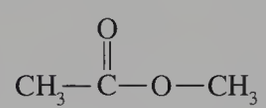
(b) C—C—C in 

(c) O—C—O in 

1.32 Based on VSEPR theory, what is the expected value of the indicated bond angle in each of the following compounds?

(a) C—O—C in 

(b) O—C—N in 

(c) O—C—O in 

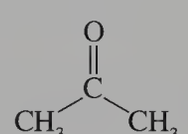
Dipole Moments

1.33 Fluorine is more electronegative than chlorine, but the bond moment for a C—F bond (1.4 D) is less than the bond moment for a C—Cl bond (1.5 D). Explain why this is so.

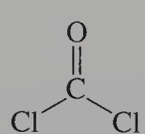
1.34 Arrange the following bond moments in order of decreasing polarity: H—N, H—O, H—S. Explain the trend that you predict.

1.35 The dipole moments of both CO_2 and CS_2 are zero. However, SCO has a dipole moment. Explain why. Draw the structure of SCO and then an arrow indicating the direction of the dipole moment.

1.36 Which compound has the larger dipole moment, acetone or phosgene? Explain why.

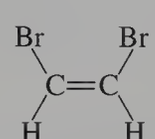


acetone

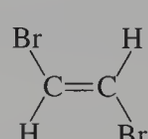


phosgene

1.37 The dipole moment of *cis*-1,2-dibromoethene is 1.35 D. The dipole moment of *trans*-1,2-dibromoethene is 0 D. Explain why this is so.

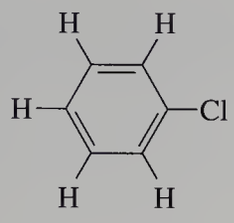


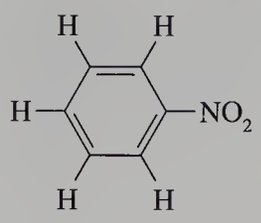
cis-1,2-dibromoethene

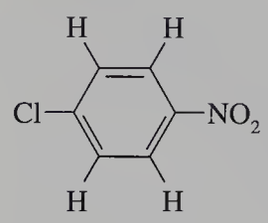


trans-1,2-dibromoethene

1.38 The dipole moment of chlorobenzene (C_6H_5Cl) is 1.56 D, and that of nitrobenzene ($C_6H_5NO_2$) is 3.97 D. The dipole moment of para-chloronitrobenzene is 2.57 D. What does this value indicate about the direction of the moments of the two groups with respect to the benzene ring?

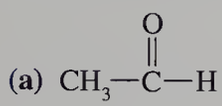
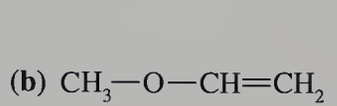
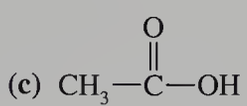
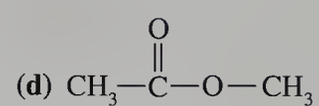

chlorobenzene


nitrobenzene

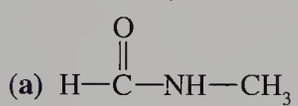
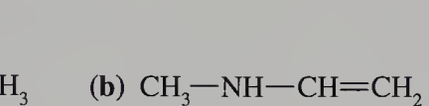
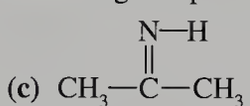
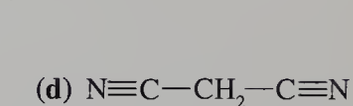

p-chloronitrobenzene

Hybridization

1.39 What is the hybridization of each carbon atom in each of the following compounds?

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

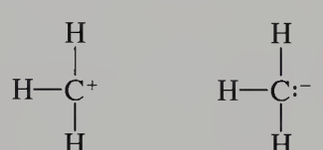
1.40 What is the hybridization of each carbon atom in each of the following compounds?

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

1.41 What is the hybridization of the oxygen atom in each compound in Exercise 1.39?

1.42 What is the hybridization of the nitrogen atom in each compound in Exercise 1.40?

1.43 Carbocations and carbanions are classes of unstable organic species with a positive and a negative charge, respectively, on the carbon atom. What is the hybridization of the carbon atom in each ion? What are the H—C—H bond angles?



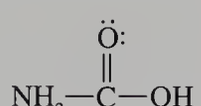
1.44 Assuming that all of the valence electrons are paired and located in hybrid orbitals, what is the H—C—H bond angle in the reactive species CH_2?

1.45 Write the Lewis structure of CO_2. What is the hybridization of the carbon atom? What is the hybridization of the oxygen atoms?

1.46 Write the Lewis structure of NO_2^+, the nitronium ion. What is the hybridization of the nitrogen atom? What is the hybridization of the oxygen atoms?

1.47 Phosgene ($COCl_2$) is a poisonous gas. Write its Lewis structure and determine the hybridization of the carbon atom.

1.48 Carbamic acid is an unstable substance that decomposes to form carbon dioxide and ammonia. Based on the following Lewis structure, what are the hybridizations of the carbon atom and the two oxygen atoms?



Bond Lengths

1.49 The oxygen–hydrogen bond length in both hydrogen peroxide (HO—OH) and hydroxylamine (NH_2—OH) is 96 pm. Explain why.

1.50 The C=N bond length of methyleneimine (CH_2=NH) is 127 pm. Compare this value to the C=C bond length of ethylene (133 pm) and suggest a reason for the difference.

1.51 The nitrogen–oxygen bond lengths of hydroxylamine (NH_2—OH) and the nitronium ion (NO_2^+) are 145 and 115 pm, respectively. Write their Lewis structures and explain why the bond lengths differ.

1.52 The C—F bond length of CF_4 is 138 pm. The estimated bond length of CF_3^+ is 127 pm. Suggest a reason for the difference between these two values.

1.53 The carbon–carbon single bond lengths of propane and propene are 154 and 151 pm, respectively. Why do these values differ?

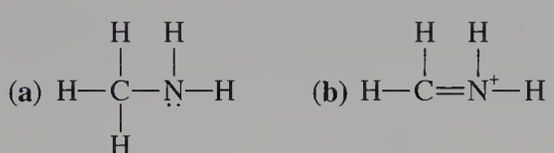
$CH_3—CH_2—CH_3$ propane $\qquad$ $CH_3—CH=CH_2$ propene

1.54 The carbon–oxygen bond length of dimethyl ether is 142 pm. Predict the lengths of each of the two carbon–oxygen bonds in methyl vinyl ether.

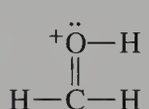
$CH_3—O—CH_3$ dimethyl ether $\qquad$ $CH_3—O—CH=CH_2$ methyl vinyl ether

Bond Angles

1.55 What is the C—N—H bond angle in each of the following species?



1.56 What is the C—O—H bond angle of protonated formaldehyde?



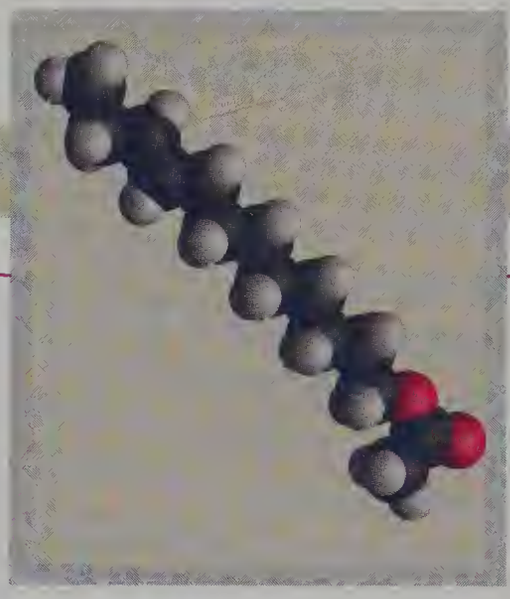
1.57 Diimide (HNNH) is a reactive reducing agent. Draw its Lewis structure. Compare its Lewis structure with that of ethylene. Based on molecular orbital theory, compare the hybridization of the two compounds. What is the H—N—N bond angle in diimide?

1.58 What is the H—C—H bond angle in allene (CH_2=C=CH_2)? What is the C—C—C bond angle? What is the hybridization of each atom?

1.59 What is the Cl—C—Cl bond angle of the CCl_3^- ion, an intermediate formed by treating CCl_3H with base?

1.60 What is the O—N—O bond angle of the nitronium ion (NO_2^+), a reactive intermediate involved in reactions with benzene compounds?

2



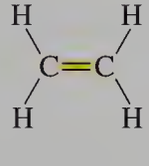
Structure and Properties of Organic Molecules

2.1 Functional Groups

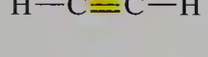
Each of the approximately 9 million known organic compounds has unique physical and chemical properties. We might imagine that determining the relationships between the structures on the one hand, and physical and chemical properties on the other, would be a very complex task. However, a major organizational principle of organic chemistry relies on dividing organic molecules into two parts: a backbone or framework of carbon atoms and specific atomic groups, called **functional groups**, attached to the backbone. If we classify organic compounds by their functional groups, they fall into a relatively small number of classes of substances.

Functional groups have characteristic properties that strongly influence the physical properties of the molecule as a whole. A molecule's physical properties reflect the intermolecular forces characteristic of the functional group. Functional groups are also the sites of chemical reactions in organic compounds. By examining the functional group (or groups) in a molecule, we can predict its physical and chemical properties.

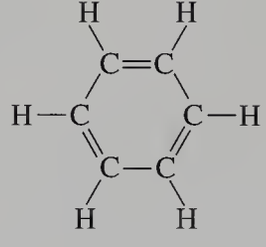
Functional groups can contain many elements, but the most common are oxygen and nitrogen. Sulfur and the halogens are less common. Some functional groups are part of the molecular backbone. These include the multiple bonds between backbone carbon atoms of compounds such as ethene (ethylene), ethyne (acetylene), and benzene.



ethylene

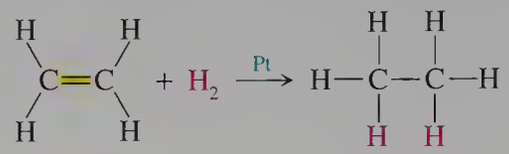


acetylene



benzene

Compounds with one carbon–carbon double or triple bond react with hydrogen gas. For example, ethylene reacts with hydrogen gas in the presence of a platinum catalyst to give ethane, which has only a single bond between the carbon atoms. Any compound containing a carbon–carbon double bond undergoes a similar reaction.

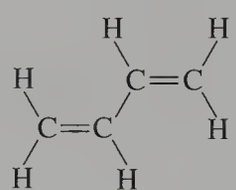


ethylene ethane

Two or more double or triple bonds are present in more complex structures. Many of these compounds undergo reactions similar to those of ethylene at each of the multiple bonds. However, benzene, which belongs to a class of compounds called aromatic hydrocarbons, reacts differently than ethylene does.

Problem 2.1

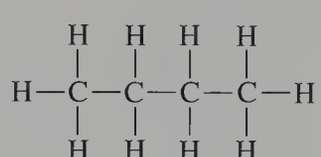
Based on the reaction of hydrogen with ethylene, draw the structure of the product of the reaction of excess hydrogen gas with 1,3-butadiene.



1,3-butadiene

Sample Solution

The molecular structure shows two double bonds. Each double bond can react with hydrogen to place an additional hydrogen atom on each carbon atom of that double bond. Each double bond is converted into a single bond. The reaction occurs with a total of two moles of hydrogen gas per mole of 1,3-butadiene. The molecular structure of the product is



Problem 2.2

Based on the reaction of hydrogen with ethylene, predict the product(s) of the reaction of one and two moles of hydrogen gas with propyne.

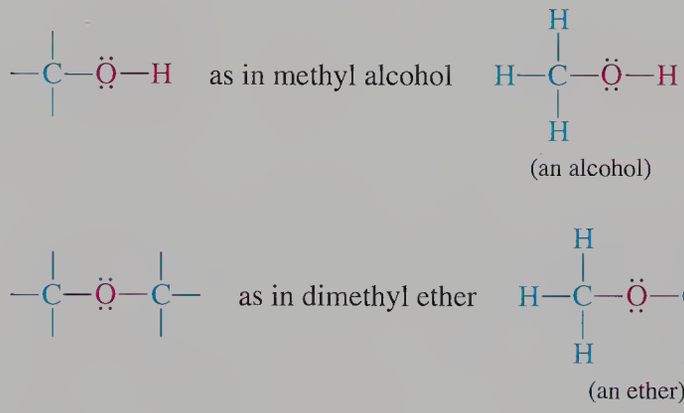
propyne

2.2 Functional Groups Containing Oxygen

After carbon and hydrogen, the next most common element in organic compounds is oxygen. Oxygen forms two bonds (it is divalent). It forms two C—O single bonds or one C=O double bond in neutral carbon compounds.

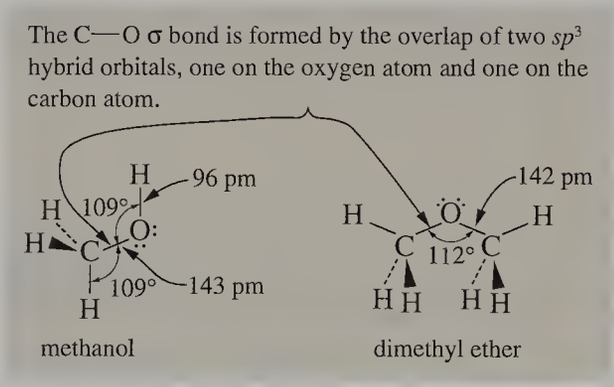
Carbon–Oxygen Single Bonds

Carbon–oxygen single bonds are present in alcohols and ethers. Alcohols contain one C—O single bond and an O—H bond. The O—H structural unit, called the **hydroxyl group,** is the functional group of **alcohols**. The functional group of **ethers** is an oxygen atom linked to two carbon atoms by single bonds. The oxygen atoms of both alcohols and ethers have two unshared electron pairs.



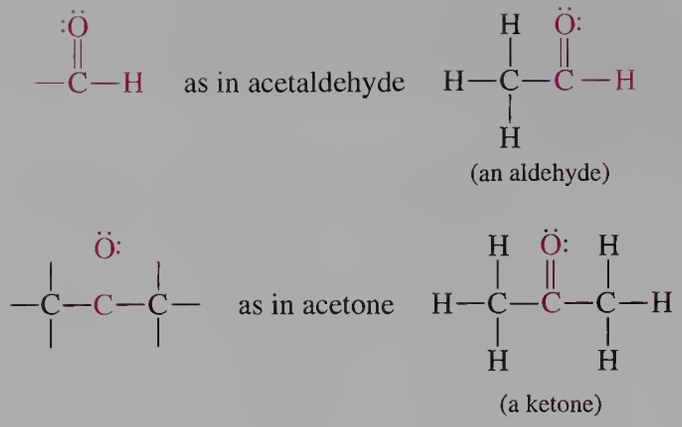
The oxygen atoms of alcohols and ethers are sp^3 hybridized. The C—O—H bond angle of alcohols and the C—O—C bond angle of ethers approach the tetrahedral value (Figure 2.1). The C—O bond is shorter than a C—C bond.

FIGURE 2.1 Structures of Alcohols and Ethers



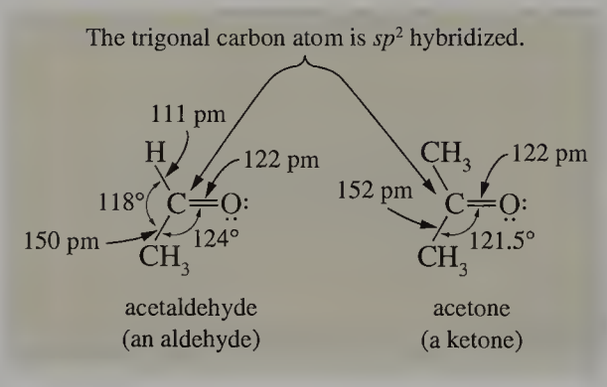
Carbon–Oxygen Double Bonds

A double bond between carbon and oxygen forms a C=O unit, called a **carbonyl group** (pronounced car-bo-neel). The carbon atom of the carbonyl group is called the **carbonyl carbon atom,** and the oxygen atom is called the **carbonyl oxygen atom**. Both **aldehydes** and **ketones** contain carbonyl groups. The carbonyl group bonds to at least one hydrogen atom in aldehydes. In ketones, the carbonyl carbon atom bonds to two other carbon atoms.



The carbonyl carbon atom is sp^2 hybridized, so it takes on a trigonal, planar arrangement (Figure 2.2). The σ bonds to carbon result from overlap of each of its sp^2 hybrid orbitals with an orbital of another atom. For example, the carbonyl carbon atom in acetaldehyde forms a σ_{sp^3-1s} bond to a hydrogen atom. The methyl groups (CH_3) of acetaldehyde and acetone are bonded to the carbonyl carbon atom via a $\sigma_{sp^3-sp^2}$ bond.

FIGURE 2.2 Structures of Aldehydes and Ketones

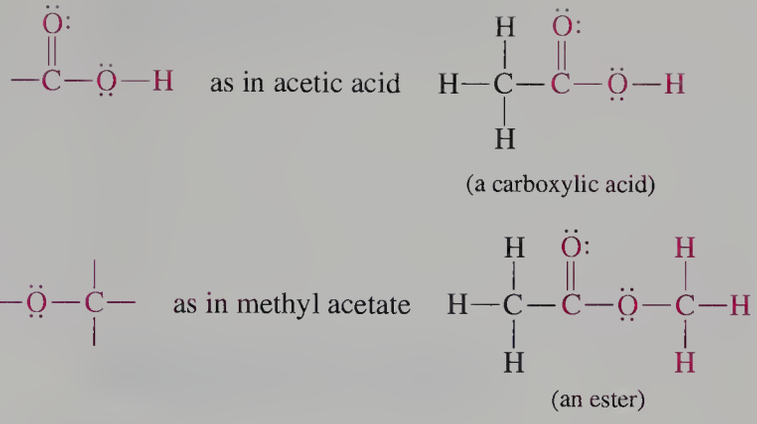


The carbonyl oxygen atom of a carbonyl group is sp^2 hybridized. One carbon–oxygen bond is an $\sigma_{sp^2-sp^2}$ bond. The second carbon–oxygen bond is a π bond formed by overlap of a 2*p* orbital of carbon and a 2*p* orbital of oxygen.

The carbonyl oxygen atom has two unshared electron pairs in sp^2 hybrid orbitals. Based on VSEPR theory, we represent them at an angle of 120° to each other and contained within the plane containing the two σ bonds of carbon.

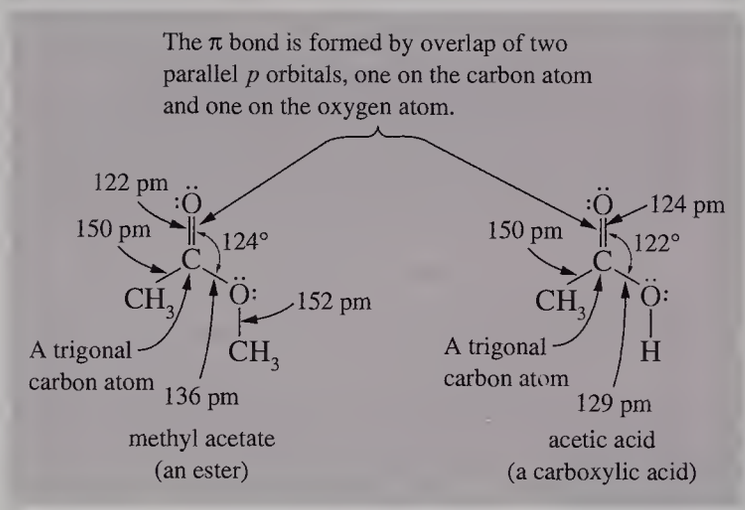
Carbon–Oxygen Single and Double Bonds

A carbonyl group is also present in carboxylic acids and esters. In a carboxylic acid, the carbonyl carbon atom bonds to a hydroxyl group (—OH). In an ester, the carbonyl carbon atom bonds to an alkoxyl group such as —OCH_3.



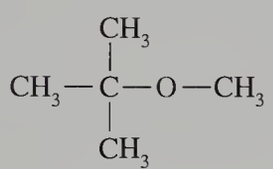
A carboxylic acid or ester has a carbon–oxygen double bond and a carbon–oxygen single bond. The oxygen atom of the C—O single bond is sp^3 hybridized. Thus the geometry of groups about the oxygen atom resembles that of alcohols and ethers (Figure 2.3).

FIGURE 2.3 Structures of Carboxylic Acids and Esters



Problem 2.3

MTBE is used as an antiknock additive in gasoline. Identify the oxygen containing functional group.



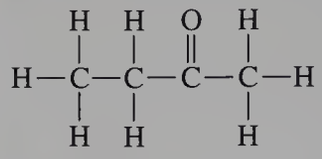
MTBE

Sample Solution

The structure has only single bonds to the oxygen atom, which is found only in alcohols or ethers. The two single bonds to oxygen are to carbon atoms. Thus, the functional group is an ether. An alcohol would have one bond from the oxygen atom to a hydrogen atom.

Problem 2.4

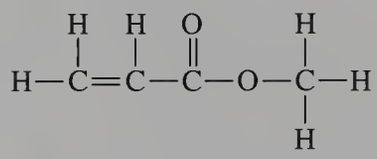
MEK is an inexpensive commercial solvent that is produced in large quantities by the chemical industry. Identify the functional group in MEK.



MEK

Problem 2.5

Methyl acrylate is used to produce poly(methyl acrylate), a transparent polymer found in windshields and shatter-proof glasses. Identify all functional groups in methyl acrylate.



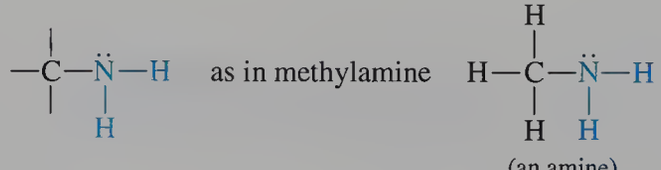
methyl acrylate

Problem 2.6

Acetic acid reacts with base to give the acetate ion ($CH_3—CO_2^-$). The two carbon–oxygen bond lengths are 126 pm. Why are the two bond lengths equal? Compare this bond length to the two nonequivalent carbon–oxygen bonds of acetic acid.

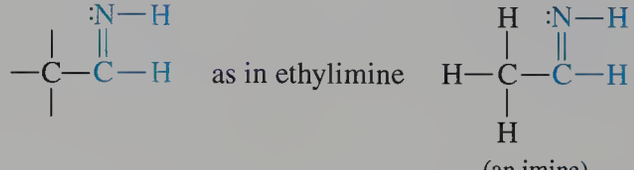
2.3 Functional Groups Containing Nitrogen

Several functional groups contain nitrogen. A nitrogen atom can form single, double, or triple bonds to a carbon atom. At least one C—N σ bond is present in amines. The other two σ bonds from nitrogen are to either hydrogen or carbon atoms. Compounds with C=N double bonds are called imines; those with C≡N triple bonds are called nitriles.



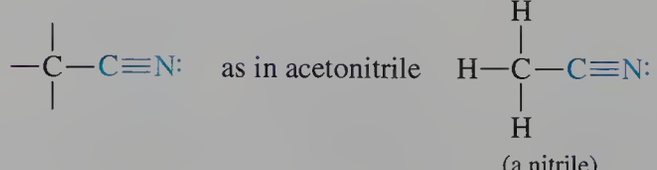
as in methylamine

(an amine)



as in ethylimine

(an imine)



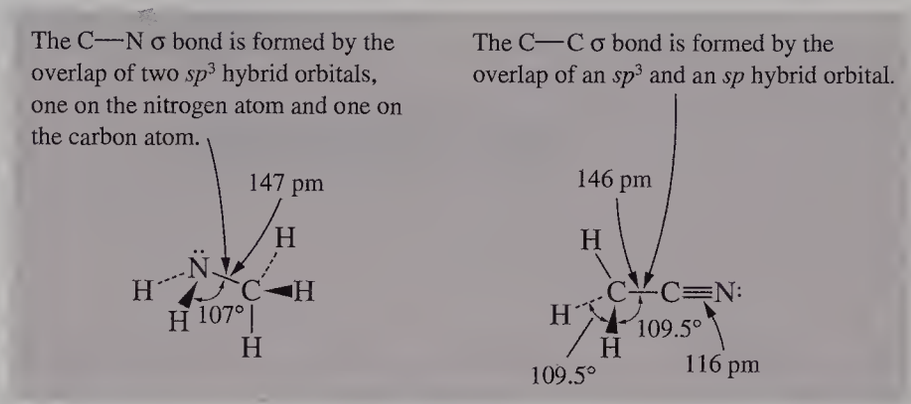
as in acetonitrile

(a nitrile)

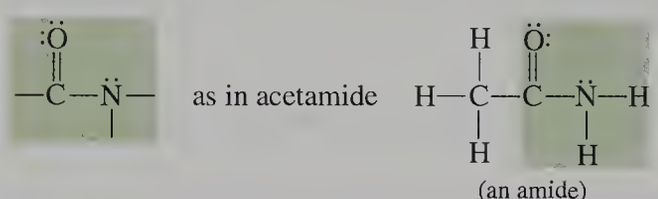
The carbon–nitrogen bond in an amine forms by overlap of an sp^3 hybrid orbital of the nitrogen atom and an sp^3 hybrid orbital of a carbon atom. The C—N bond length, 147 pm, is less than the C—C bond length of 154 pm in ethane (Figure 2.4). The H—N—C bond angle is 107°, a value close to the tetrahedral angle of 109.5°.

In imines, both the carbon atom and the nitrogen atom are sp^2 hybridized. They form a σ bond by overlap of two sp^2 hybrid orbitals and a π bond by overlap of two $2p$ orbitals. In nitriles, the carbon atom and nitrogen atom are sp hybridized. They form a triple bond that consists of one σ_{sp-sp} bond and two π bonds between two sets of $2p$ orbitals. The C≡N triple bond of nitriles therefore resembles the C≡C triple bond of acetylene. The molecular geometry of acetonitrile is shown in Figure 2.4.

FIGURE 2.4 Structures of Nitrogen Compounds

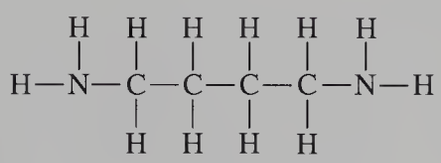


Nitrogen is also present in amides. Amides contain nitrogen linked by a single bond to a carbonyl carbon atom. The amide nitrogen atom forms two other bonds to either hydrogen or carbon atoms. Amides have structures similar to carboxylic acids and esters.



Problem 2.7

Putrescine is one of the compounds responsible for the odor of decaying animal tissue. Identify the nitrogen-containing functional groups in putrescine. What is the hybridization of the nitrogen atom?

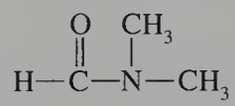


Sample Solution

Both nitrogen atoms have three single bonds. One bond is to a carbon atom and the other two bonds are to hydrogen atoms. Three single bonds to a nitrogen atom are characteristic of an amine. The nitrogen atom of amines is sp^3 hybridized. The nitrogen atom forms σ bonds to the three attached atoms.

Problem 2.8

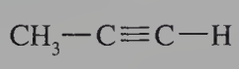
DMF is an excellent solvent for a variety of organic compounds. Identify the functional group in DMF.



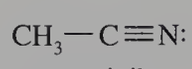
DMF

Problem 2.9

Why is the carbon–nitrogen triple bond of acetonitrile shorter than the carbon–carbon triple bond of propyne?



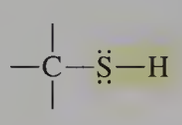
propyne



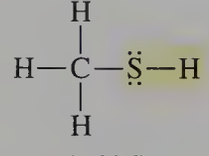
acetonitrile

2.4 Functional Groups Containing Sulfur or Halogens

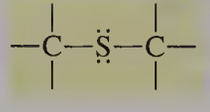
Sulfur forms single bonds to sp^3-hybridized carbon atoms in two classes of compounds: thiols (also called mercaptans) and thioethers (also called sulfides). Because sulfur, like oxygen, is a Group VI element, thiols have structures resembling alcohols, and thioethers have structures resembling ethers.



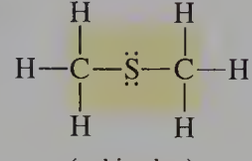
as in methanethiol



(a thiol)

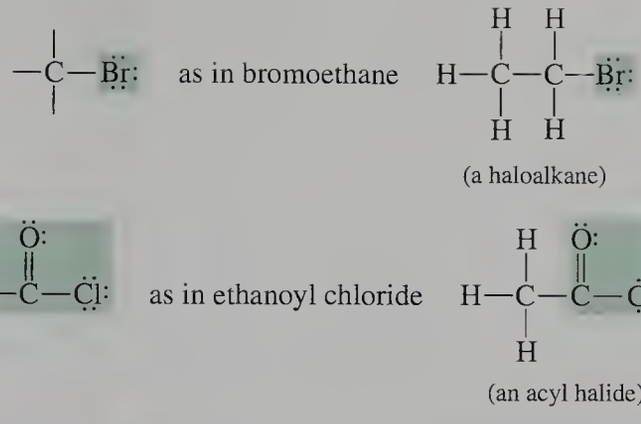


as in dimethyl sulfide



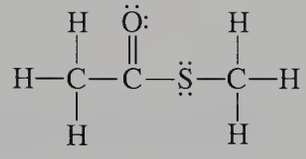
(a thioether)

Some organic compounds contain halogens. A halogen atom can form a single bond to a carbon atom. Compounds in which a halogen atom bonds to an sp^3-hybridized carbon atom are structurally related to alcohols and thiols. Compounds in which a halogen atom bonds to the sp^2-hybridized carbon atom of a carbonyl group are structurally related to carboxylic acids and esters.



Problem 2.10

Acetyl coenzyme A is involved in many biochemical reactions. The structure of the simplest compound containing the functional group responsible for the activity of acetyl coenzyme A is given below. What functional group is similar to this sulfur-containing functional group? What is the O—C—S bond angle?



2.5 Structural Formulas

The backbones of many organic compounds are sp^3-hybridized carbon atoms. In most compounds, this backbone is comparatively unreactive, but the location of a functional group on the backbone influences its reactivity. In this section we will learn to draw **structural formulas** that show the arrangement of atoms and bonds in a molecule.

Structural formulas are often drawn in abbreviated or condensed versions to save time and space. **Condensed structural formulas** show only specific bonds. Other bonds are implied, but left out. For example, because hydrogen forms only a single bond to carbon, C—H bonds are not shown in condensed structural formulas. A condensed formula for butane is shown below.

$$CH_3—CH_2—CH_2—CH_3$$

butane

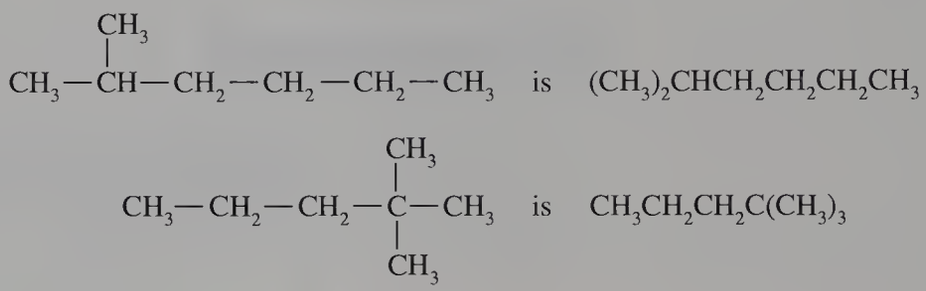
The terminal carbon atoms are understood to have single bonds to three hydrogen atoms. The carbon atoms in the interior of the molecule each have two implied carbon–hydrogen bonds. By convention, the symbol for the hydrogen atom is usually written to the right of the symbol for the carbon atom. The above structure for butane can be condensed further by leaving out the C—C bonds.

$$CH_3CH_2CH_2CH_3$$

Butane is a rather small molecule. Larger molecules may consist of repeated units. If a hydrocarbon has repeated structural subunits, they are grouped within parentheses. A subscript following the closing parenthesis tells us how many times the unit is repeated.

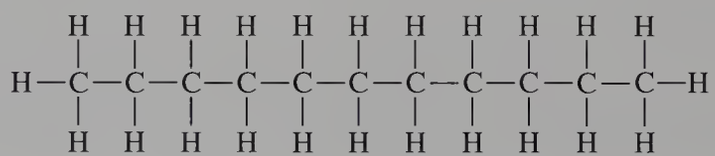
$$CH_3(CH_2)_2CH_3$$

The $—CH_2—$ unit is a **methylene** group. It occurs twice in butane. Two or more identical groups of atoms bonded to a common central atom may also be represented within parentheses with an appropriate subscript in a condensed formula. The groups within parentheses may be placed to the right or left of a carbon atom, depending on the way in which the structure of the molecule is drawn.



Problem 2.11

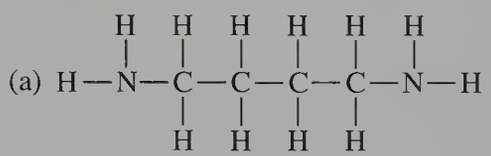
A species of cockroach secretes the substance shown below, which attracts other cockroaches. Write three condensed structural formulas for the substance.



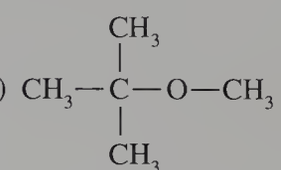
Problem 2.12

Write fully condensed formulas for each of the following structures.

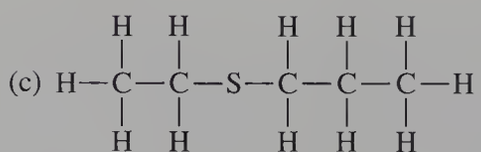
(a)



(b)



(c)



Functional Groups in Pheromones—Chemical Signals in Insects

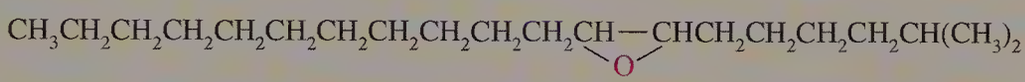
Pheromones (Greek *pherein*, to transfer + *hormon*, to excite) are compounds (occasionally mixtures of compounds) that insects and other animals use to communicate. Insects release pheromones to mark trails, warn of dangers, attract other members of the species, for defensive purposes, and to attract members of the opposite sex.

The whip scorpion, for example, ejects a defensive spray to ward off predators. Some species of ants warn other ants of danger by releasing an alarm pheromone. The bark beetles responsible for Dutch elm disease emit a pheromone that causes thousands of beetles to congregate. When these insects infest an elm tree, they transmit a fungus that kills the tree.

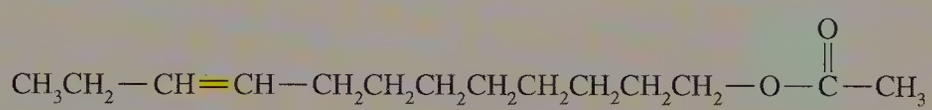
Sex attractants, usually emitted by the female of the species, attract members of the opposite sex. Sex attractants signal that the female is ready to mate. They also help the male to locate the female. Some male moths can detect a few molecules of sex aattractant miles from the female.

Each species releases a unique sex attractant. The compounds usually contain long chains of carbon atoms. However, the functional groups in their pheromones vary considerably. The structures of gypsy moth and grape berry moth pheromones are shown below. The oxygen atom in the three-membered ring of the gypsy moth pheromone forms an ether with two carbon atoms. The oxygen atoms in the grape berry moth pheromone are part of an ester functional group. Note that this compound also contains a carbon–carbon double bond.

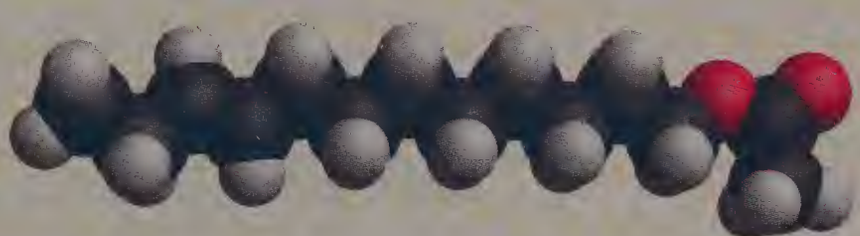
When the structures of some sex attractants were first determined, researchers hoped that traps might be baited with synthesized pheromones to attract one sex and break the reproductive cycle. Unfortunately, this "ideal" way to control insects and eliminate the use of pesticides has not proven effective for most species. However, there is some evidence that pheromone traps at least cause some confusion, and may inhibit mating. Traps baited with pheromones can also serve as an early warning of infestation by showing the presence of a particular species in the area of the trap.



(gypsy moth sex attractant)



(grape berry moth sex attractant)



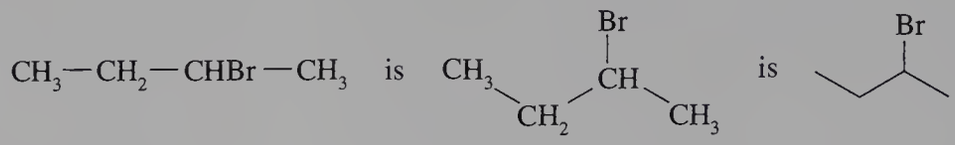
2.6 Bond-Line Structures

A **bond-line structure** is a less cluttered drawing than a condensed structural formula. However, to understand the simplified bond-line structure, the reader has to mentally add many more features to comprehend the overall structure. The rules for drawing bond-line structures are

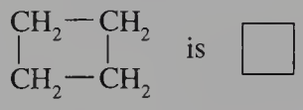
1. Carbon and hydrogen atoms are not shown unless needed for special emphasis or clarity.

2. All other atoms are shown.
3. Line segments indicate bonds.
4. Multiple bonds are shown with multiple lines.
5. A carbon atom is assumed to be at the end of each line segment or at the intersection of lines.

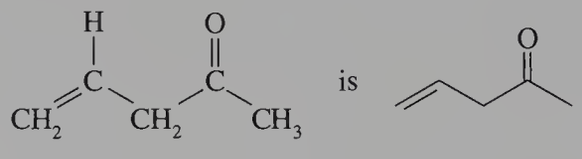
For a bond-line structure, it is best to start by drawing a zigzag arrangement of the carbon atoms and then mentally remove them.



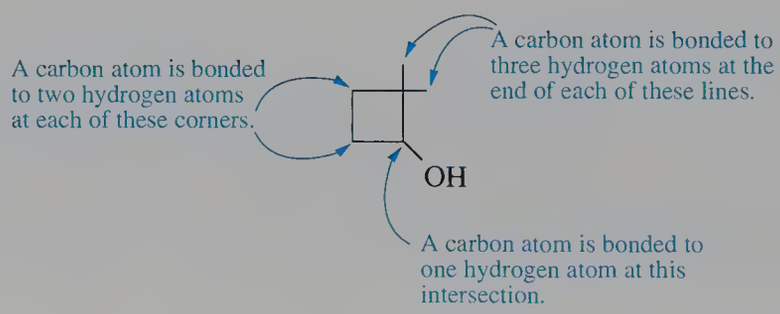
Bond-line structures are also used to show cyclic structures or "rings." Rings of carbon atoms are shown as regular polygons. For example, an equilateral triangle represents a three-membered ring, a square represents a four-membered ring, and so on.



Note that when a molecule contains double or triple bonds, carbon atoms are not shown, but oxygen and nitrogen atoms are.



When writing bond-line structures, remember that carbon, nitrogen, and oxygen form 4, 3, and 2 bonds, respectively.

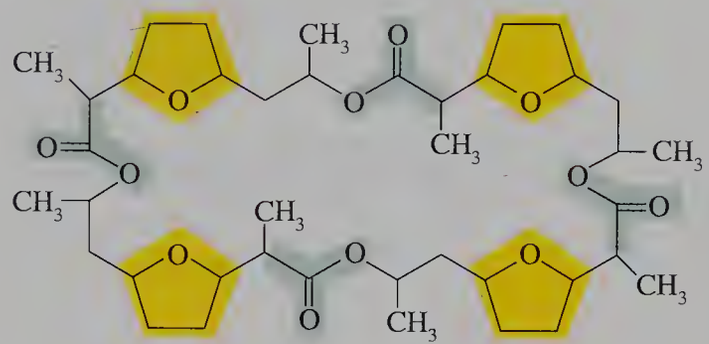


Recognizing Structural Features in Complex Molecules

The structural features that allow us to predict the physical and chemical properties of naturally occurring molecules are often only a small part of a larger structure. When we "read" such structures, we should ignore the many lines that show carbon–car-

bon bonds and focus on the functional groups. Are there multiple bonds? If atoms such as oxygen and nitrogen are present as part of functional groups, how are they bonded, and what other atoms are nearby? For example, if a carbonyl group (C=O) is present, it may be part of an aldehyde, ketone, acid, ester, or amide. These functional groups can be distinguished by looking at the atoms bonded to the carbonyl carbon atom.

Consider the structure for nonactin, an antibiotic that transports ions across cell membranes. The many oxygen atoms in the large ring bind potassium ions. Nonactin allows free passage of potassium ions across bacterial cell membranes, killing the cells.



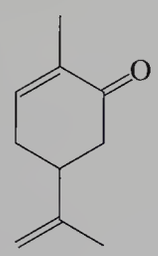
nonactin

What are the oxygen-containing functional groups in this complex structure? Concentrate on one oxygen atom at a time. Four oxygen atoms form part of carbonyl groups. Now look at the atoms bonded to the carbonyl carbon atoms of the C=O groups. In each case, the carbonyl carbon bonds to a carbon atom and to an oxygen atom. Both carboxylic acids and esters have such features. The single-bonded oxygen atom of carboxylic acids is in an OH group, whereas the oxygen atom of esters is bonded to another carbon atom. Convince yourself that nonactin has four ester groups.

Now concentrate on the second type of oxygen-containing functional group in the molecule. Oxygen atoms are present in four five-membered rings. These functional groups are ethers.

Problem 2.13

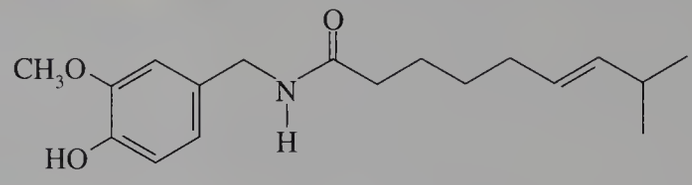
What are the functional groups of carvone, which is found in oil of caraway?



carvone

Problem 2.14

Identify the structural units contained in capsaicin, the molecule responsible for the spiciness of chili peppers.

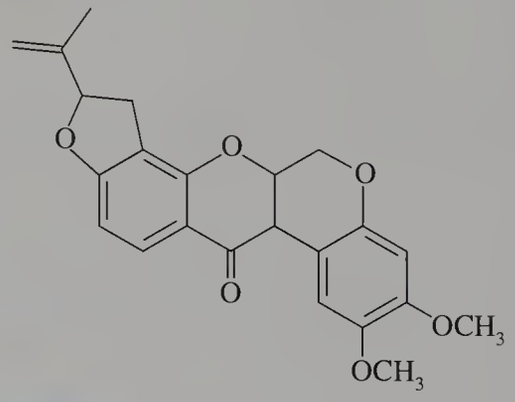


Sample Solution

The six-membered ring on the left of the structure is a benzene ring. A carbon–carbon double bond is located on the right of the structure. The nitrogen atom is bonded by a single bond to a carbonyl carbon atom, a characteristic of an amide. One of the two oxygen atoms bonded to the benzene ring by a single bond is also bonded to a CH_3 unit. Two single bonds from an oxygen atom to carbon atoms is a characteristic of an ether. The other oxygen atom bonded to the benzene ring is also bonded to a hydrogen atom. The —OH unit is a hydroxyl group.

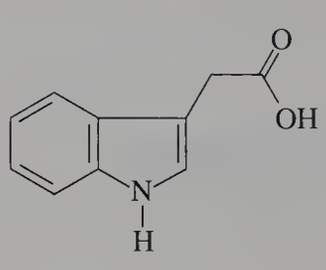
Problem 2.15

Rotenone is an insecticide used in home gardening. What oxygen-containing functional groups are in this molecule?

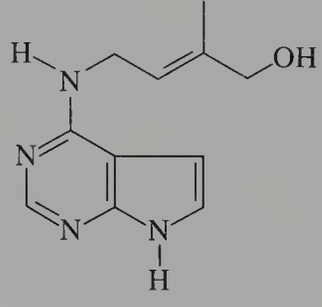


Problem 2.16

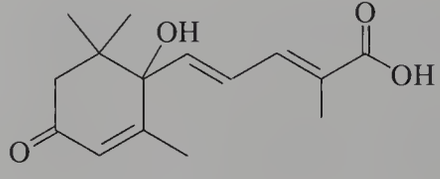
What is the molecular formula of each of the following plant growth hormones?



indoleacetic acid
(promotes shoot growth)



zeatin
(promotes root growth)



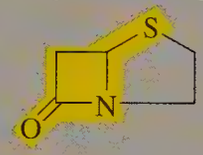
abscisic acid
(inhibits germination)

Penicillins and Cephalosporins

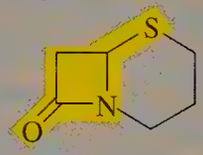
Chemists have discovered compounds in nature that have pharmaceutical activity and can be used to treat a variety of illnesses. Often these compounds are modified to improve their therapeutic properties. Some minor modifications involve changing the structure either to increase the water solubility of the compound or to allow more effective transport across biological membranes to the desired site. Sometimes larger changes are made that modify the essential functional group responsible for the therapeutic action. The goal is to enhance the desired activity and decrease side effects. Chemists may also alter antibacterial drugs to combat bacteria that have gained resistance to the original compound. Random mutation can alter genes so that they confer antibiotic resistance in bacteria. Continued use of the same antibiotic allows resistant strains to flourish because they don't have to compete with nonresistant strains.

Several compounds, collectively called penicillins, are used to treat bacterial infections. The first penicillins, isolated from molds, affected only a narrow range of bacterial species. The continued use of the available penicillins eventually led to drug-resistant strains. Many minor modifications of the penicillin structure have increased the effectiveness of the drug in a wider range of bacteria (see the figure), and we have been able to stay one step ahead of the penicillin-resistant strains.

In each penicillin, significant portions of the molecule—the essential structural unit—remain identical. The four-membered ring containing an amide functional group is essential for antibiotic activity. This ring is fused to a five-membered ring containing a sulfur atom.

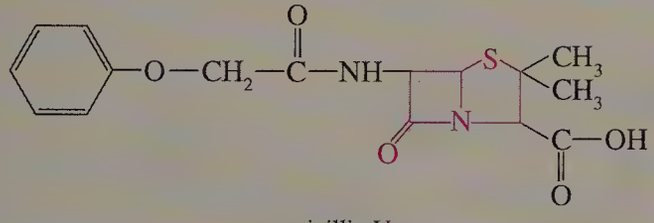


A modification of part of the structure closer to the essential site of antibiotic activity led to the development of cephalosporins. They also contain a four-membered ring with an amide functional group, but this ring is fused to a six-membered ring that contains a sulfur atom.

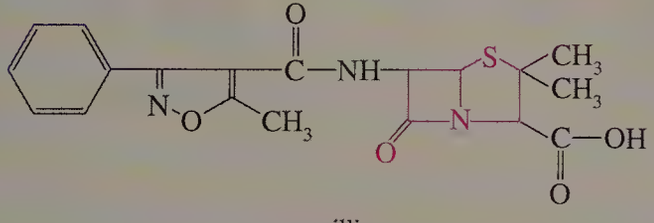


Structural variations of cephalosporins have also been developed to increase the effectiveness of the antibiotic and to overcome the resistance fostered in bacteria when one antibiotic is used too frequently.

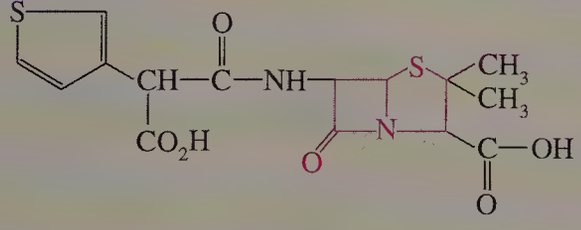
Penicillins



penicillin V

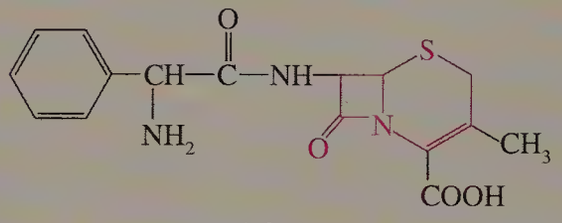


oxacillin

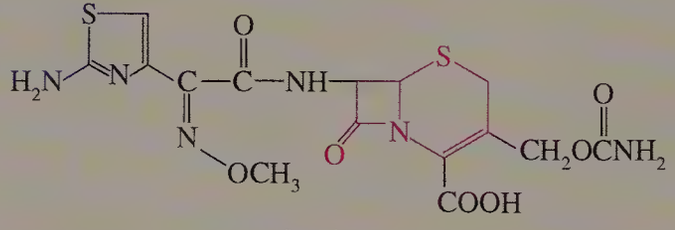


ticarcillin

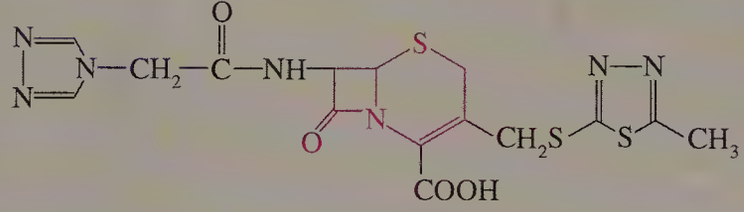
Cephalosporins



cephalexin



cefotaxime



cefazolin

Structures of Penicillins and Cephalosporins

2.7 Isomers

Compounds that have the same molecular formula whose atoms are linked in different ways are called **isomers**. We call an atomic linkage a structure. As we examine the structure of organic compounds in detail, we will find that subtle structural differences profoundly affect the physical and chemical properties of isomers.

We can divide isomers into two broad classes. Substances that differ in the order in which atoms, are bonded are called **constitutional isomers**. Isomers that have the same connectivity of atoms, but differ in the arrangement of the atoms in space, are called stereoisomers. One example of stereoisomerism was illustrated in Section 1.16. We will consider stereoisomers in greater detail in Chapters 6 and 9.

Constitutional isomers can differ in their carbon backbones. Consider the structural differences in the two isomers of C_4H_{10}, butane and isobutane. Butane has an uninterrupted chain of carbon atoms (Figure 2.5), but isobutane has only three carbon atoms connected in sequence. The fourth carbon atom is bonded to the chain as a "branch".

Constitutional isomers can also have different functional groups. For example, both ethyl alcohol and dimethyl ether have the same molecular formula: C_2H_6O. Although the molecular formulas of the two compounds are identical, their functional groups differ (Figure 2.5). The atomic connectivity is C—C—O in ethyl alcohol and the oxygen atom is part of an alcohol. In contrast, the C—O—C connectivity in the isomer forms an ether.

Constitutional isomers can have the same functional groups, but they are located at different points on the carbon skeleton. For example, the isomers 1-propanol and 2-propanol have hydroxyl group on different carbon atoms.

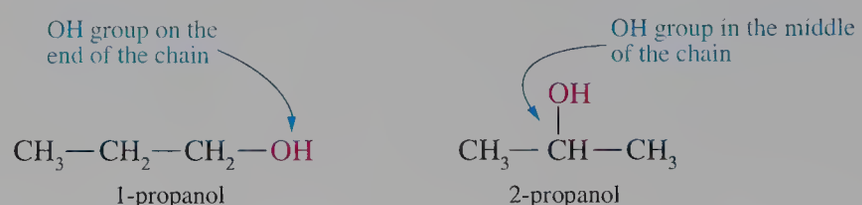
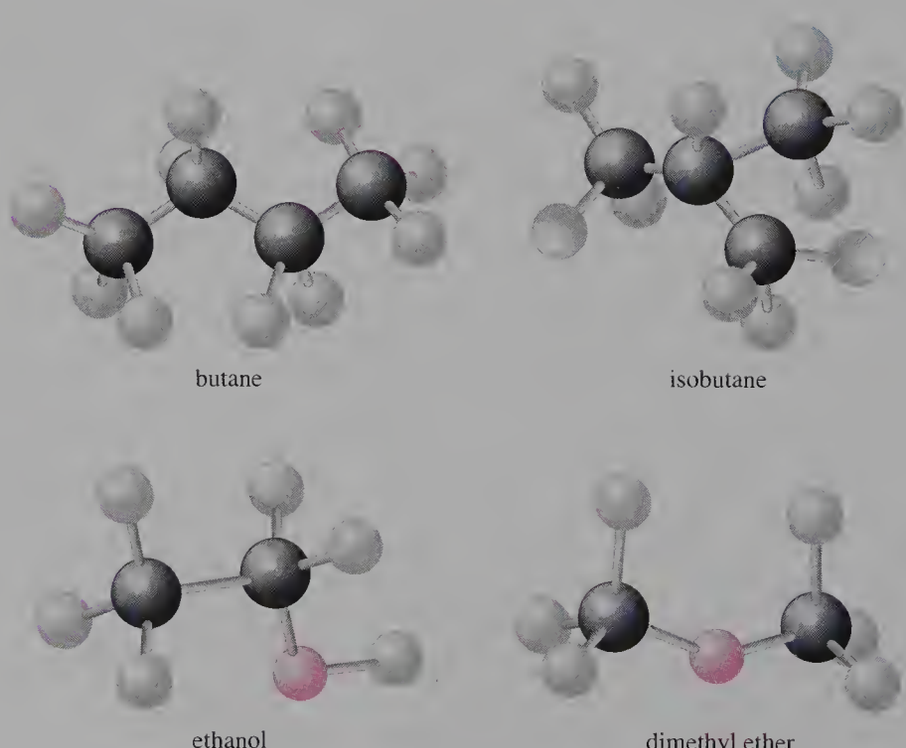
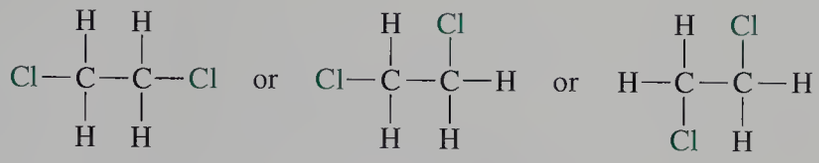


FIGURE 2.5 Structures of Constitutional Isomers

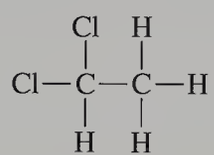


Sometimes two structural formulas appear to be isomers, but represent the same compound. For example, 1,2-dichloroethane can be written in several ways. But the bonding sequence is Cl—C—C—Cl in each formula, so all three structural formulas represent the same molecule.



1,2-dichloroethane (CH_2ClCH_2Cl)

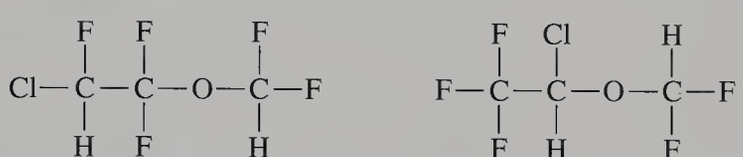
The isomer of 1,2-dichloroethane is 1,1-dichloroethane. In 1,1-dichloroethane, the two chlorine atoms are bonded to the same carbon atom, but in 1,2-dichlorethane, the two chlorine atoms are bonded to different carbon atoms. The different condensed structural formulas, $CHCl_2CH_3$ and CH_2ClCH_2Cl, also convey information about the different structures.



1,1-dichloroethane ($CHCl_2CH_3$)

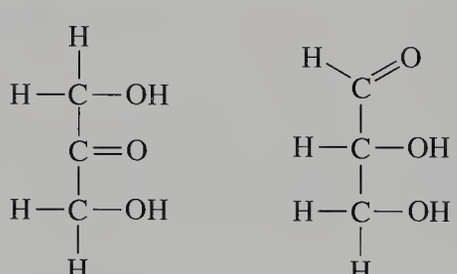
Problem 2.17

Consider the following structural formulas for two compounds used as general anesthetics. Do they represent isomers? How do they differ?



Problem 2.18

Compare the following structures of two intermediates in the metabolism of glucose. Do they represent isomers? How do they differ?



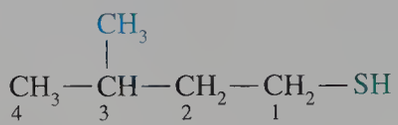
Nomenclature

As the number of atoms represented in a molecular formula increases, the number of isomers increases exponentially. Each isomer must be uniquely identified by a name. **Nomenclature** in organic chemistry is the systematic method of naming

compounds. The method was devised at a meeting in Geneva, Switzerland, in 1892. Compounds are now named by rules developed by the International Union of Pure and Applied Chemistry (IUPAC). The rules generate a single definitive name for each compound. A universal, systematic method for naming organic compounds is essential to avoid confusion. In the past, different names have often been given to the same compound. For example, CH_3CH_2OH has been called alcohol, spirit, grain alcohol, ethyl alcohol, and ethanol.

A chemical name consists of three parts: **prefix, parent**, and **suffix**. The parent indicates how many carbon atoms are in the main carbon backbone. The suffix identifies most of the functional groups present in the molecule, for example *-ol* for alcohols, *-al* for aldehydes, and *-one* for ketones. The prefix specifies the location of the functional group designated in the suffix plus some types of functional groups on the parent chain.

Once the rules are applied, there is only one name for each structure, and one structure for each name. Consider, for example, 3-methyl-1-butanethiol, a compound partly responsible for the odor of skunk.



3-methyl-1-butanethiol

Butane is the parent name of the four-carbon unit written horizontally. The prefix "3-methyl" identifies and locates the CH_3 written above the chain of carbon atoms. The prefix "1-" and the suffix "thiol" specify the position and identity of the SH group. This method of assigning numbers to the carbon chain, and other features of the IUPAC system, will be discussed in greater detail in subsequent chapters.

In spite of the IUPAC system, many common names are so well established that both common and IUPAC names are accepted. The IUPAC name for CH_3CH_2OH is ethanol, but the common name ethyl alcohol is still used.

As we introduce the nomenclature of each class of organic compounds, we will see that the assignment of a systematic name is straightforward when the rules are followed. In this text, the common names will often be given within parentheses after the IUPAC name.

2.8 Structure and Physical Properties

The structure of a substance determines its physical properties. These properties result from weak intermolecular forces between individual molecules in the liquid and solid states. These forces are typically less than 10% as strong as covalent bond forces. Intermolecular forces are of three types: **dipole–dipole forces**, **London forces**, and **hydrogen-bonding forces**.

Dipole–Dipole Forces

The bonding electrons in polar covalent bonds are not shared equally. This means that one atom of the bonded pair of atoms has a partial positive charge, represented as δ^+, and the other atom has a partial negative charge, represented as δ^-. As a result, the bond is polar. The separation of charge (δ^+ and δ^-) produces a bond moment (Section 1.11). However, a molecule may have polar bonds and yet be nonpolar, depending on its geometry. For example, tetrachloromethane (carbon tetrachloride, CCl_4) has

polar C—Cl bonds, but the tetrahedral arrangement of the four bonds around the central carbon atom causes the individual bond moments to cancel. In contrast, dichloromethane (methylene chloride, CH_2Cl_2) is a polar molecule with a net polarity away from the partially positive carbon atom toward the partially negative chlorine atoms.

Polar molecules have a negative "end" and a positive "end". The positive end of one molecule attracts the negative end of another molecule (Figure 2.6), resulting in relatively strong intermolecular interactions. The physical properties of polar molecules reflect these intermolecular interactions. A strong attraction between molecules causes a low vapor pressure. This results in a high boiling point because more energy is required to attain a temperature at which vapor pressure equals atmospheric pressure.

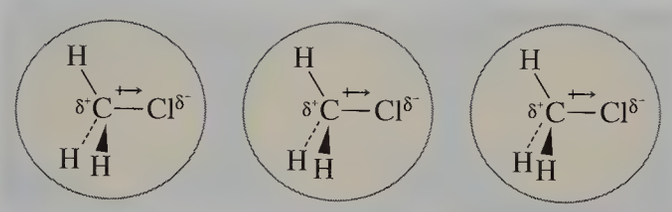


FIGURE 2.6
Intermolecular Forces in Polar Molecules

Let's compare the physical properties of ethanal (acetaldehyde, CH_3CHO) and propane ($CH_3CH_2CH_3$). Their molecular weights are similar, but ethanal boils at a higher temperature than propane. Ethanal contains a polar carbonyl group, whereas propane is a nonpolar molecule. The higher boiling point of ethanal results from the dipole–dipole interaction between ethanal molecules.

propane
dipole moment 0 D
bp –42 °C

ethanal
dipole moment 2.7 D
bp 20 °C

London Forces

The electrons in nonpolar molecules are distributed more or less uniformly throughout the molecule. However, when molecules come close to one another, as they do in the liquid state, electrons in one molecule can become transiently polarized by electrons in a neighboring molecule, resulting in a nonuniform distribution of electrons. One molecule induces a temporary dipole in the other (Figure 2.7). The **induced dipoles** interact by a weak attraction called **London forces**.

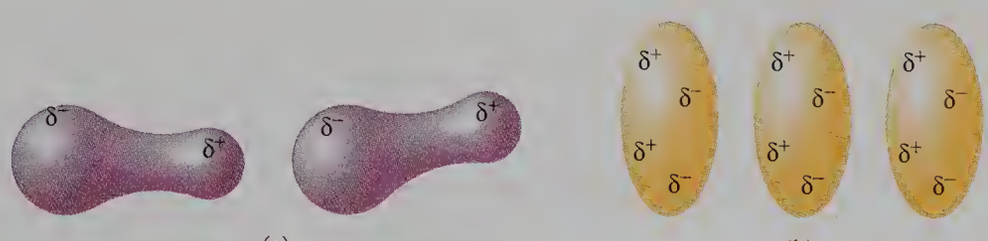
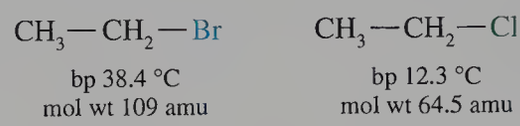


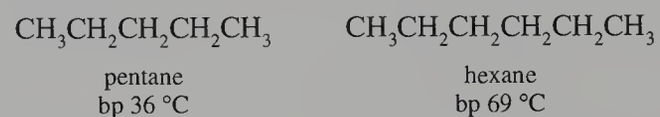
FIGURE 2.7 London Forces in Nonpolar Molecules
In a molecule represented by (a), the electrons are distorted toward one end of the molecule.
In a molecule represented by (b) the electrons are distorted toward one side of the molecule.

The ease with which the electron distribution is changed is called **polarizability**. The strength of London forces depends on the number of electrons in a molecule and on the types of atoms containing those electrons. Electrons far from atomic nuclei are more easily polarizable than electrons closer to atomic nuclei. For example, the polarizability of the halogens increases in the order F < Cl < Br < I.

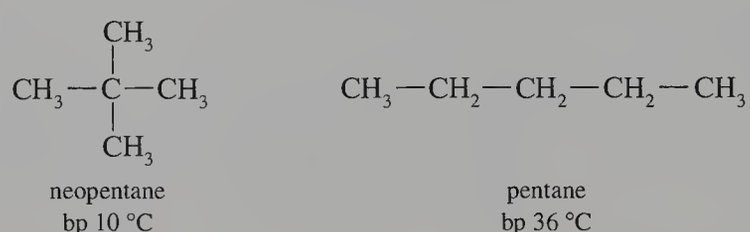
We cannot rely solely on molecular polarity to predict the relative boiling points of two molecules. For example, bromoethane has a higher boiling point than chloroethane. Because a C—Cl bond is more polar than a C—Br bond, we might expect chloroethane to have a higher boiling point than bromoethane. However, their molecular weights and hence the number of electrons in the two compounds differ considerably. Second, bromine is more polarizable than chlorine. The order of boiling points reflects the relative polarizability of the molecules and the larger London forces of bromoethane.



London forces also depend on molecular surface area. For example, the boiling points of pentane and hexane are 36 and 69°C, respectively. These two nonpolar molecules contain the same types of atoms, but the numbers of atoms are different. The London forces are stronger in hexane than in pentane because hexane has a larger surface area to interact with neighboring molecules. The stronger intermolecular attraction holds molecules together more tightly, decreasing the vapor pressure of hexane and giving it a higher boiling point than pentane.



London forces also depend on molecular shape. For example, neopentane has a lower boiling point than pentane. Neopentane is more spherical than pentane; therefore it has less surface area than the more cylindrical pentane molecule (Figure 2.8). As a consequence, the London forces are smaller in neopentane.



To compare the strengths of intermolecular forces, we must consider only molecules of similar size and shape, or similar polarity and shape. If molecules have similar polarity and are approximately the same shape, then attractive forces are stronger for molecules of higher mass because the London forces are stronger. If molecules have similar shape and have approximately the same mass, then attractive forces are stronger for molecules with higher polarity because the dipole–dipole forces are stronger.

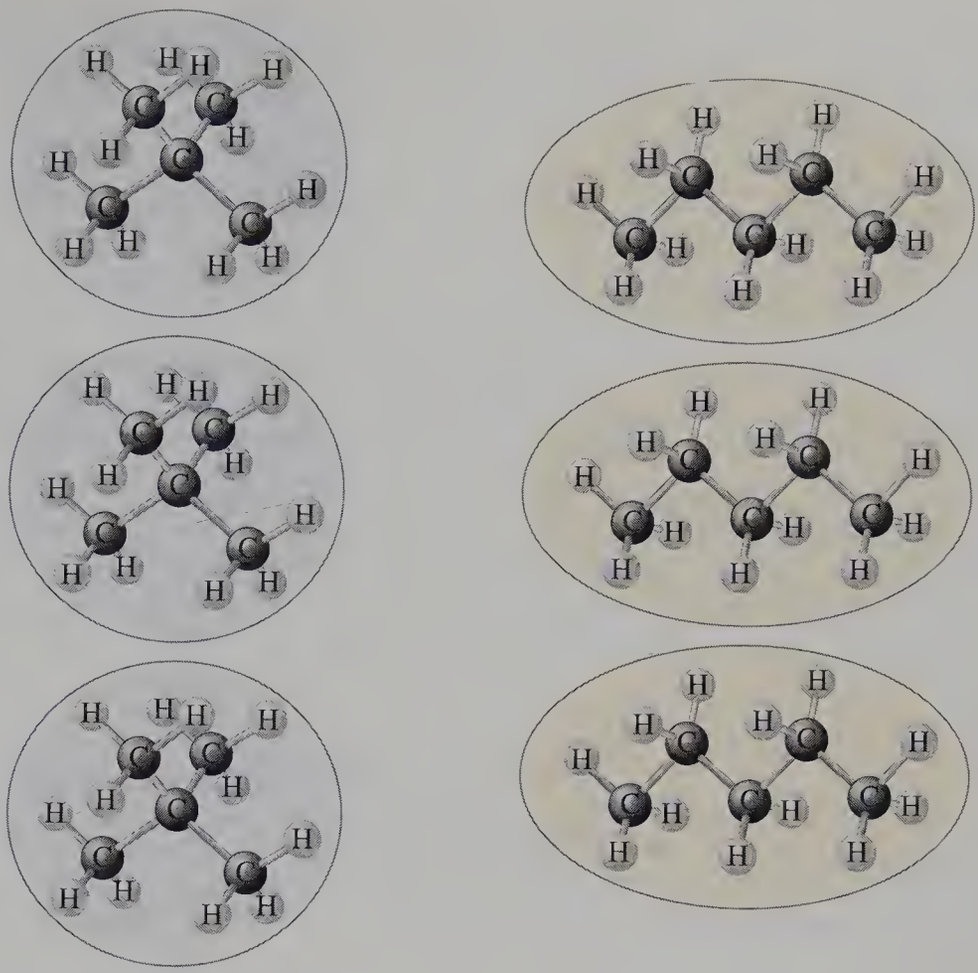
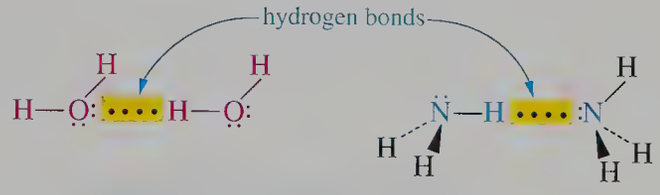


FIGURE 2.8 Shapes of Molecules and London Forces
The shape of neopentane is nearly spherical. Neighboring molecules cannot approach each other closely. Pentane is an extended molecule with an ellipsoid chape and neighboring molecules can more closely approach each other.

Hydrogen-Bonding Forces

The hydrogen atom involved in a polar covalent bond to nitrogen or oxygen has a partial positive charge. The electrostatic attraction between that hydrogen atom and the lone pair electrons of another nitrogen or oxygen atom produces a hydrogen bond whose strength is about 20 kJ mole^{-1} (5 kcal mole^{-1}). As a result, compounds containing O—H and N—H bonds—H_2O and NH_3, for example—can form intermolecular (between molecule) **hydrogen bonds**.



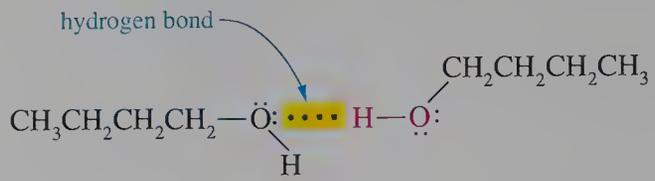
Organic compounds with N—H and O—H bonds, such as amines and alcohols, can also form hydrogen bonds. These bonds greatly affect the physical properties of low molecular weight alcohols and amines. For example, the boiling point of 1-butanol (117 °C) is substantially higher than the boiling point of diethyl ether (35 °C), which has the same molecular weight.

$CH_3—CH_2—CH_2—CH_2—OH$
bp 117.7 °C
mol wt 74 amu

$CH_3—CH_2—O—CH_2—CH_3$
bp 36 °C
mol wt 74 amu

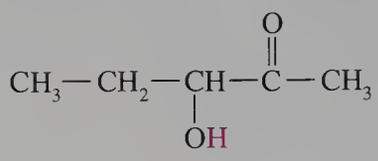
Because the number and types of atoms are the same, and the shapes of the molecules are similar, the boiling point difference cannot come from differences in London forces. Both molecules have polar bonds and interact by similar dipole–dipole

forces. The higher boiling point of 1-butanol results from hydrogen bonding of the hydroxyl groups of neighboring 1-butanol molecules.

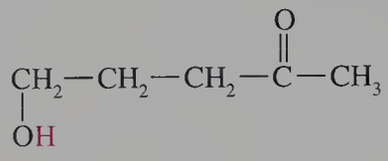


1-butanol

Two groups within a molecule sometimes form intramolecular (within molecule) hydrogen bonds. Intramolecular hydrogen bonds are likely to form if they result in a structure with a five- or six-membered ring. Consider the boiling points of two isomeric compounds containing a hydroxyl group and a carbonyl group.

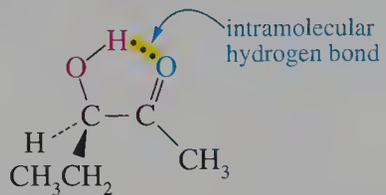


1
bp 147 °C



2
bp 210 °C

Compound 1 forms an intramolecular hydrogen bond between the hydroxyl hydrogen atom and the carbonyl oxygen atom rather than intermolecular hydrogen bonds. As a result of this decrease in intermolecular hydrogen bonding, the boiling point of compound 1 is lower.



Note that the structure with an intramolecular hydrogen bond has a five-membered ring. We will see many times in this text that covalent bonds form easily in chemical reactions to give five-membered and six-membered rings. The same pattern is found for intramolecular interactions. Seven-membered and higher membered rings are far less likely to form because so many more bonds must be oriented to close the ring. A seven-membered ring closed by an intramolecular hydrogen bond is unlikely in the case of compound 2. It forms predominantly intermolecular hydrogen bonds and as a result has a much higher boiling point.

Problem 2.19

The dipole moment of dimethyl ether ($CH_3—O—CH_3$) is 1.3 Debye. Estimate its boiling point based on the properties of propane and ethanal.

Problem 2.20

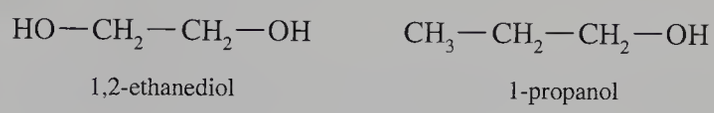
Based on the boiling points of pentane and hexane, predict the boiling point of heptane ($CH_3CH_2CH_2CH_2CH_2CH_2CH_3$).

Problem 2.21

The boiling points of CCl_4 and $CHCl_3$ are 77 and 62 °C, respectively. Which compound is more polar? Are the polarities of the two molecules consistent with their boiling points?

Problem 2.22

The boiling point of 1,2-ethanediol (ethylene glycol), which is used as antifreeze, is 190°C. It can form intramolecular hydrogen bonds. Why, then, is the boiling point of ethanediol higher than that of 1-propanol (97°C)?



1,2-ethanediol　　1-propanol

2.9 Solubility

Because most organic reactions occur between reactants (solutes) dissolved in liquid solvents, let's consider the factors that affect solubility. A maxim of the chemistry laboratory is "like dissolves like". This generalization means that polar solvents dissolve polar solutes and nonpolar solvents dissolve nonpolar solutes. We will see why these solubility "rules" are true by considering solute–solute, solvent–solvent, and solute–solvent interactions.

A Model for the Solution Process

The solution process is a rather complicated phenomenon, but we can divide it into the three hypothetical steps shown in Figure 2.9. The sum of the enthalpy changes for each step is equal to the **heat of solution** (ΔH°_{soln}) for the actual dissolution process.

Step 1. The separation of solute molecules held together by intermolecular attractive forces.
Step 2. The separation of the solvent molecules to create a "hole" for the solute molecule.
Step 3. The interaction of the solute and solvent molecules to form a solution.

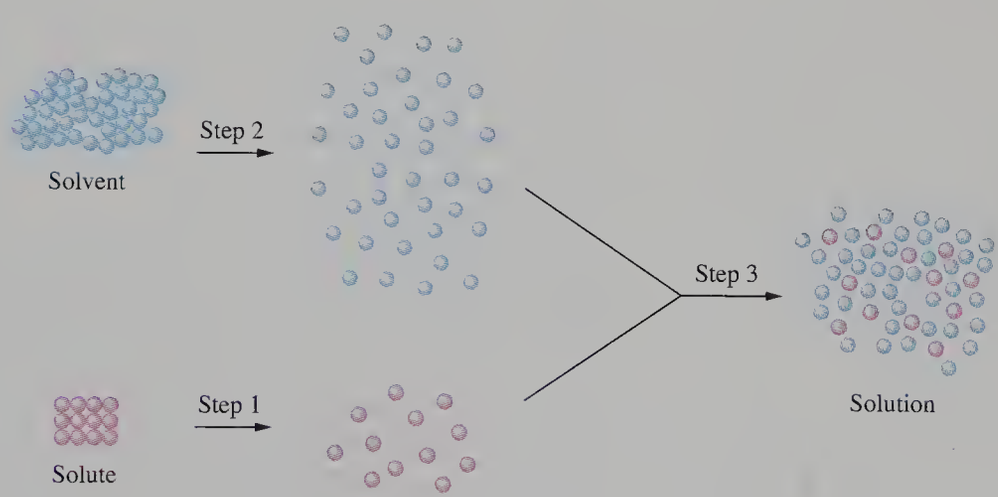


FIGURE 2.9 Solubility Viewed as a Stepwise Process

Steps 1 and 2 require energy regardless of the type of intermolecular forces present in the solute and solvent. That is, steps 1 and 2 are endothermic ($\Delta H^\circ > 0$). For step 3, ΔH° is usually negative, although its magnitude may be small if the solvent and solute have substantially different polarities. The heat of solution (ΔH°_{soln}) is equal to the sum

of two endothermic terms and one exothermic term. Depending on the magnitude of the endothermic and exothermic terms, the ΔH°_{soln} can be positive or negative.

For the case where ΔH°_{soln} is negative, the intermolecular forces between solvent and solute molecules in solution are stronger than the solute–solute and solvent–solvent interactions. Thus, the solution is enthalpically more stable than the isolated solvent and solute.

However, the solution process also occurs even when ΔH°_{soln} is somewhat positive. In this case, the solute–solvent interaction is smaller than either solute–solute or solvent–solvent interaction. Why, then, does such a solute dissolve in the solvent? The answer is that the formation of solutions, like all physical and chemical processes, is governed by two factors: the enthalpy change and the entropy change. The entropy of a system—whether we consider a solute, solvent, or solution—is a measure of the amount of disorder or randomness. Processes in which the final state of the system is more disordered, and hence more random, than the initial state are entropically favored. The entropy of a pure substance is lower than the entropy of a mixture of substances. Hence, the solution process occurs with an increase in entropy. This fact allows some solutes and solvents to form solutions even though ΔH°_{soln} is positive. We will discuss the quantitative relationship between enthalpy and entropy in greater detail in the next chapter.

Types of Solutions

Now let's consider the possibilities of combining polar and nonpolar solutes and solvents to form solutions. The possible combinations are

1. Nonpolar solute and nonpolar solvent.
2. Polar solute and polar solvent.
3. Nonpolar solute and polar solvent.
4. Polar solute and nonpolar solvent.

Nonpolar solutes dissolve in nonpolar solvents—a clear case of "like dissolves like". Nonpolar substances interact by weak London forces. Thus, only small amounts of energy are required to separate the solute molecules and the solvent molecules. When the solute and solvent molecules are mixed, they interact by weak London forces. As a consequence, ΔH°_{soln}, which may be positive or negative, is small. In such cases, the dissolution process is driven by the increase in entropy that results from the mixing of the solute and solvent.

Polar solutes dissolve in polar solvents, also a case of "like dissolves like". Polar substances interact by both London forces and dipole–dipole forces. Thus, a large amount of energy is required to separate the solute molecules and the solvent molecules. However, when the solute and solvent molecules are mixed, the solute–solvent interactions are also quite strong, and the energy released is similar to that required to separate pure solute and pure solvent molecules. Therefore, enthalpy considerations are more critical for combinations of polar solutes and solvents than for nonpolar solutes and solvents. However, the solution process occurs with an increase in entropy, which favors the formation of a solution.

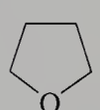
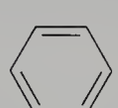
Now consider the possibility of dissolving a nonpolar solute in a polar solvent or a polar solute in a nonpolar solvent. The nonpolar molecules only weakly attract each other and are easily separated from each other. However, considerable energy is required to separate polar molecules. When solute and solvent are mixed, little energy is released as the solution forms because the attractive forces between polar and

nonpolar materials are small. As a consequence, the overall process may be so enthalpically disfavored that the entropy change for mixing the solute and solvent is insufficient for solution to occur.

Common Solvents

The ability of a solvent to dissolve polar substances is characterized by an experimental quantity called the **dielectric constant**, symbolized by ε (Table 2.1). In a vacuum ε = 1, the lowest possible value.

TABLE 2.1
Dielectic Constant of Solvents

Solvent	*Structure*	*Dielectric Constant*
water	HOH	78.5
dimethyl sulfoxide (DMSO)	$(CH_3)_2S{=}O$	49
N,N-dimethylformamide (DMF)	$(CH_3)_2NCH{=}O$	37
acetonitrile	$CH_3C{\equiv}N$	36
methanol	CH_3OH	33
ethanol	CH_3CH_2OH	24
acetone	$(CH_3)_2C{=}O$	21
tetrahydrofuran		7
diethyl ether	$(CH_3CH_2)_2O$	4
benzene		2
pentane	$CH_3(CH_2)_3CH_3$	2

Although polar solvents have higher dielectric constants than nonpolar solvents, the dielectric constant is not directly related to the dipole moment of selected solvents. The dipole moment is a measure of the properties of a molecule in an electric field. If a molecule has polar bonds, then it might have a dipole moment depending on its geometry. The dielectric constant of a solvent reflects the interaction between the solvent and solute. Solvents with high dielectric constants also tend to dissolve polar solutes.

Some compounds with no dipole moment can have dielectric constants comparable to the dielectric constants of compounds that have dipole moments. For example, the dipole moments of hexane and tetrachloromethane are zero. Their dielectric constants are small but not zero. Furthermore, their dielectric constants are only slightly smaller than the dielectric constant for diethyl ether, a polar molecule.

$CH_3CH_2CH_2CH_2CH_2CH_3$	CCl_4	$CH_3CH_2{-}O{-}CH_2CH_3$
dipole moment 0 D	dipole moment 0 D	dipole moment 1.15 D
ε = 1.89	ε = 2.34	ε = 4.33

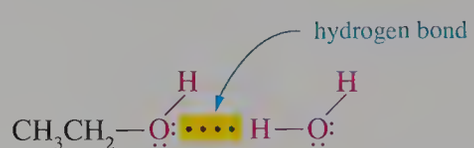
Alkanes (compounds containing only carbon and hydrogen) are nonpolar compounds. Thus, hexane ($CH_3CH_2CH_2CH_2CH_2CH_3$) dissolves nonpolar organic materials such as fats and oils. Replacing hydrogen atoms of an alkane with chlorine atoms gives chloroalkanes, which have a variety of solubility characteristics. Dichloromethane (methylene chloride, CH_2Cl_2) and trichloromethane (chloroform, $CHCl_3$) have dipole moments, but tetrachloromethane (carbon tetrachloride, CCl_4) has no dipole moment. The dielectric constants in these compounds parallel their dipole moments. Dichloromethane is considered a polar solvent, trichloromethane moderately polar, and tetrachloromethane nonpolar.

CH_2Cl_2	$CHCl_3$	CCl_4
dipole moment 1.6 D	dipole moment 1.0 D	dipole moment 0 D
$\varepsilon = 9.08$	$\varepsilon = 4.81$	$\varepsilon = 2.34$

Tetrachloromethane (carbon tetrachloride, CCl_4) is a good solvent for nonpolar compounds such as fats and oils. At one time CCl_4 was used as a dry cleaning agent to dissolve grease and dirt, which tend to be nonpolar. However, it is no longer used because of potential liver damage from continued exposure to the vapor.

Solvents with large dielectric constants tend to be good solvents for ions. For example, the dielectric constant of water is 78.5, a very high value, and water is a good solvent for ionic compounds. In contrast, hexane ($CH_3(CH_2)_4CH_3$) is a nonpolar molecule that has a dielectric constant of 1.89; hexane does not dissolve ionic compounds.

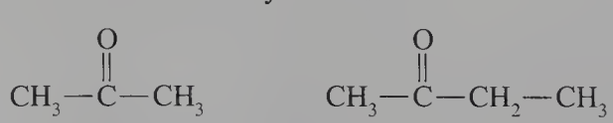
Specific structural features also strongly affect solubility. Thus, water dissolves not only ions and polar solutes but also compounds that can form hydrogen bonds with it. For example, water and ethyl alcohol form a solution (they are miscible) because they form intermolecular hydrogen bonds.



Ethanol is an excellent solvent for polar solutes because it has lone pair electrons, which are hydrogen bond acceptors. Polar compounds dissolve readily in the "like" polar solvent. Ethanol and low molecular weight alcohols dissolve nonpolar compounds to some extent, but the solubility is often limited because the extensive hydrogen-bonding network of the alcohol must be broken to accommodate the solute.

Polar solvents such as diethyl ether ($CH_3CH_2—O—CH_2CH_3$) and other ethers dissolve many nonpolar and polar compounds. Nonpolar compounds are generally more soluble in diethyl ether than in alcohols because ethers do not have a hydrogen-bonding network that would have to be broken up to dissolve the solute. Polar compounds that can serve as hydrogen bond donors dissolve in diethyl ether because they can form hydrogen bonds to the lone pair electrons of ether's oxygen atom.

Both acetone and 2-butanone (known in industry as methyl ethyl ketone or MEK) are excellent solvents for many polar solutes, including carboxylic acids and alcohols, which are quite polar. These solvents have a carbonyl group, a hydrogen bond acceptor for alcohols and carboxylic acids.

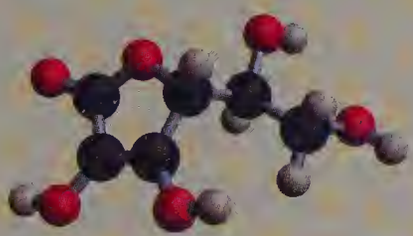


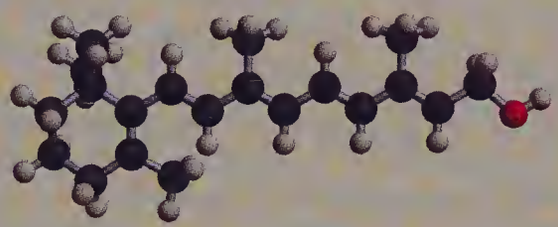
Water-Soluble and Fat-Soluble Vitamins

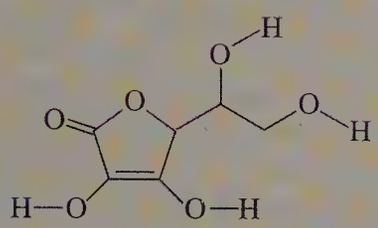
The different solubilities of two vitamins illustrate the maxim that "like dissolve like". Vitamin C is water soluble, whereas vitamin A is fat soluble.

The vitamin C molecule is small, with many —OH groups that can form hydrogen bonds to water. The vitamin A molecule is nonpolar, with the exception of one —OH group. The vitamin A molecule is not "like" water and has a very low solubility in water. On the other hand, vitamin A, which structurally resembles the carbon compounds in fats, dissolves in fatty tissue.

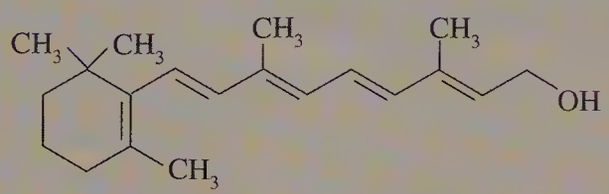
Because it is water soluble, vitamin C is not stored in the body and should be part of one's daily diet. Excess vitamin C is eliminated from the body. Fat-soluble vitamins, on the other hand, are stored by the body for future use. If excessive quantities of fat-soluble vitamins are consumed in vitamin supplements, an illness known as hypervitaminosis can result.







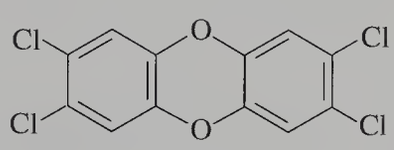
vitamin C



vitamin A

Problem 2.23

Dioxin, which is thought to be only a product of the chemical industry produced in small quantities as a by-product, is widely produced in incinerators and other combustion processes. It accumulates in the relatively nonpolar fatty tissues of animals. (The biological damage depends on the species.) Based on solubility concepts discussed in this chapter, explain why dioxin "dissolves" in these tissues.



dioxin

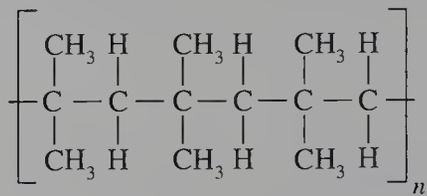
Sample Solution

The like-dissolves-like concept suggests that the dioxin molecule must be nonpolar. However, there are both polar carbon–oxygen and polar carbon–chlorine bonds in the molecule. The polarity of the molecule depends on the orientation of those bonds. We can consider part of the molecule to determine if there is a cancellation of bond moments. The net re-

sultant of the two carbon–chlorine bonds in one ring is opposite the net resultant of the two carbon–chlorine bonds in the other ring. Furthermore the resultant of the two carbon–oxygen bonds at the top of the structure is opposite to the resultant of the two carbon–oxygen bonds on the bottom of the structure. Overall the molecule has no dipole moment and is nonpolar. Thus, it should be soluble in nonpolar tissues.

Problem 2.24

A solid polymer of 2-methylpropene (isobutylene) is contained in Elastol, a commercial product that is used in cleaning up oil spills. The liquid oil in an oil spill associates with the polymer and forms a viscous material that is easier to skim from the surface of the water than the more fluid oil which tends to spread in thin layers. Why does the oil associate with this polymer, represented by the following partial structure?



2.10 Chemical Properties

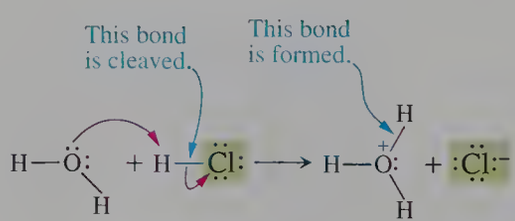
Predicting the chemical properties of compounds—that is, how they react with other compounds—is a more complex problem than predicting their physical properties. The number of potential chemical reactions among the dozens of functional groups in the millions of organic compounds is astronomically large. However, we shall find that we can understand these myriad reactions by dividing them into several different classes and learning a few fundamental concepts that underlie all organic chemical reactions. In this way, we can discern patterns of chemical behavior that unify many disparate facts. Acid–base reactions (Section 2.11) and oxidation–reduction reactions (Section 2.12) are two classes of reactions that you have encountered in your general chemistry course. Each type of reaction provides a unifying theme that occurs again and again in organic chemistry.

Several classes of reactions that are new to you are presented in Section 2.13. The classes of organic reactions we will describe are

1. Addition reactions.
2. Elimination reactions.
3. Substitution reactions.
4. Hydrolysis reactions.
5. Condensation reactions.
6. Rearrangement reactions.

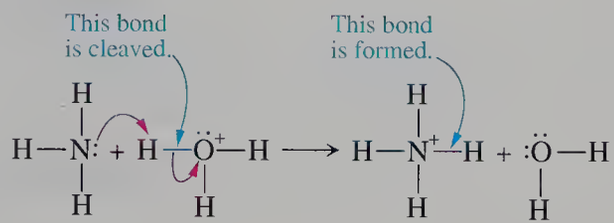
2.11 Acid–Base Reactions

A **Brønsted acid** is a proton (H^+) donor; a **Brønsted base** is a proton acceptor. For example, gaseous hydrogen chloride dissolves in water to produce a solution of hydronium ions and chloride ions.

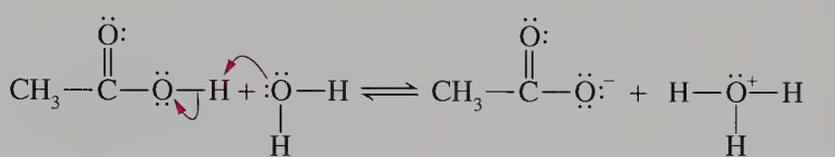


In the acid–base reaction shown above, we use curved arrows to indicate the "movement" of pairs of electrons associated with the transfer of the proton. Electrons move from the start of the arrow toward the arrow head. The sequence of arrows in the above reaction shows that a nonbonded pair of electrons of the oxygen atom of water forms a bond to the hydrogen atom of HCl and the bonded pair of electrons in the H—Cl bond moves to the chlorine atom.

The most common Brønsted base is the hydroxide ion. It can accept a proton from an acid to give water. Ammonia is also a base; it can accept a proton from an acid to give the ammonium ion. A curved arrow in the following equation shows the movement of the pair of electrons.

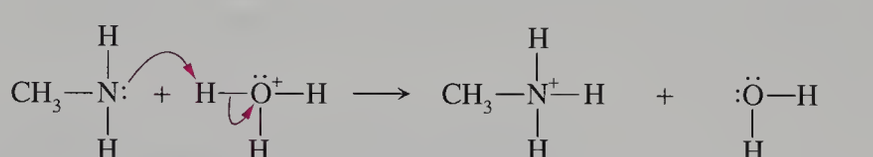


Several classes of organic compounds are Brønsted acids or bases. For example, a carboxylic acid, such as acetic acid, can donate a proton to a base, such as water.



acetic acid (an acid) | water (a base) | acetate ion (a conjugate base) | hydronium ion (a conjugate acid)

Amines are organic bases whose acid–base chemistry is like that of ammonia. For example, methylamine behaves as a Brønsted base because the nonbonded electron pair of the nitrogen atom can accept a proton from an acid such as the hydronium ion.



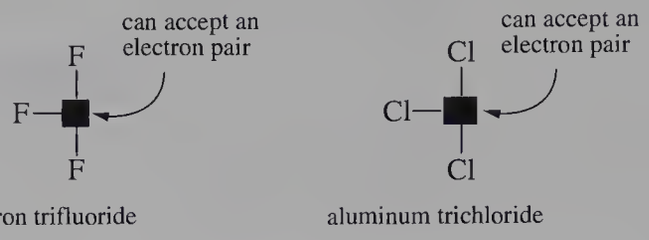
methylamine (a base) | hydronium ion (an acid) | methylammonium ion (a conjugate acid) | water (a conjugate base)

When an acid transfers a proton to a base, another base and acid are produced. The acid loses a proton and becomes a **conjugate base**. For example, the conjugate base of acetic acid is acetate ion. When a base accepts a proton, the substance formed is a **conjugate acid**. The conjugate acid of methylamine is the methylammonium ion.

Lewis Acids and Bases

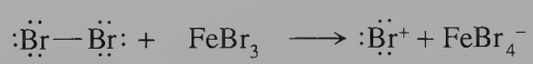
Some acid–base reactions occur without proton transfer. The Lewis concept of acids and bases focuses on electron pairs. A **Lewis acid** is an electron pair acceptor; a **Lewis base** is an electron pair donor. Thus, the Brønsted acid HCl is also a Lewis acid because it contains a proton that accepts an electron pair. Ammonia is a Lewis base because it can donate an electron pair.

Two Lewis acids often used as acid catalysts in organic chemistry are boron trifluoride (BF_3) and aluminum trichloride ($AlCl_3$). Each has only six electrons in its valence shell and each can accept an electron pair from a Lewis base.



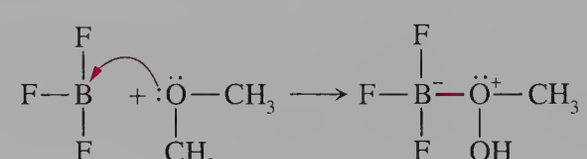
boron trifluoride aluminum trichloride

Other Lewis acids include transition metal compounds such as iron(III) bromide ($FeBr_3$) that react by accepting a pair of electrons. For example, $FeBr_3$ reacts with molecular bromine to accept a bromide ion. In this reaction, $FeBr_3$ behaves as a Lewis acid and bromine behaves as a Lewis base.



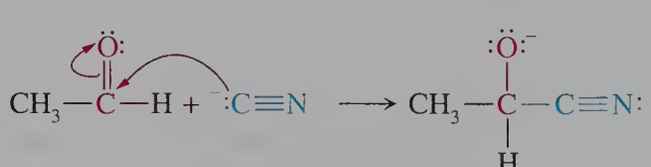
Lewis base Lewis acid

Many organic compounds that contain oxygen and nitrogen atoms are Lewis bases because these atoms have nonbonded electrons that can react with Lewis acids. For example, ethers react with boron trifluoride to give a product that has a coordinate covalent bond (Section 1.5) between the boron and oxygen atoms.



Lewis acid Lewis base

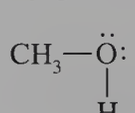
Another somewhat less obvious example of a Lewis acid–base reaction is the reaction of the cyanide ion with a carbonyl group of ethanal (acetaldehyde). The cyanide ion is a Lewis base, and the carbonyl carbon atom of ethanal is a Lewis acid.



Lewis acid Lewis base

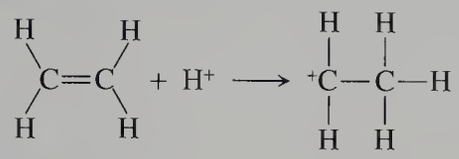
Problem 2.25

Methanol can behave as a Brønsted acid or a Brønsted base. Explain why. What is the conjugate base of methanol? What is the conjugate acid of methanol?



Problem 2.26

Consider the reaction of a hydrogen ion with ethylene to give a charged intermediate called a carbocation. Classify the reactants using Lewis acid–base nomenclature.



Problem 2.27

Write the structure of the cation formed by protonation of dimethyl ether (CH_3OCH_3) by sulfuric acid. What is the H—O—C bond angle? Which atom bears the formal positive charge?

Problem 2.28

Formaldehyde reacts with acids to form $CH_2{=}O^{+}{-}H$. Draw the structure of the cation. What is the C—O—H bond angle?

2.12 Oxidation–Reduction Reactions

Oxidation–reduction reactions occur by the transfer of one or more electrons from one species to another. **Oxidation** occurs when a reactant loses electrons; **reduction** occurs when a reactant gains electrons. The oxidation number of a substance increases when it is oxidized; the oxidation number of a substance decreases when it is reduced.

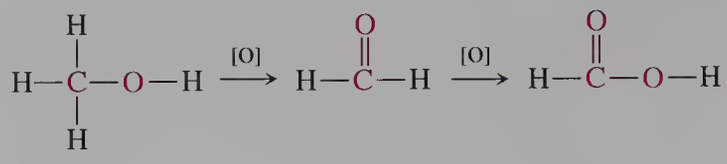
Oxidation and reduction stand in a close and necessary relationship to each other. When a substance is reduced, it gains electrons from the substance that becomes oxidized. This relationship is emphasized further in the terms "oxidizing agent" and "reducing agent". In an oxidation–reduction reaction, the substance reduced is the **oxidizing agent** because, by gaining electrons, it causes oxidation of another substance. The substance that is oxidized is called the **reducing agent** because, by losing its electrons, it causes the reduction of another substance.

Changes in Hydrogen and Oxygen Content

In contrast to oxidation–reduction reactions of inorganic compounds, in which the results of electron transfer are easily discernible, oxidation–reduction reactions of organic compounds are less obvious. An oxidation of an organic compound occurs if one of its carbon atoms bonds to a more electronegative atom, such as oxygen. The carbon atom has been oxidized because the electrons in the carbon–oxygen bond are drawn toward the more electronegative oxygen atom. If a carbon atom bonds to a less electronegative atom, such as hydrogen, the carbon atom has been reduced. The electronegativity of carbon is 2.5 and that of hydrogen is 2.1. Although this difference is small, there is a small net polarity in a carbon–hydrogen bond. The electrons in the carbon–hydrogen bond are drawn slightly toward the carbon atom.

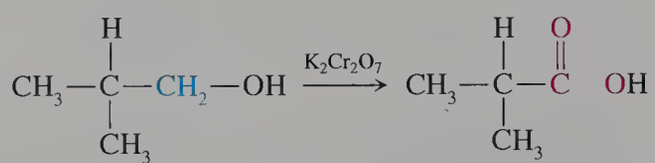
In an oxidation–reduction reaction of an organic compound, we can often determine the change in its oxidation state by counting the number of hydrogen atoms or oxygen atoms gained or lost. The oxidation state of a molecule increases (oxidation) if its hydrogen content decreases or its oxygen content increases. The oxidation state of a molecule decreases (reduction) if its hydrogen content increases or its

oxygen content decreases. For example, the conversion of methanol (CH_3OH) to methanal (formaldehyde, CH_2O) is an oxidation because methanol loses two hydrogen atoms. Further reaction of methanal to produce methanoic acid (formic acid) occurs with an increase in the oxygen content, so it is also an oxidation process.



methanol (methyl alcohol) — methanal (formaldehyde) — methanoic acid (formic acid)

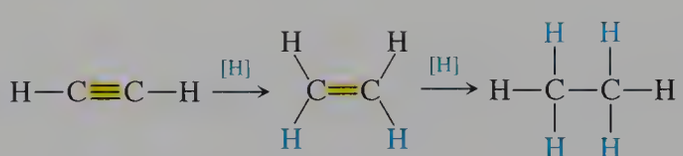
In these reactions, the symbol [O] represents an unspecified oxidizing agent. Note that the equations are not balanced. In organic chemistry we focus on the reaction of the organic compound. Oxidizing agents such as potassium dichromate, which might be used in the above oxidation reaction, are seldom balanced; they are placed above the reaction arrow.



2-methyl-1-propanol (an alcohol) — 2-methylpropanoic acid (a carboxylic acid)

In the conversion of an alcohol into an acid, an oxidation has occurred, and the substance above the arrow must be an oxidizing agent.

The conversion of a carbon–carbon triple bond into a double bond and finally into a single bond involves reduction because the hydrogen content increases in each step. The symbol [H] represents an unspecified reducing agent. Hydrogen gas in the presence of a platinum catalyst is a common reducing agent for carbon–carbon double and triple bonds.



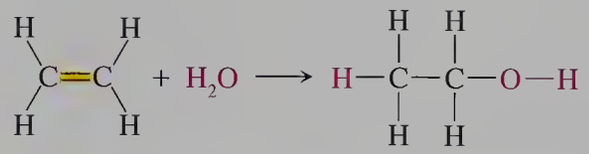
ethyne (acetylene) — ethene (ethylene) — ethane

Oxidation–reduction reactions do not require changes in the hydrogen or oxygen content of organic compounds. Oxidation or reduction may accompany other classes of reactions such as addition, elimination, or substitution reactions (Section 2.13). For example, replacement of hydrogen by chlorine in the conversion of methane to chloromethane can be considered an oxidation of the carbon atom.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

The carbon atom is oxidized because chlorine is a more electronegative atom than hydrogen. The carbon–chlorine bond is polar, and the bonding electrons are drawn toward the more electronegative chlorine atom. Thus, the carbon atom is oxidized in the same sense that it is oxidized when bonded to an oxygen atom.

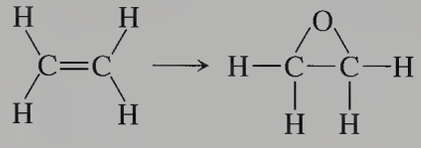
Some reactions in which there is a simultaneous change in the hydrogen and oxygen content are not oxidation–reduction reactions. For example, the conversion of ethene to ethanol is not an oxidation–reduction reaction. There is an increase of two hydrogen atoms, a reduction, but there is also a simultaneous increase of one oxygen atom, an oxidation. Thus there is no net oxidation or reduction.



ethene ethanol

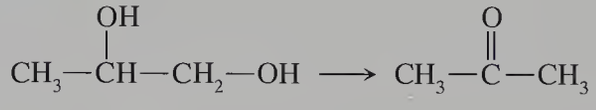
Problem 2.29

Ethylene oxide is used to sterilize medical equipment that cannot withstand the steam heat of an autoclave. The gas is produced from ethylene by the following process. Classify the type of reaction. Is an oxidizing or reducing agent required?



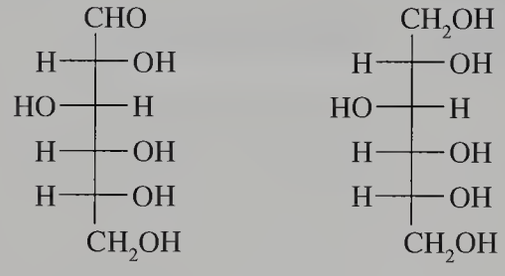
Problem 2.30

Consider the following reaction, and determine whether oxidation or reduction occurs.



Problem 2.31

Sorbitol, a sugar substitute, is produced in large quantities in chemical industry starting from glucose. What type of chemical reaction is used? What type of reagent is required?



glucose sorbitol

Sample Solution

Glucose contains five hydroxyl groups and an aldehyde. Sorbitol contains six hydroxyl groups. Thus the aldehyde group must be reduced to give the additional hydroxyl group. A reducing agent must be used.

Cytochrome P-450—Oxidative Transformations in the Liver

Foreign compounds, called xenobiotics, and many common drugs are eliminated from the body by metabolic reactions. Water-soluble substances are easily excreted, but most organic compounds are nonpolar. They dissolve only in fatty components of cells and are said to be **lipophilic**. If lipophilic xenobiotics or drugs were not eliminated, they would accumulate, and an organism would eventually become a living (soon dead) "toxic dump".

Organisms ordinarily transform lipophilic substances into more polar water-soluble products, which can be excreted. The metabolic reactions by which drugs are detoxified are usually oxidation reactions. Although the "intent" of biological oxidation is detoxification and elimination of xenobiotics, some pharmaceutical products are converted into active drugs by the same type of process. The body oxidizes these drugs, known as **prodrugs**, into pharmacologically active products.

The oxidation of xenobiotics and drugs occurs primarily in the liver. Other tissues have some metabolizing capabilities, but they are limited to reactions of a small number of substrates. The oxidation of reduced compounds (represented by R—H) in the liver requires molecular oxygen and nicotinamide adenosine dinucleotide phosphate, or NADPH (shown in the figure). One of the oxygen atoms is incorporated in the substrate and the other oxygen atom in water.

$$R{-}H + NADPH + O_2 + H^+ \longrightarrow R{-}OH + NADP^+ + H_2O$$

The enzyme responsible for catalyzing this reaction is cytochrome P-450, an iron-containing heme–protein (see figure). Heme contains an iron atom bound to four nitrogen atoms. The iron atom is coordinatively bonded to oxygen and to the surrounding protein by a nitrogen atom of the amino acid lysine. Cytochrome P-450 has a specific site, called the active site, to which the substrate binds. Then, with the help of NADPH—a coenzyme—the substrate is oxidized by the oxygen molecule bonded to heme iron.

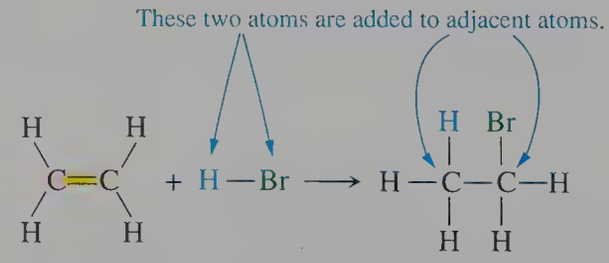
Most enzymes act upon only one molecule, but "cytochrome P-450" actually refers to a family of enzymes, not a single species. It exists in different forms with different three-dimensional shapes. These structural differences account for their broad specificity.

2.13 Other Common Classes of Organic Reactions

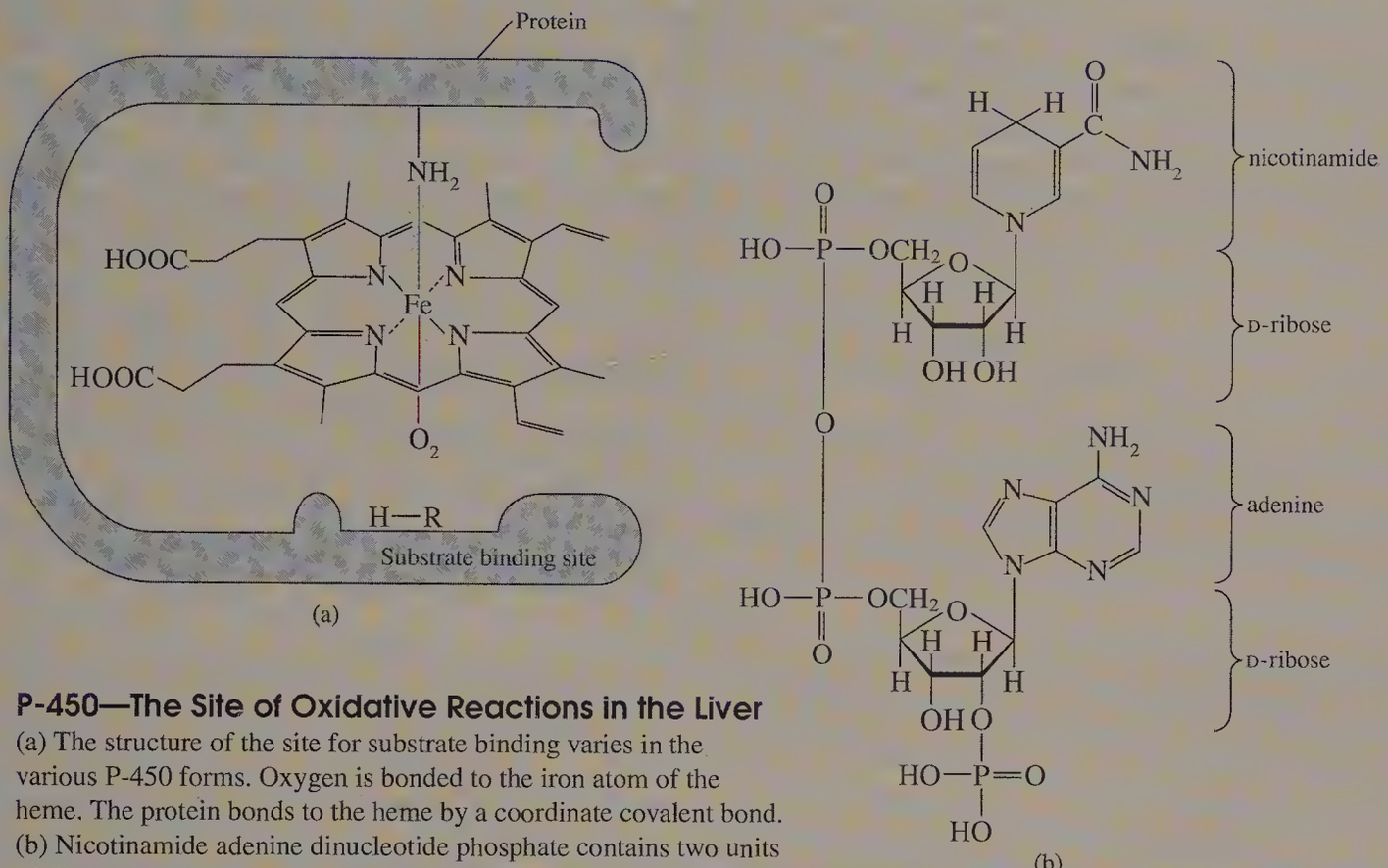
Now we will look at several other classes of organic reactions. These examples represent only a preview of the many reactions that we will consider in much greater detail in subsequent chapters.

Addition Reactions

Addition reactions occur when two reactants combine to give a single product. For example, ethylene reacts with HBr to form bromoethane. The hydrogen and bromide atoms add to adjacent atoms.



Addition reactions occur with many compounds that have multiple bonds. These include not only compounds with a carbon–carbon double bond, but com-

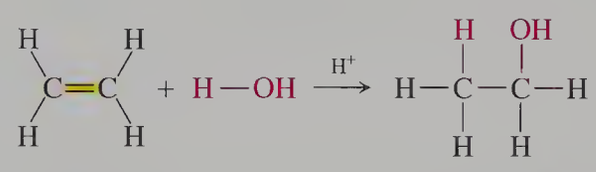


P-450—The Site of Oxidative Reactions in the Liver
(a) The structure of the site for substrate binding varies in the various P-450 forms. Oxygen is bonded to the iron atom of the heme. The protein bonds to the heme by a coordinate covalent bond. (b) Nicotinamide adenine dinucleotide phosphate contains two units of ribose (a carbohydrate), one adenine unit (a nitrogen base found in DNA), and nicotinamide (a vitamin).

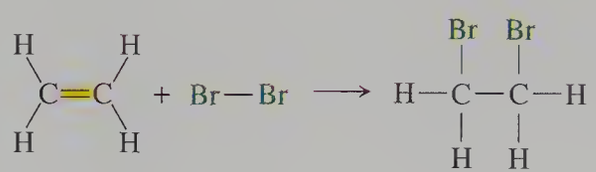
pounds with carbon–oxygen double bonds, carbon–nitrogen double bonds, carbon–carbon triple bonds, and carbon–nitrogen triple bonds as well.

Addition reactions can be subdivided into several types, depending on the reagent that adds to the double (or triple) bond. For example, an addition of a hydrogen halide to a double bond is **hydrohalogenation**. If HBr is the reagent, the reaction is **hydrobromination**. Other examples of reagents and the names of the corresponding addition reactions are

Hydration



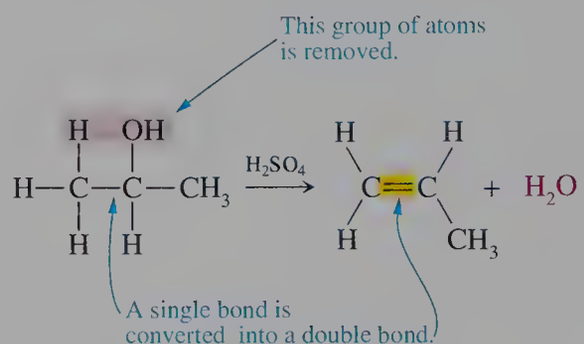
Bromination



Elimination Reactions

An **elimination reaction** is the opposite of an addition reaction. In an elimination reaction, a single compound splits into two products, one of which has a multiple bond. Many elimination reactions form a product with a carbon–carbon double bond containing the majority of the atoms in the reactant. However, carbon–oxygen double bonds, carbon–nitrogen double bonds, carbon–carbon triple bonds, and carbon–nitrogen triple bonds are also formed in elimination reactions.

The second product formed in an elimination reaction is often a smaller molecule such as H_2O or HCl. The atoms eliminated to form the smaller molecule are usually located on adjacent carbon atoms in the reactant. For this reason, the most common type of elimination reactions are called **1,2-elimination reactions**. For example, 2-propanol reacts with concentrated sulfuric acid to produce propene. Water is eliminated in this reaction.



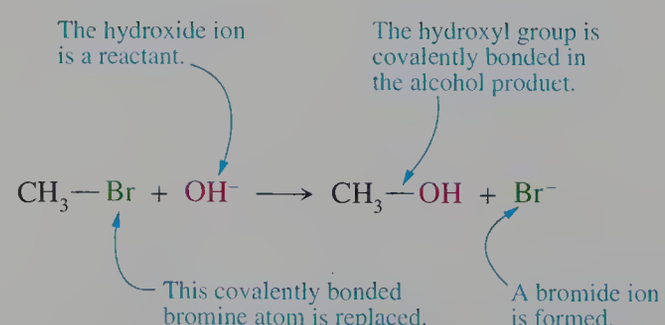
Elimination reactions are often named for the small molecule eliminated. The terminology is similar to that used for addition reactions except the prefix *de-* is used. For example, the elimination of water is **dehydration**; the elimination of a halogen molecule is **dehalogenation** or, in the case of a specific halogen such as bromine, **debromination**.

Substitution Reactions

A **substitution reaction** occurs when one atom or group of atoms supplied by one reagent replaces an atom or group of atoms in a second reagent. A generalized reaction in which Y substitutes for X follows.

$$A{-}X + Y \longrightarrow A{-}Y + X$$

An example of a substitution reaction is the conversion of bromomethane into methanol.



The reaction of methane with chlorine is also a substitution reaction. A chlorine atom replaces a hydrogen atom.

$$CH_3—H + Cl_2 \longrightarrow CH_3—Cl + H—Cl$$

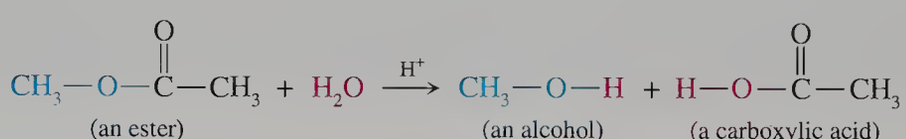
However, we will learn in Chapter 5 that this reaction is very different from the reaction of bromomethane with hydroxide ion. Although not shown by the balanced chemical equation, the reaction of methane with chlorine requires several steps, whereas the reaction of bromomethane with hydroxide occurs in a single step. Thus, seemingly similar types of reactions can differ substantially in the details of the actual steps of making and breaking bonds. The detailed step-by-step pathway from reactants to products in a chemical reaction is called the **reaction mechanism** (Chapter 3).

Hydrolysis Reactions

In **hydrolysis reactions** (Greek *hydro*, water + *lysis*, splitting) a bond is broken by reaction with water. Hydrolysis reactions often split a reactant molecule into two smaller product molecules. In these reactions, the generalized equation is

$$A—B + H_2O \longrightarrow A—H + HO—B$$

One product molecule is bonded to a hydrogen atom derived from water. The other product is bonded to an —OH group derived from water. The hydrolysis of an ester to produce a carboxylic acid and an alcohol is an example of this process.



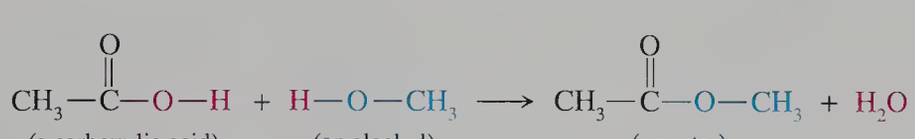
Hydrolysis reactions can be classified in other ways. For example, the hydrolysis of an ester can also be considered a substitution reaction because an —OH group replaces $—OCH_3$ by a reaction at the carbonyl carbon atom.

Condensation Reactions

A **condensation reaction** occurs when two reactants combine to form one larger product. Thus, a bond is formed between certain atoms of the two reactants. Often condensation reactions occur with the simultaneous formation of a second, smaller product such as water. When the second product is water, the reaction is the reverse of a hydrolysis reaction. The general equation for such a reaction is

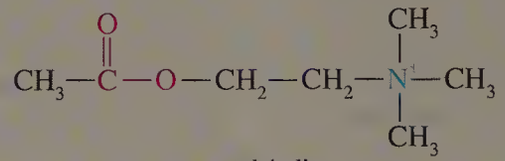
$$A—H + H—O—B \longrightarrow A—B + H_2O$$

An example of this process is the formation of an ester from an alcohol and a carboxylic acid. The reaction is specifically called an **esterification** of a carboxylic acid.

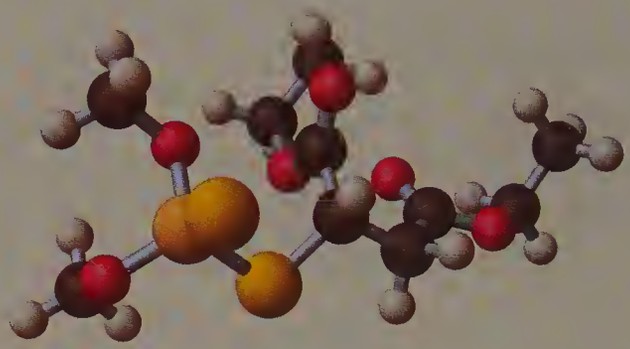


Toxicity of Insecticides

The neurons of animals communicate through chemical messengers called neurotransmitters. Acetylcholine, one of the most important of these messengers, sends signals from motor neurons to muscle cells, causing muscle contraction. Hydrolysis of the ester functional group of acetylcholine, catalyzed by the enzyme acetylcholinesterase, is required to return the muscle to a relaxed state. Any substance that inhibits any of the chemical reactions responsible for muscle control can cause death.



acetylcholine



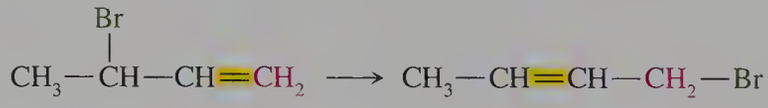
malathion

Some modern insecticides are designed to block the action of acetylcholinesterase and thus disrupt the nervous system of the insect. The insecticide is designed to be as specific as possible, so that only the target species is affected. Because we depend on the same acetylcholinesterase enzyme as insects, some care is required in the design of the insecticide.

The insecticide malathion is deadly to insects but has little effect on mammals. In mammalian tissues, the enzyme carboxyesterase catalyzes the hydrolysis of one ester linkage of malathion to produce ethanol (CH_3CH_2OH) and a nontoxic carboxylic acid. However, insects do not have a high concentration of carboxyesterase, and an alternate reaction occurs. Malathion is catalytically oxidized by an oxidase to give malaoxon. This oxidation product is a more ef-

Rearrangement Reactions

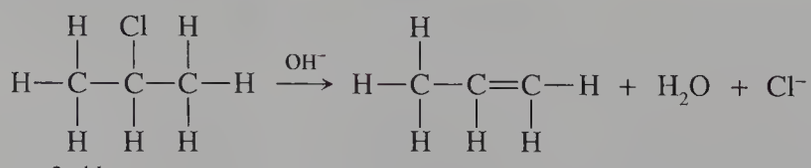
The vast majority of organic reactions occur at functional groups and leave the carbon skeleton unchanged. However, the carbon skeleton changes or functional groups "migrate" from one site in the carbon skeleton to another in some reactions. Reactions that result from the reorganization of bonds within a single reactant to give an isomeric product are called **rearrangement reactions**. In the following rearrangement both the location of a double bond and the position of the bromine atom change.



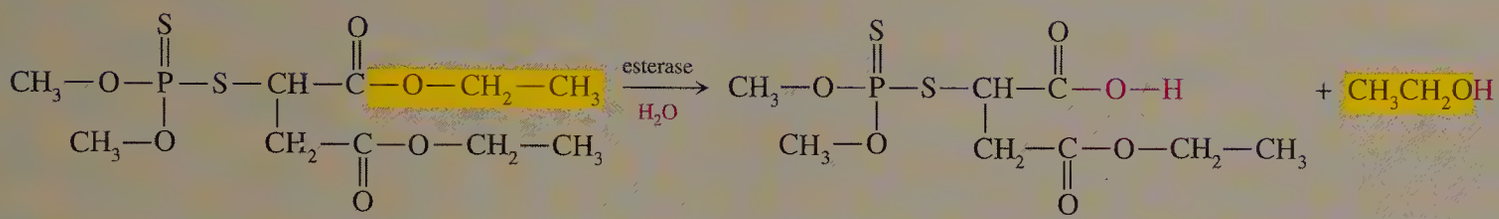
3-bromo-1-butene → 1-bromo-2-butene

Problem 2.32

What general and specific terms can be used to describe the following reaction?



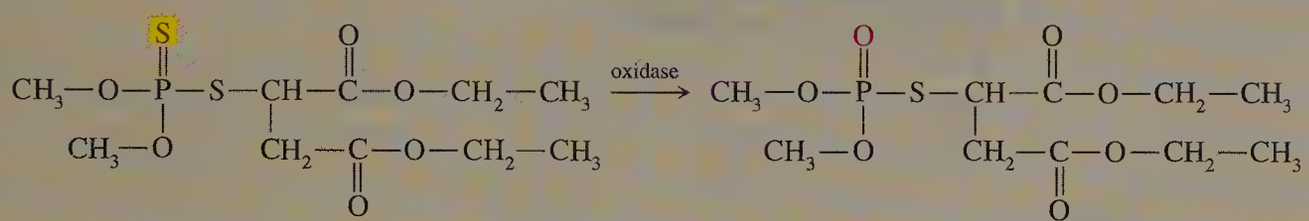
2-chloropropane → propene



malathion

fective inhibitor of acetylcholinesterase than malathion by a factor of 1000. Thus, the insect's own metabolic process produces a poison that causes its demise.

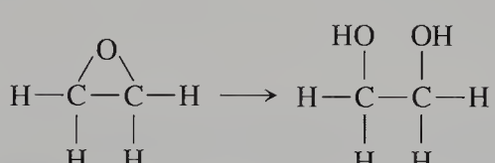
In spite of the difference in the toxicity of malathion to mammals and insects, any insecticide should be used with care, especially around children.



malathion malaoxon

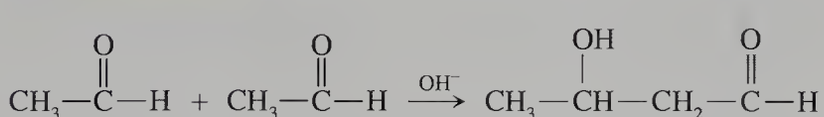
Problem 2.33

The following reaction of ethylene oxide, a cyclic ether, to form ethylene glycol, a compound used as antifreeze, is a hydrolysis reaction even though only one product is produced. Is the classification of this reaction inconsistent with the definition? Could the reaction also be classified as an addition reaction?



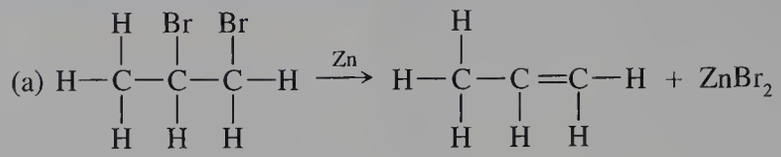
Problem 2.34

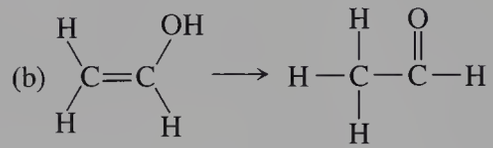
Can the following reaction be classified as a condensation reaction? Explain why or why not.

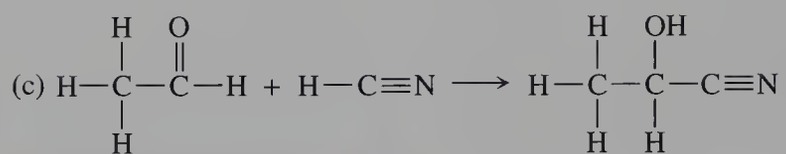


Problem 2.35

Classify each of the following reactions.

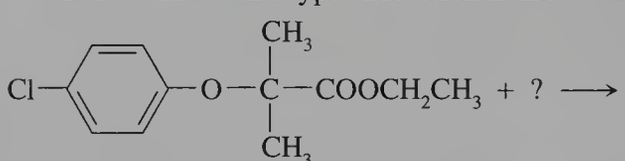
(a) 

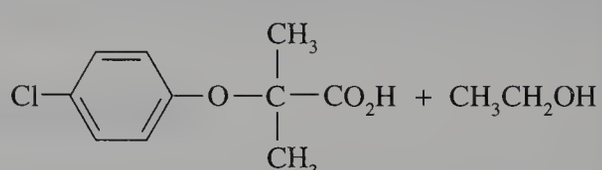
(b) 

(c) 

Problem 2.36

A drug called clofibrate is used to lower triacylglycerol and cholesterol levels in the blood. The following reaction occurs in the body to yield a related compound that is more effective in its action. What type of reaction is this? What reactant is required?



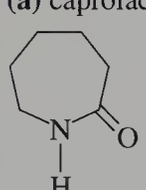


EXERCISES

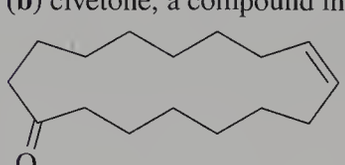
Functional Groups

2.1 Identify the functional groups contained in each of the following structures.

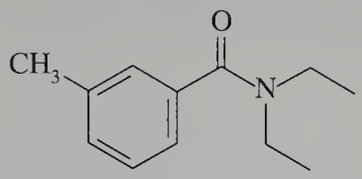
(a) caprolactam, a compound used to produce a type of nylon



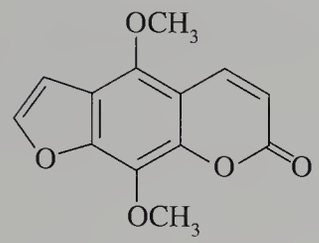
(b) civetone, a compound in the scent gland of the civet cat



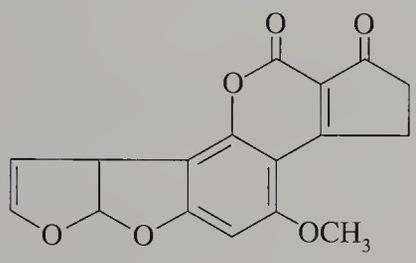
(c) DEET, the active ingredient in some insect repellents



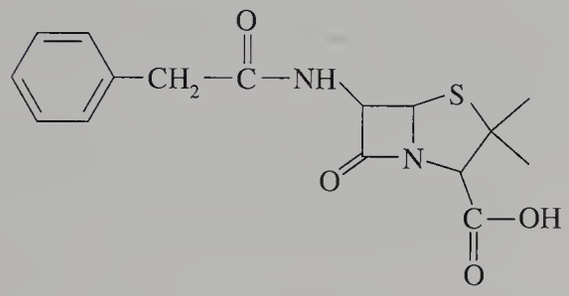
2.2 Identify the oxygen-containing functional groups in each of the following compounds.
(a) isoimpinellin, a carcinogen found in diseased celery



(b) aflatoxin B_1, a carcinogen found in moldy foods



(c) penicillin G, an antibiotic first isolated from a mold.



Molecular Formulas

2.3 Write the molecular formula for each of the following.
(a) $CH_3—CH_2—CH_2—CH_2—CH_3$ (b) $CH_3—CH_2—CH_2—CH_3$ (c) $CH_2=CH—CH_2—CH_3$
(d) $CH_3—CH_2—C\equiv C—H$ (e) $CH_3—CH_2—CH_2—CH=CH_2$ (f) $CH_3—CH_2—C\equiv C—CH_3$

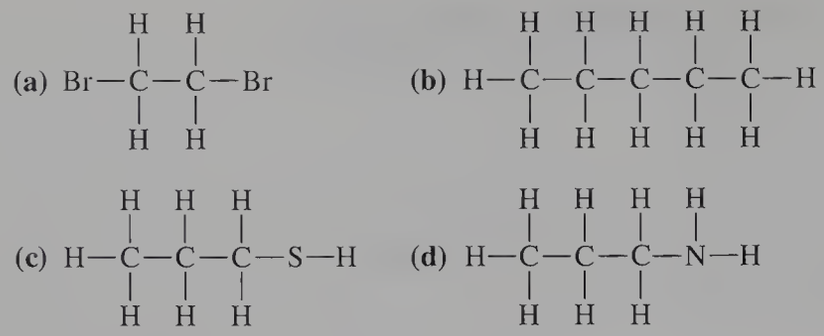
2.4 Write the molecular formula for each of the following.
(a) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ (b) $CH_3CH_2CH_2CH_2CH_2CH_2CH_3$ (c) $CH_3CH_2C\equiv CH$
(d) $CH_3CH_2C\equiv CCH_3$ (e) $CH_3CH_2CH_2CH=CHCH_3$ (f) $CH_2=CHCH_2CH_2CH_3$

2.5 Write the molecular formula for each of the following.
(a) $CH_3—CH_2—CHCl_2$ (b) $CH_3—CCl_2—CH_3$ (c) $Br—CH_2—CH_2—Br$
(d) $CH_3—CHBr—CHBr_2$ (e) $CH_3—CF_2—CH_2F$ (f) $F—CH_2—CHF—CH_2—F$

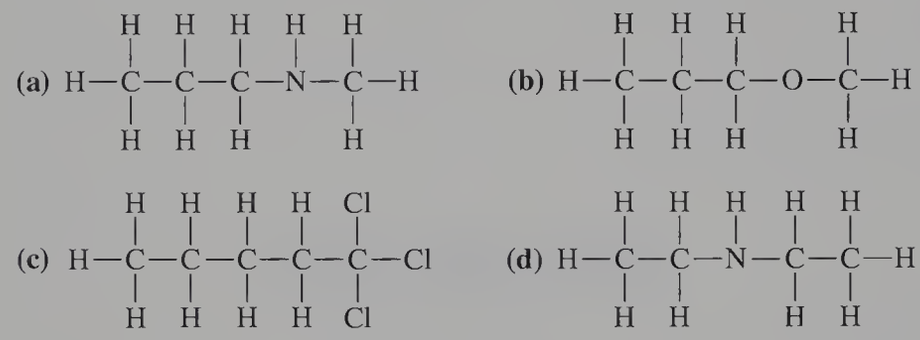
2.6 Write the molecular formula for each of the following.
(a) $CH_3—CH_2—CH_2—OH$ (b) $CH_3—CH_2—O—CH_2—CH_3$ (c) $CH_3—CH_2—SH$
(d) $CH_3—CH_2—S—CH_3$ (e) $CH_3—CH_2—CH_2—NH_2$ (f) $CH_3—CH_2—NH—CH_3$

Condensed Structural Formulas

2.7 For each of the following, write a condensed structural formula in which only the bonds to hydrogen are not shown.



2.8 For each of the following, write a condensed structural formula in which only the bonds to hydrogen are not shown.



2.9 Write a condensed structural formula in which no bonds are shown for each substance in Exercise 2.7.

2.10 Write a condensed structural formula in which no bonds are shown for each substance in Exercise 2.8.

2.11 Write a complete structural formula, showing all bonds, for each of the following condensed formulas.

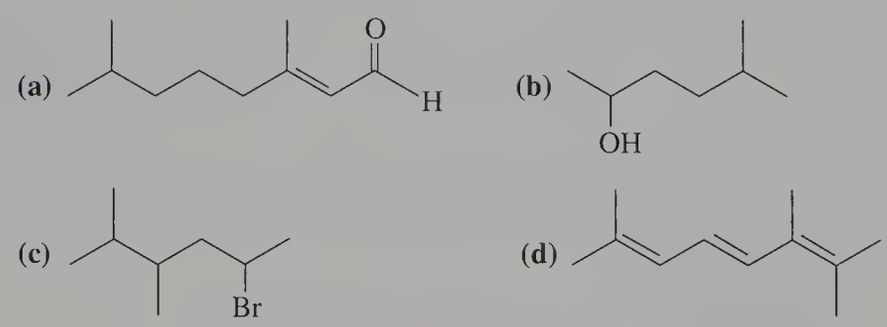
(a) $CH_3CH_2CH_2CH_3$ **(b)** $CH_3CH_2CH_2Cl$ **(c)** $CH_3CHClCH_2CH_3$
(d) $CH_3CH_2CHBrCH_3$ **(e)** $CH_3CH_2CHBr_2$ **(f)** $CH_3CBr_2CH_2CH_2CH_3$

2.12 Write a complete structural formula, showing all bonds, for each of the following condensed formulas.

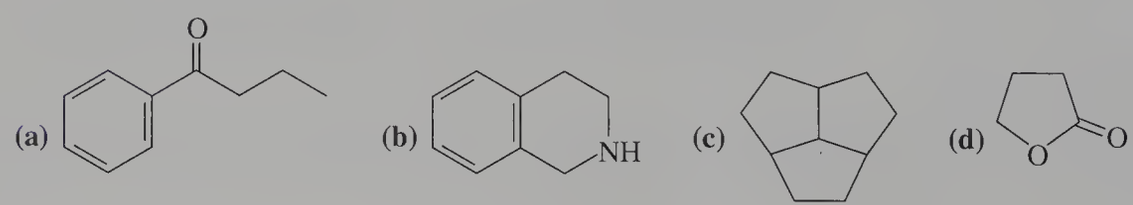
(a) $CH_3CH_2CH_3$ **(b)** $CH_3CH_2CHCl_2$ **(c)** $CH_3CH_2CH_2CH_2SH$
(d) $CH_3CH_2C{\equiv}CCH_3$ **(e)** $CH_3CH_2OCH_2CH_2CH_3$ **(f)** $CH_3CH_2CH_2C{\equiv}CH$

Bond-Line Structures

2.13 What is the molecular formula for each of the following bond-line representations?

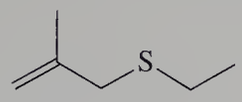


2.14 What is the molecular formula for each of the following bond-line representations?

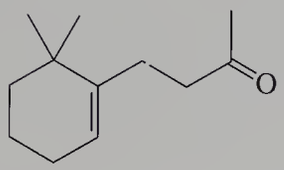


2.15 What is the molecular formula for each of the following bond-line representations?

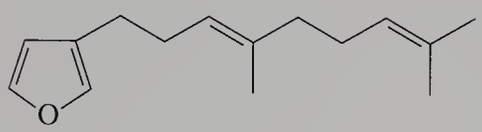
(a) a scent marker of the red fox



(b) a compound responsible for the odor of the iris

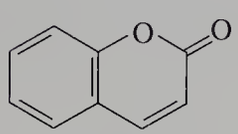


(c) a defense pheromone of some ants

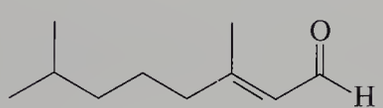


2.16 What is the molecular formula for each of the following bond-line representations?

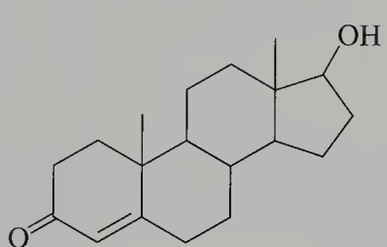
(a) a compound found in clover and grasses



(b) an oil found in citrus fruits

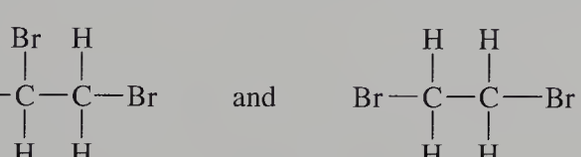


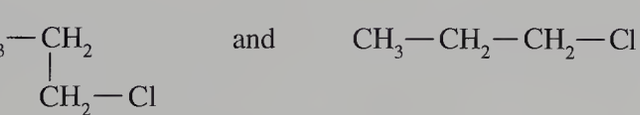
(c) a male sex hormone



Isomerism

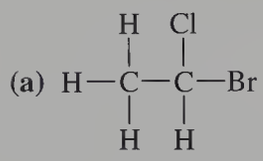
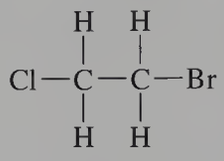
2.17 Indicate whether the following pairs of structures are isomers or different representations of the same compound.

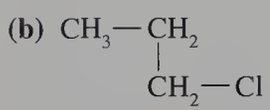
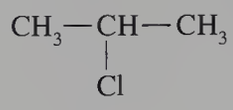
(a)  and

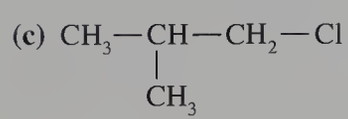
(b) 

(c) 

2.18 Indicate whether the following pairs of structures are isomers or different representations of the same compound.

(a)  and 

(b)  and 

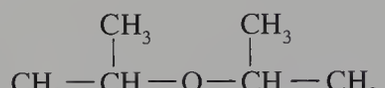
(c)  and 

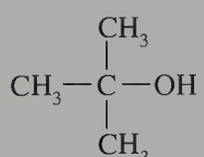
2.19 There are two isomers for each of the following molecular formulas. Draw their structural formulas.
(a) $C_2H_4Br_2$ **(b)** C_2H_6O **(c)** C_2H_4BrCl
(d) C_3H_7Cl **(e)** C_2H_7N **(f)** $C_2H_3Br_3$

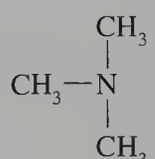
2.20 There are three isomers for each of the following molecular formulas. Draw their structural formulas.
(a) $C_2H_3Br_2Cl$ **(b)** C_3H_8O **(c)** C_3H_8S

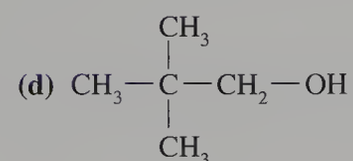
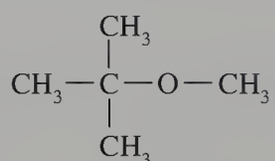
Physical Properties

2.21 Suggest a reason for the difference in boiling points for each of the following isomeric pairs of compounds. (Several structural features may be responsible.)

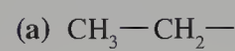
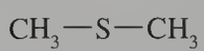
(a)  bp 90.5 °C and  bp 68 °C

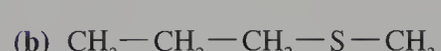
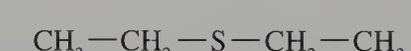
(b)  bp 117.7 °C and  bp 82.5 °C

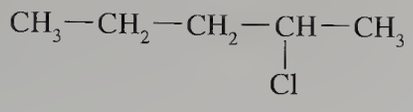
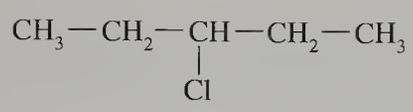
(c)  bp 49 °C and  bp 3 °C

(d)  bp 113 °C and  bp 55 °C

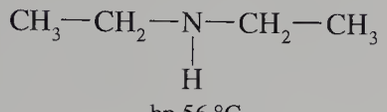
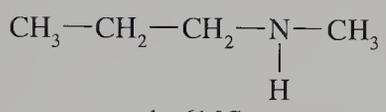
2.22 Explain why the boiling points of the isomeric compounds of the following pairs are very similar.

(a)  bp 35 °C and  bp 37 °C

(b)  bp 95.5 °C and  bp 92.1 °C

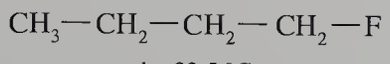
(c)  and 

bp 96.9 °C bp 97.8 °C

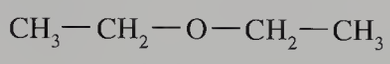
(d)  and 

bp 56 °C bp 61 °C

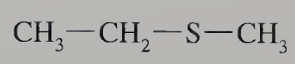
2.23 Suggest reasons for the order of boiling points for the following compounds.



bp 32.5 °C
I

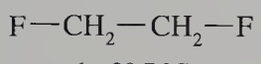


bp 34.6 °C
II

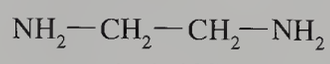


bp 66.6 °C
III

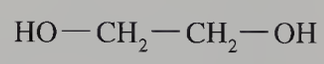
2.24 Suggest reasons for the order of boiling points for the following compounds.



bp 30.7 °C
I

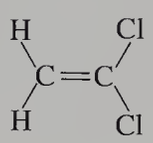


bp 116 °C
II

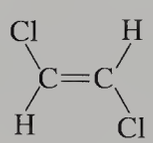


bp 190 °C
III

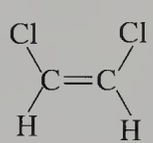
2.25 The ethene molecule is planar, and all bond angles are close to 120°. There are three isomeric dichloroethenes. Two isomers have dipole moments, and the third does not. Which of the following three is nonpolar? Explain why.



I

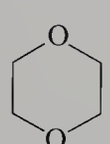


II

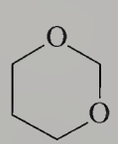


III

2.26 One of the following compounds has a dipole moment and the other does not. Select the polar compound and explain why the other compound has no dipole moment.

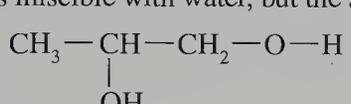


I

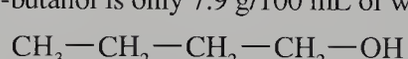


II

2.27 Propylene glycol is miscible with water, but the solubility of 1-butanol is only 7.9 g/100 mL of water. Explain why.

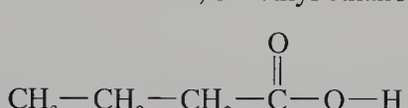


propylene glycol

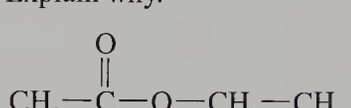


1-butanol

2.28 Butanoic acid is miscible with water, but ethyl ethanoate is not. Explain why.

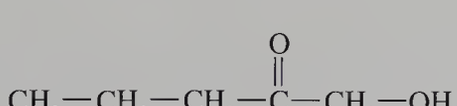


butanoic acid

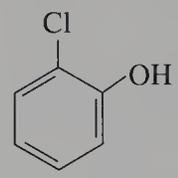


ethyl ethanoate

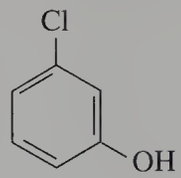
2.29 The boiling point of the following compound is 152°C. Compare this value to those of two of its isomers (Section 2.8) and determine whether intermolecular or intramolecular hydrogen bonds are responsible for its boiling point.



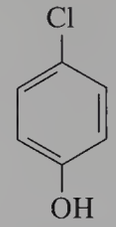
2.30 The boiling points of three isomeric chlorophenols are listed below. What do these data indicate about the type of hydrogen bonding present in these molecules?



bp 175 °C



bp 214 °C



bp 220 °C

Conjugate Acids and Bases

2.31 Write the structure of the conjugate acid of each of the following species.

(a) H—O—O—H **(b)** NH_2—NH_2 **(c)** CH_3—S—CH_3

(d) CH_3—O—CH_3 **(e)** CH_3—NH_2 **(f)** CH_3—OH

2.32 Write the structure of the conjugate base of each of the following species.

(a) CH_3—SH **(b)** CH_3—NH_2 **(c)** CH_3—O—SO_3H

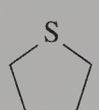
(d) CH_2=CH_2 **(e)** CH≡CH **(f)** CH_3—CN

2.33 Write the structure of the conjugate acid of each of the following species.

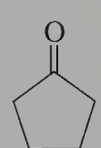
(a) H_2C=O **(b)** CH_3—NH—CH_3 **(c)** CH_2=NH **(d)** CH_3—C(=O)—OH

2.34 Write the structure of the conjugate acid of each of the following species.

(a) 

(b) 

(c) 

(d) 

Lewis Acids and Bases

2.35 Identify the Lewis acid and Lewis base in each of the following reactions.

(a) CH_3—CH_2—Cl + $AlCl_3$ ⟶ CH_3—CH_2^+ + $AlCl_4^-$

(b) CH_3—CH_2—SH + CH_3—O^- ⟶ CH_3—CH_2—S^- + CH_3—OH

(c) CH_3—CH_2—OH + NH_2^- ⟶ CH_3—CH_2—O^- + NH_3

(d) $(CH_3)_2N^-$ + CH_3—OH ⟶ $(CH_3)_2NH$ + CH_3—O^-

2.36 Identify the Lewis acid and Lewis base in each of the following reactions.

(a) $(CH_3)_2O$ + HI ⟶ $(CH_3)_2OH^+$ + I^-

(b) CH_3—CH_2^+ + H_2O ⟶ CH_3—CH_2—OH_2^+

(c) CH_3—CH=CH_2 + HBr ⟶ $(CH_3)_2CH^+$ + Br^-

(d) CH_3—C≡CH + CH_3—NH^- ⟶ CH_3—C≡C^- + CH_3—NH_2

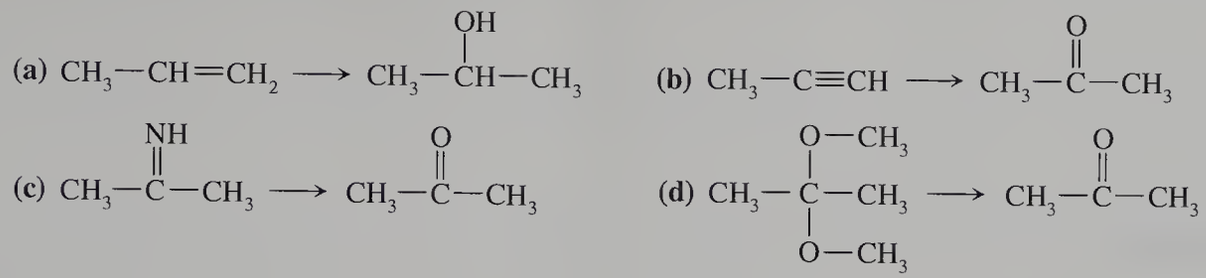
Oxidation–Reduction Reactions

2.37 Determine if each of the following transformations given by unbalanced equations involves oxidation, reduction, or neither.

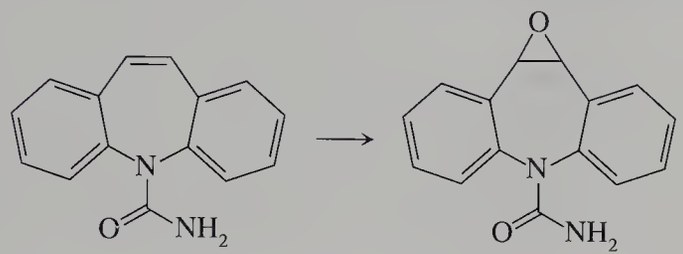
(a) CH_3—C≡N ⟶ CH_3—CH_2—NH_2 **(b)** 2 CH_3—SH ⟶ CH_3—S—S—CH_3

(c) CH_3—S—CH_3 ⟶ CH_3—S(=O)—CH_3 **(d)** CH_3—S(=O)(=O)—CH_3 ⟶ CH_3—S(=O)—CH_3

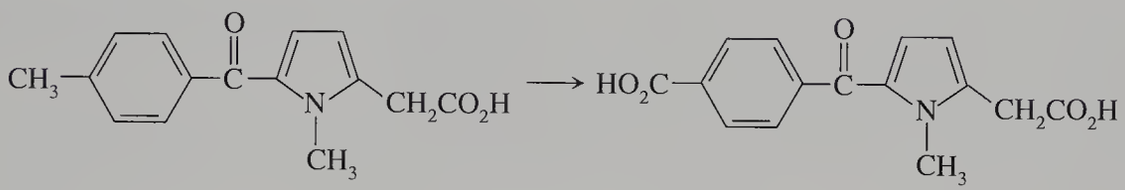
2.38 None of the following reactions involve oxidation or reduction, although they may appear to be redox reactions. Explain why.



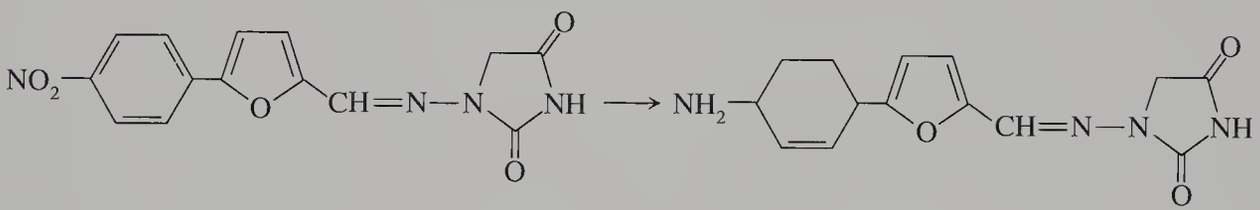
2.39 Consider each of the following reactions for the metabolism of drugs. Is oxidation or reduction involved?
(a) carbamazepine, an anticonvulsant



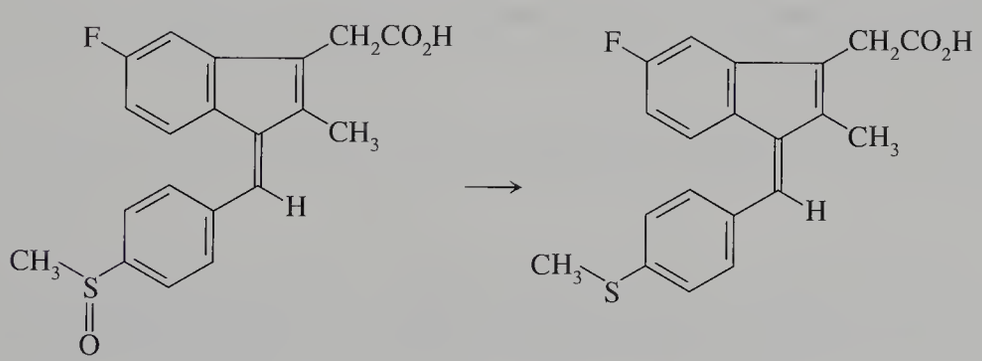
(b) tolmetin, an anti-inflammatory drug



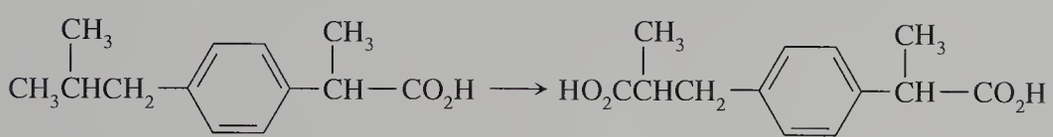
(c) dantrolene, a muscle relaxant



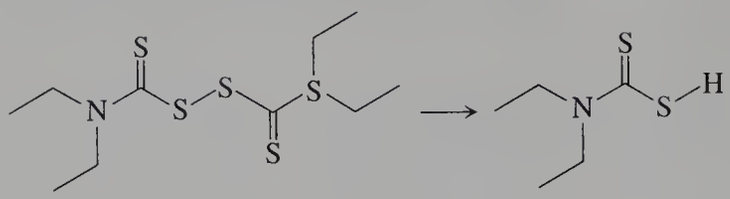
2.40 Consider each of the following reactions for the metabolism of drugs. Is oxidation or reduction involved?
(a) sulindac, an anti-inflammatory drug



(b) ibuprofen, an analgesic



(c) disulfiram, a drug used in treating alcoholism



Types of Reactions

2.41 Classify the type of reaction represented by each of the following unbalanced equations. Identify any additional reagents required for the reaction or any additional products formed.

(a) $CH_3-\overset{\overset{O}{\|}}{C}-CH_3 \longrightarrow CH_3-\overset{\overset{OH}{|}}{\underset{\underset{OCH_3}{|}}{C}}-CH_3$

(b) $CH_3-CH_2-Br \longrightarrow CH_3-CH_2-CN$

(c) $\begin{matrix} CH_2-CH-OH \\ | \quad\quad | \\ CH_2-CH_2 \end{matrix} \longrightarrow \begin{matrix} CH_2-CH \\ | \quad\quad \| \\ CH_2-CH \end{matrix}$

(d) $CH_3-C\equiv CH \longrightarrow CH_2=C=CH_2$

2.42 Classify the type of reaction represented by each of the following unbalanced equations. Identify any additional reagents required for the reaction or any additional products formed.

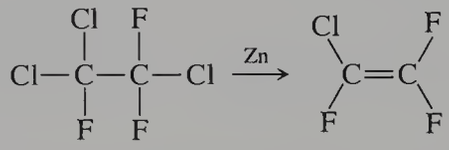
(a) $2\,CH_3-CH_2-O-H \longrightarrow CH_3-CH_2-O-CH_2-CH_3$

(b) $CH_3-\overset{\overset{O}{\|}}{C}-S-CH_3 \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-S-H + CH_3OH$

(c) $CH_3-\overset{\overset{OH}{|}}{\underset{\underset{OCH_3}{|}}{C}}-CH_3 \longrightarrow CH_3-\overset{\overset{OCH_3}{|}}{\underset{\underset{OCH_3}{|}}{C}}-CH_3$

(d) $CH_3-CH=CH_2 \longrightarrow CH_3-\overset{\overset{OH}{|}}{CH}-CH_3$

2.43 The following reaction is used in industry to prepare the monomer chlorotrifluoroethylene, which is used to produce a polymer. What type of reaction occurs? What is the by-product of the reaction?

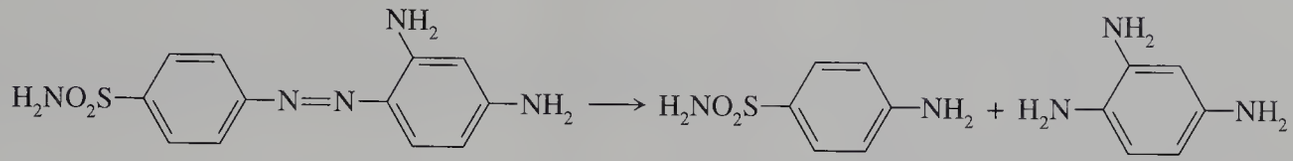


2.44 The following reaction is used in industry to prepare isoprene, which is converted into polymers used for the manufacture of rubber products. What type of reaction occurs? What is the by-product of the reaction?

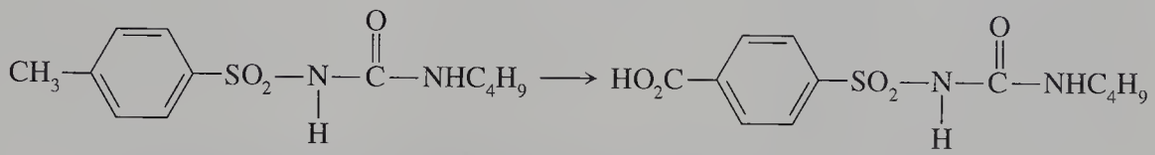
$$CH_2=\overset{\overset{CH_3}{|}}{C}-CH_2-CH_3 \longrightarrow CH_2=\overset{\overset{CH_3}{|}}{C}-CH=CH_2$$

isoprene

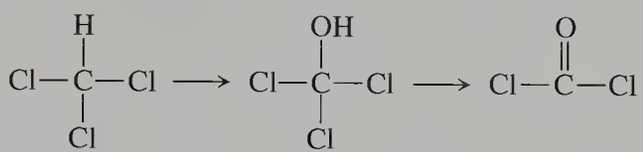
2.45 The antibacterial prontosil, a prodrug, is metabolized to produce sulfanilamide, an antibacterial compound. What type of reaction occurs to produce sulfanilamide?



2.46 Tolbutamide, a hypoglycemic agent used to lower blood sugar in diabetics, is metabolized in a series of steps to the indicated product. How is the net overall reaction classified?

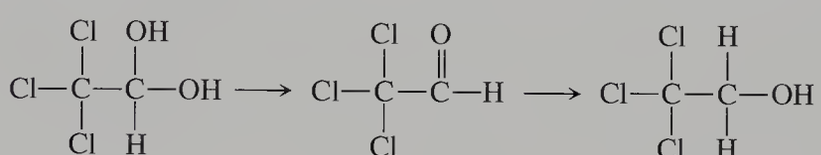


2.47 Chloroform is metabolized via an intermediate to phosgene, a compound that causes liver damage. What type of reactions are involved in the formation and decomposition of the intermediate?



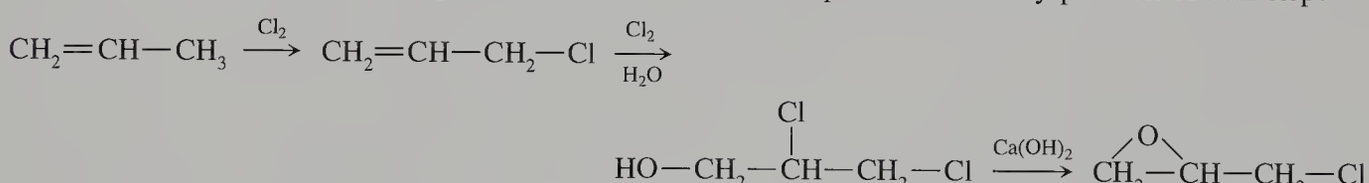
chloroform phosgene

2.48 The sedative-hypnotic chloral hydrate is metabolized as follows. What type of reaction occurs in each step?



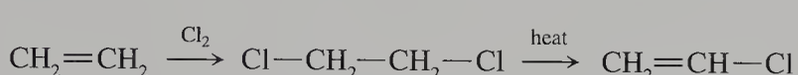
chloral hydrate

2.49 The following series of reactions is used as an industrial synthesis of epichlorohydrin, a compound used in the production of epoxy resins. What type of reaction occurs in each step? What are the by-products of each step?

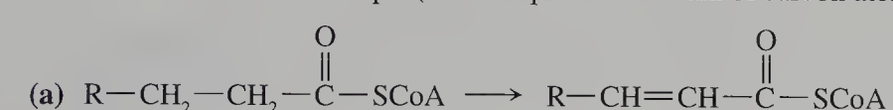


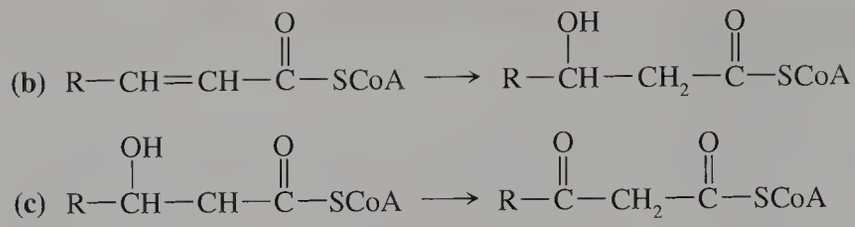
epichlorohydrin

2.50 The following series of reactions is used as an industrial synthesis of vinyl chloride, a compound used in the production of polyvinyl chloride (PVC). What type of reaction occurs in each step? What are the by-products of each step?

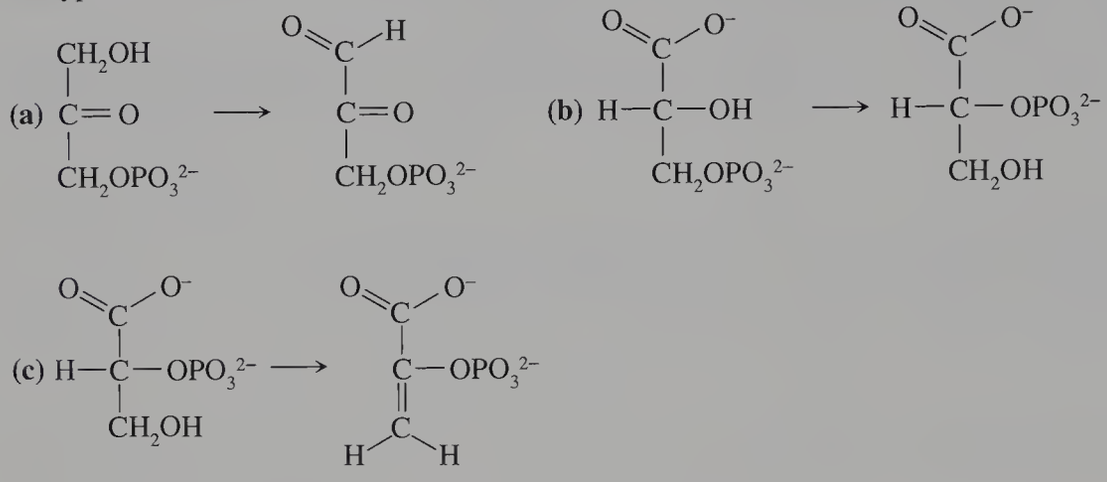


2.51 The metabolism of fatty acids (long-chain carboxylic acids) involves several steps. Indicate the type of reaction involved in three of these steps. (The R represents a chain of carbon atoms. The CoA represents coenzyme A.)

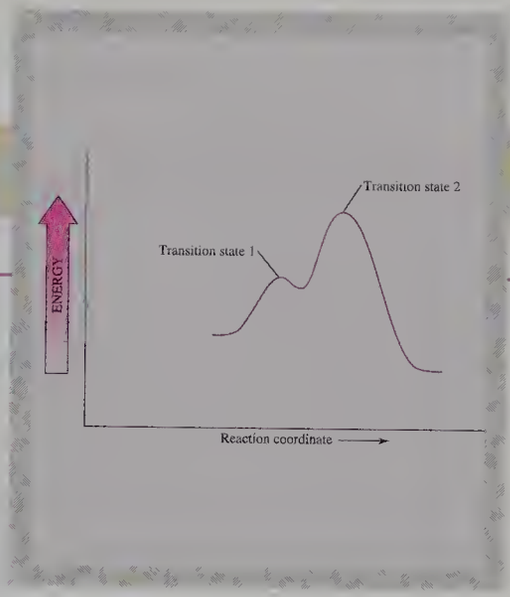




2.52 A series of ten steps involved in glycolysis (metabolism of glucose) includes the following three steps. Indicate the type of reaction involved in each step.



3



Chemical Energetics

3.1 Equilibria and Thermodynamics

In principle, all chemical reactions are reversible, and given sufficient time an equilibrium is established. That is, the reaction and its reverse reaction will occur at equal rates. The extent to which reactants are converted to products is expressed by an equilibrium constant. The quantitative aspects of chemical equilibria are reviewed in Section 3.2. Acid–base reactions of organic compounds, which relate the effect of structure on the position of an equilibrium, are quantitatively considered in Section 3.3.

Next we will see that the equilibrium constant for a reaction reflects the relative energies of the reactants and products. The difference in energy between products and reactants is the "force" that "drives" a reaction to a specific equilibrium system. Thermodynamics tells us how this driving force, called the free energy, is partitioned between the potential energy change, the enthalpy, and a change in the molecular order, or entropy, of the system.

Thermodynamics does not provide information about the required experimental conditions for a reaction, nor can it predict how fast the reaction will occur. The study of the speed, or rate, of chemical reactions is called **kinetics**. Kinetic studies help us determine the step-by-step path or **mechanism** of reactions. A reaction mechanism describes the sequence of bond cleavage and bond formation during the reaction and the energy associated with those steps. The establishment of a reaction mechanism for a reaction is a powerful tool in understanding organic chemistry.

3.2 Chemical Equilibrium

For a general chemical reaction at equilibrium, where A and B are reactants, X and Y are products, and m, n, p, and q are their respective stoichiometric coefficients, the value of the equilibrium constant expression is a constant at a specific temperature.

The brackets indicate molar concentrations, and the exponents are the coefficients in the balanced chemical equation.

$$m\,A + n\,B \underset{\text{reverse reaction}}{\overset{\text{forward reaction}}{\rightleftharpoons}} p\,X + q\,Y$$

$$\frac{[X]^p[Y]^q}{[A]^m[B]^n} = K_{eq}$$

Position of Equilibrium

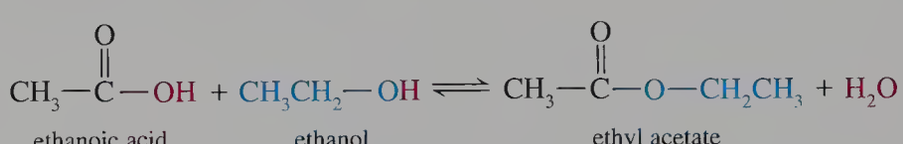
The equilibrium constant, K_{eq}, is a measure of the intrinsic tendency of a chemical reaction to go from reactants to products in the direction written. If $K_{eq} \gg 1$, little reactant is present at equilibrium, and the reaction has a large tendency to occur. If $K_{eq} \ll 1$, little product is present at equilibrium, and the reaction has a small tendency to occur in the direction written. Consider the equilibrium constant for the addition reaction of gaseous ethylene and gaseous hydrogen bromide at 25 °C.

$$CH_2{=}CH_2 + HBr \rightleftharpoons CH_3{-}CH_2{-}Br$$

$$\frac{[CH_3CH_2Br]}{[CH_2{=}CH_2][HBr]} = K_{eq} = 10^8$$

Because the equilibrium constant is very large, almost no reactant remains at equilibrium. That is, the reaction is quantitative. Reactions with equilibrium constants greater than 10^4 are quantitative because the amount of reactant remaining at equilibrium is about 0.01% or less.

The condensation reaction of ethanoic acid (acetic acid) and ethanol (ethyl alcohol) to produce ethyl ethanoate (ethyl acetate) at 25 °C is not quantitative.

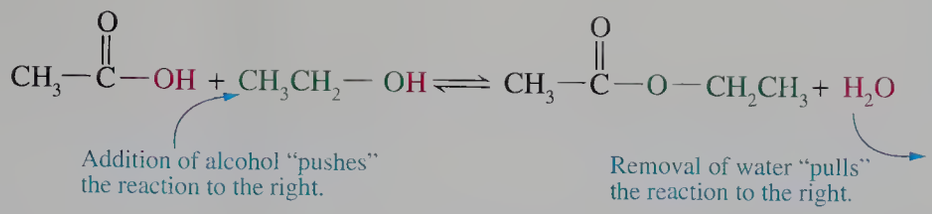


$$\frac{[CH_3CO_2CH_2CH_3][H_2O]}{[CH_3CO_2H][CH_3CH_2OH]} = K = 4.0$$

In this reaction, significant concentrations of reactants are present at equilibrium. Thus, the amount of product is significantly less than 100%.

Le Châtelier's Principle

Le Châtelier's principle states that a change in the conditions of a chemical system at equilibrium alters the concentrations of reactants and products, and a new equilibrium system results. For example, if more reactant is added to a reaction at equilibrium, the concentrations of both reactants and products change to reestablish the equilibrium and the equilibrium constant remains unchanged. After adding reactant, the total concentration of reactant is initially increased, but then decreases to establish a new equilibrium concentration. As a result, the concentration of the product increases. In short, the change imposed on the system by adding reactant is offset when some of the added reactant is converted to product. If a product is removed from a chemical system at equilibrium, the forward reaction occurs to give more product. Consider the equilibrium in the formation of ethyl ethanoate.



If water is removed from the system, the equilibrium is disturbed and more of the ethanoic acid and ethanol are converted into ethyl ethanoate. If the amount of ethanol is increased, a larger amount of ethanoic acid will also be converted into product.

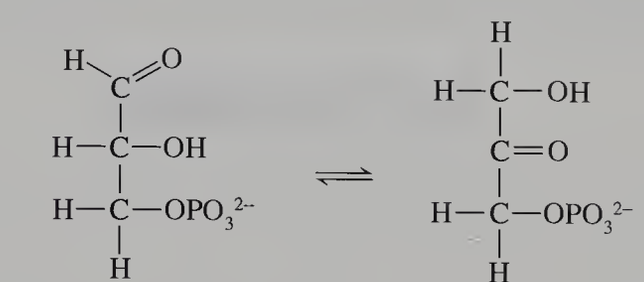
Problem 3.1

Chloromethane reacts in a substitution reaction with sodium hydroxide in aqueous solution to produce methanol and sodium chloride. Write the equilibrium constant expression for this substitution reaction. The equilibrium constant is 5×10^{16}. Is the reaction quantitative?

$$OH^-(aq) + CH_3Cl(aq) \rightleftharpoons CH_3OH(aq) + Cl^-(aq)$$

Problem 3.2

Consider the following equilibrium between glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, a step in the metabolism of glucose. At equilibrium, approximately 96% of the material is present as dihydroxyacetone phosphate. Calculate the equilibrium constant.



glyceraldehyde 3-phosphate dihydroxyacetone phosphate

Sample Solution

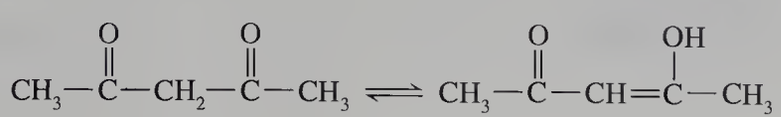
The amount of glyceraldehyde 3-phosphate is 4%. Molar concentrations must be used in the equilibrium constant expression. However, the order of the concentration terms in the equilibrium constant expression is the same. Thus, the ratio of the concentrations is the same as the ratio of the percent composition of the two components.

$$K = \frac{[\text{dihydroxyacetone phosphate}]}{[\text{glyceraldehyde 3-phosphate}]} = \frac{\%\ \text{dihydroxyacetone phosphate}}{\%\ \text{glyceraldehyde 3-phosphate}}$$

$$= \frac{96\%}{4\%} = 24$$

Problem 3.3

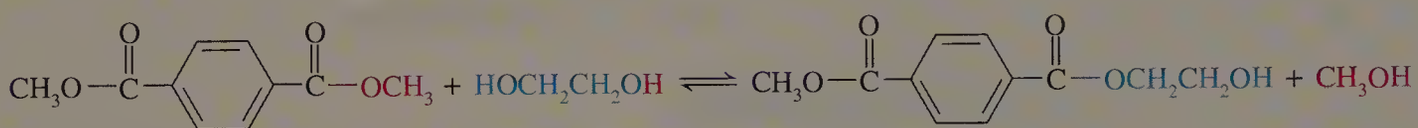
The equilibrium constant for the following rearrangement reaction, known as an enolization reaction, is 5. Calculate the percent composition of the equilibrium mixture.



Le Châtelier's Principle in Industrial Chemistry

For economic reasons, the most desirable reactions for industry are those with large equilibrium constants. Otherwise it is necessary to isolate the product from the reactant, a process that increases the overall cost of the product. However, it is often possible to select reaction conditions that easily drive the reaction to product. Consider the first step in the polymerization reaction to give the polyester Dacron. This step has an equilibrium constant close to 1.

However, the reaction is carried out at 140 °C and the methanol, which has the lowest boiling point of all of the components, is vaporized. Because one of the products is removed, the reaction is driven to the right. The high molecular weight product continues to react to give a polymer. The hydroxyl group reacts with another molecule of dimethyl phthalate and releases another molecule of methanol, which is also vaporized under the reaction conditions. Thus the polymerization process continues even though the reactions do not have large equilibrium constants.



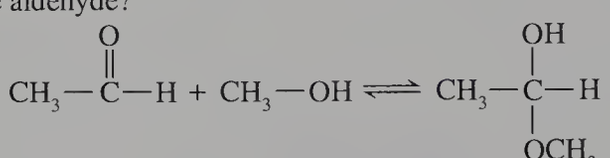
dimethyl phthalate
bp 283 °C

ethylene glycol
bp 198 °C

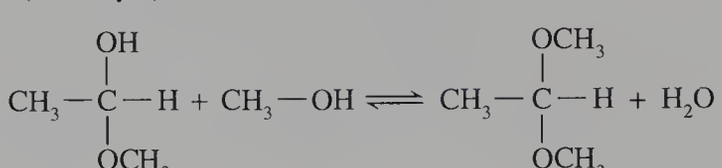
methanol
bp 65 °C

Problem 3.4

Aldehydes react with alcohols and are converted into hemiacetals and acetals by two equilibrium reactions. What experimental conditions would increase the yield of the acetal derived from the aldehyde?



(an aldehyde) (a hemiacetal)



(an acetal)

3.3 Equilibria in Acid–Base Reactions

The strengths of acids are measured by their tendencies to transfer protons to water, which we regard as the reference solvent. Weak acids do not transfer their protons completely to water, and produce a low concentration of ions. Strong acids ionize completely.

K_a and pK_a

The acidity of an acid with the general formula HA is given by the equilibrium constant for ionization, obtained from the equation for ionization.

$$K = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$$

The concentration of water, about 55 M, is so large compared to that of the other components of the equilibrium mixture that its value changes very little when the acid HA is added. Therefore, the concentration of water is included in the acid ionization constant, K_a.

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

Acids with $K_a > 10$ are strong acids. Most organic acids have $K_a < 10^{-4}$ and are weak acids. Acid dissociation constants are often expressed as pK_a values, where $pK_a = -\log K_a$. Note that the pK_a values increase as the acidity (K_a) decreases. The acid ionization constants of some acids are given in Table 3.1.

An example of a weak organic acid is ethanoic acid (acetic acid), some of which ionizes in water to give an ethanoate ion (acetate ion) and a hydronium ion.

$$\underset{\text{weaker acid}}{CH_3CO_2H} + H_2O \rightleftharpoons CH_3CO_2^- + \underset{\text{stronger acid}}{H_3O^+}$$

Ethanoic acid is a weaker acid than H_3O^+, and ethanoate ($CH_3CO_2^-$) is a stronger base than H_2O. The equilibrium between an acid and a base on the one hand, and their respective conjugate base and acid on the other, can be viewed as a "contest", where the goal is to gain a proton. A strong acid, with its great tendency to lose protons, has a weak conjugate base that has a low affinity for protons. Thus, as the tendency of an acid to lose a proton increases, the tendency of its conjugate base to accept a proton decreases. At equilibrium, the favored "side" of an acid–base reaction has the weaker acid and weaker base.

TABLE 3.1
K_a and pK_a Values of Inorganic and Organic Acids

Acid	K_a	pK_a
HBr	10^9	−9
HCl	10^7	−7
H_2SO_4	10^5	−5
HNO_3	10^1	−1
HF	6×10^{-4}	3.2
CH_3CO_2H	2×10^{-5}	4.7
$(CF_3)_3COH$	2×10^{-5}	4.7
CH_3CH_2SH	3×10^{-11}	10.6
CF_3CH_2OH	4×10^{-13}	12.4
CH_3OH	3×10^{-16}	15.5
$(CH_3)_3COH$	1×10^{-18}	18
CCl_3H	10^{-25}	25
$HC{\equiv}CH$	10^{-25}	25
NH_3	10^{-36}	36
$CH_2{=}CH_2$	10^{-44}	44
CH_4	10^{-49}	49

K_b and pK_b

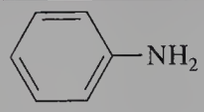
Basicity of bases is qualitatively and quantitatively compared to the properties of water. A base, A^-, removes a proton from water to form hydroxide ion and the conjugate acid HA. The base dissociation constant, K_b, for the reaction is

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

$$K_b = K_{eq}[H_2O] = \frac{[HA][OH^-]}{[A^-]}$$

The K_b values of bases are conveniently expressed as pK_b values, where $pK_b = -\log K_b$. The pK_b values increase with decreasing basicity. The K_b and pK_b values of some organic bases are listed in Table 3.2. A strong base has a large K_b (small pK_b) and

TABLE 3.2
K_b and pK_b of Bases

Base	K_b	pK_b
	4×10^{-10}	9.4
$CH_3CO_2^-$	5×10^{-10}	9.3
CN^-	1.6×10^{-5}	4.8
NH_3	1.7×10^{-5}	4.8
CH_3NH_2	4.3×10^{-4}	3.4
CH_3O^-	3.3×10^{1}	−1.5

completely removes the proton of an acid. The most common strong base is hydroxide ion, which will remove and accept protons from even weak acids, such as ethanoic acid.

$$CH_3CO_2H + \underset{\text{strong base}}{HO^-} \rightleftharpoons \underset{\text{weak base}}{CH_3CO_2^-} + H_2O$$

Weak bases do not have a large attraction for the protons of an acid. A small fraction of the molecules of a weak base accept protons at equilibrium. For example, methylamine is a weak base. When it dissolves in water, a low concentration of methylammonium ions forms.

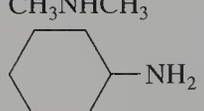
$$\underset{\text{weak base}}{CH_3NH_2} + H_2O \rightleftharpoons CH_3NH_3^+ + \underset{\text{strong base}}{OH^-}$$

The strengths of bases such as amines are often listed using the pK_a values of their conjugate acids. Since a strong base (large K_b and small pK_b) holds a proton more tightly, its corresponding conjugate acid is a weak acid (small K_a and large pK_a). This relationship between the pK_a and pK_b for a conjugate acid–base pair is given by the following relationships.

$$K_a \times K_b = 1 \times 10^{-14} \quad \text{and} \quad pK_a + pK_b = 14$$

The pK_a values of the ammonium ions of some simple amines are given in Table 3.3. The structure of the groups attached to the nitrogen atom for these amines has little effect on these values, which are in the 10 to 11 range.

TABLE 3.3
Basicity of Amines and Acidity of Ammonium Ions

Compound	K_b	K_a	pK_b	pK_a
NH_3	1.8×10^{-5}	5.5×10^{-10}	4.74	9.26
CH_3NH_2	4.6×10^{-4}	2.2×10^{-11}	3.34	10.7
$CH_3CH_2NH_2$	4.8×10^{-4}	2.1×10^{-11}	3.20	10.8
CH_3NHCH_3	4.7×10^{-4}	2.1×10^{-11}	3.20	10.8
	4.6×10^{-4}	2.2×10^{-11}	3.34	10.66

Use of pK_a Values

Many organic reactions occur by one or more steps in which a proton is added to a basic site or is removed from an acidic site. It is important to be able to predict the position of an acid–base reaction from the pK_a values of the two acids involved. The equilibrium constant for the general equilibrium between two acids, HA and HB, is given by the ratio of the acid dissociation constants, K_{HA}/K_{HB}.

$$HA + B^- \rightleftharpoons A^- + HB \qquad K_{eq} = K_{HA}/K_{HB}$$

If we take the negative logarithm of K_{eq} we obtain

$$pK_{eq} = pK_{HA} - pK_{HB}$$

Let's consider the conversion of acetylene, a weak acid with $pK_a = 25$, to its conjugate base by reaction with a base B^-.

$$H{-}C{\equiv}C{-}H + B^- \rightleftharpoons H{-}C{\equiv}C{:}^- + HB$$

To convert acetylene to its conjugate base, $H{-}C{\equiv}C{:}^-$, a base stronger than the conjugate base of acetylene is required. In other words, the acid HB must be a weaker acid than acetylene. Because the pK_a of acetylene is 25, the conjugate acid of B^- must have $pK_a > 25$. Can we use OH^- as the base? The pK_a of water, the conjugate acid of OH^-, is 15.7. Thus, hydroxide is not sufficiently basic to remove a proton from acetylene. In fact, the equilibrium constant is only about 10^{-9}.

$$H{-}C{\equiv}C{-}H + OH^- \rightleftharpoons H{-}C{\equiv}C{:}^- + H_2O \qquad K_{eq} = 10^{-9}$$

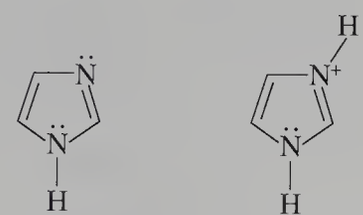
Now let's consider using the amide ion (NH_2^-), the conjugate base of ammonia ($pK_a = 36$). This base is more basic than the conjugate base of acetylene. The calculated equilibrium constant is 10^{11}. Thus, amide ion quantitatively removes a proton from acetylene.

$$H{-}C{\equiv}C{-}H + NH_2^- \rightleftharpoons H{-}C{\equiv}C{:}^- + NH_3 \qquad K_{eq} = 10^{11}$$

We will use this process to determine the position of equilibrium reactions throughout our study of organic chemistry. However, we know that, qualitatively, the position of the equilibrium is on the side of the weaker acid.

Problem 3.5

The amino acid histidine contains an imidazole ring. The pK_a of the imidazolinium ion, the conjugate acid of imidazole, is 7.0. What is the K_a of the imidazolinium ion? What fraction of the conjugate acid exists as imidazole at pH = 7?



imidazole

imidazolinium ion

Problem 3.6

The pK_b values for diethylamine and triethylamine are 3.51 and 2.99, respectively. Which compound is the stronger base? What are the pK_a values for the related ammonium ions? Which ammonium ion is the stronger acid?

Problem 3.7

Predict the position of the equilibrium for the following reaction.

$$CH_3{-}C{\equiv}C{:}^- + CH_3CH_2NH_2 \rightleftharpoons CH_3{-}C{\equiv}C{-}H + CH_3CH_2NH^-$$

Problem 3.8

Using the indicated pK_a values of the ammonium ions in the following equation, calculate the K_{eq} for the reaction.

$$\underset{(9.8)}{(CH_3)_3NH^+} + NH_3 \rightleftharpoons (CH_3)_3N + \underset{(9.4)}{NH_4^+}$$

Sample Solution

The reaction as written produces a stronger acid (lower pK_a) than the reactant. Acid–base reactions proceed in the direction to give the weaker acid and weaker conjugate base. Thus, we know that the above reaction is not favorable and must have $K < 1$. Designating $(CH_3)_3NH^+$ as HA and NH_4^+ as HB, we can substitute in the following equation and calculate the equilibrium constant.

$$pK_{eq} = pK_{HA} - pK_{HB} = 9.8 - 9.4 = 0.4$$

For $-\log K_{eq} = 0.4$ we obtain $K = 0.4$.

It is often easier to understand these types of calculations by using equilibrium constants. First convert the pK_a values into their corresponding equilibrium constants, which are 2.5×10^{-10} and 6.85×10^{-10} for the trimethylammonium ion and ammonium ion, respectively. Then substitute the equilibrium constants into the following expression.

$$K = \frac{K_{HA}}{K_{HB}} = \frac{2.5 \times 10^{-10}}{6.8 \times 10^{-10}} = 0.4$$

3.4 Structure and Acidity

Because acid–base reactions play such a prominent role in organic chemistry, it is important to understand how structure affects K_a of acids and K_b of bases. When an electrically neutral acid, HA, ionizes in a solvent, a bond to hydrogen breaks and a conjugate base, A^-, forms. Thus, the solvation of all species—especially ions—is most important in controlling the equilibrium constant. However, for a given solvent, we still need to understand how structure affects acidity, so we must consider four properties of the acid and its conjugate base.

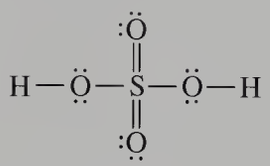
1. Periodic trends.
2. Resonance effects.
3. Inductive effects.
4. Hybridization effects.

Periodic Trends

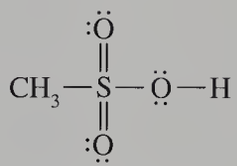
The strength of an acid, HA, depends in part upon the strength of the H—A bond. The bond strength decreases as we move down a column of the periodic table. This trend results from progressively less effective overlap of higher energy atomic orbitals with the hydrogen 1*s* orbital. Because the bond strength is in part inversely related to the acidity, the acidity of the halogen acids increases in the order HF < HCl < HBr < HI. For the same reasons, H_2O is a weaker acid than H_2S.

Acidity increases from left to right in a given row of the periodic table. The order of increasing acidity is $CH_4 < NH_3 < H_2O < HF$. This trend reflects the stabilization of the negative charge, which varies directly with the electronegativity of the atom of the conjugate base. That is, the order of increasing strength of conjugate bases is $F^- < OH^- < NH_2^- < CH_3^-$.

Many organic compounds are structurally related to inorganic acids and bases. As a consequence, we can predict the acid–base properties by comparing an organic acid with its inorganic counterpart. We know that sulfuric acid is a strong acid. Thus, we expect methanesulfonic acid to be a strong acid because it has an O—H bond that is structurally similar to the O—H bond in sulfuric acid.

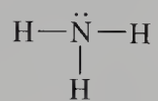


sulfuric acid
(a strong acid)

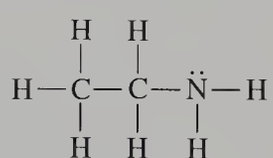


methanesulfonic acid
(a strong acid)

We can make similar comparisons with bases. For example, we know that ammonia is a weak base. Therefore, we expect ethylamine ($CH_3CH_2NH_2$), structurally related to ammonia, to be a weak base also. Both compounds have an unshared pair of electrons.



ammonia
$pK_b = 4.74$
(a weak base)



ethylamine
$pK_b = 3.25$
(a weak base)

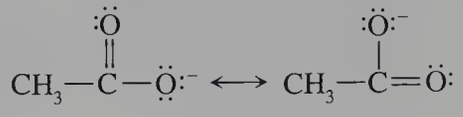
Resonance Effects

A reaction in which relatively unstable reactants are converted to more stable products has a large equilibrium constant. We can apply this general idea to acidity. When an electrically neutral acid ionizes, a conjugate base having a negative charge is produced. Stabilizing the negative charge in the conjugate base increases K_a. One way the conjugate base is stabilized is by delocalization of the negative charge over two or more atoms. This effect is called resonance stabilization. When an anion produced by ionization of an acid is resonance stabilized, acid strength increases substantially. For example, both methanol and ethanoic acid ionize to form conjugate bases with a negative charge on oxygen. However, ethanoic acid is about 10^{10} times as acidic as methanol.

$$CH_3OH + H_2O \rightleftharpoons CH_3O^- + H_3O^+ \qquad K_a = 10^{-16}$$

$$CH_3CO_2H + H_2O \rightleftharpoons CH_3CO_2^- + H_3O^+ \qquad K_a = 1.8 \times 10^{-5}$$

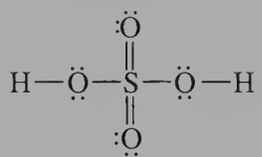
Ethanoic acid is more acidic because the conjugate base, ethanoate ion, is resonance stabilized. The negative charge of the ion is distributed equally over two oxygen atoms. In contrast, the conjugate base of methanol, methoxide ion (CH_3O^-), has its negative charge concentrated on a single oxygen atom.



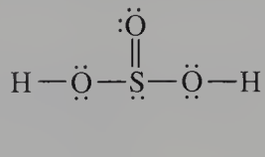
Inductive Effects

The acidity of organic compounds also depends in part upon the presence of atoms or groups of atoms that can polarize neighboring bonds in the acid and the conjugate base. These groups, which can be electron withdrawing or electron donating, act through σ bonds by an **inductive effect**.

Let's consider the acidities of sulfuric acid and sulfurous acid. Sulfuric acid is a strong acid, whereas sulfurous acid is a weak acid. In both acids, electron density flows away from the oxygen atom of the O—H group toward the sulfur atom. The several oxygen atoms bonded to the central sulfur atom cause electron density to flow away from the sulfur atom. The sulfur atom in turn attracts electrons from the OH group and causes the proton to ionize more easily. Because sulfuric acid has one more oxygen atom bonded to the sulfur atom than does sulfurous acid, the electron withdrawing effect is larger in sulfuric acid than in sulfurous acid. Thus, the OH group of sulfuric acid ionizes more easily.

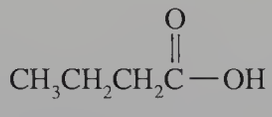


sulfuric acid
(a strong acid)

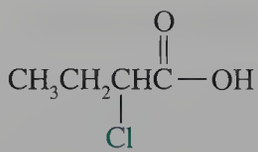


sulfurous acid
(a weak acid)

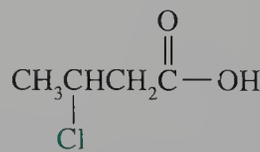
Any atom or group of atoms that withdraws electron density from the bond between hydrogen and another atom—such as carbon, oxygen, or nitrogen—in an organic molecule increases its acidity by an inductive effect. However, the inductive effect decreases with increasing distance between the electron-withdrawing group and the acidic site. Consider the acidities of butanoic acid, 2-chlorobutanoic acid, and 3-chlorobutanoic acid.



butanoic acid
$pK_a = 4.82$



2-chlorobutanoic acid
$pK_a = 2.86$



3-chlorobutanoic acid
$pK_a = 4.02$

The chlorine atom in 2-chlorobutanoic acid is close enough to the carboxyl group to significantly polarize the O—H bond. Thus, when a hydrogen atom at C-2 of butanoic acid is replaced by a chlorine atom, the strength of the acid is increased (its pK_a decreases). In 3-chlorobutanoic acid, the chlorine atom is farther from the carboxyl group and its effect on the acidity is reduced.

Hybridization Effects

In many organic compounds, the ionizable hydrogen atom is attached to an electronegative atom such as oxygen. But some organic compounds have slightly acidic hydrogen atoms bonded to a carbon atom. These "carbon acids" are usually quite weak acids. Therefore, a very strong base is required to remove a proton from these slightly acidic hydrocarbons.

$CH_3—CH_3$	$CH_2=CH_2$	$HC\equiv CH$
$K_a = 10^{-49}$	$K_a = 10^{-44}$	$K_a = 10^{-25}$

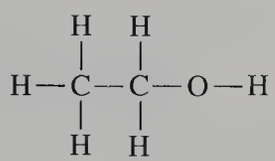
The K_a values of hydrocarbons are very small, but there are substantial differences between various classes of hydrocarbons. The acidity of hydrocarbons is related to the hybridization of the carbon atom of the C—H bond. The K_a of a carbon acid increases in the order $sp^3 < sp^2 < sp$. The order of acidities parallels the contribution of the lower energy of the 2*s* orbital to the hybrid orbitals in the σ bond. The average distance of hybrid orbitals from the nucleus depends on the percent contribution of the *s* and *p* orbitals. For an sp^3 hybrid orbital, the contribution of the *s* orbital is 25% because one *s* and three *p* orbitals contribute to the four hybrid orbitals. The contribution of the *s* orbital is 33% and 50% for the sp^2 and *sp* hybrid orbitals, respectively. Because an *sp* hybrid orbital has more *s* character than an sp^2 or sp^3 orbital, its electrons are located closer to the nucleus. Because the strength of an acid depends upon the stability of the conjugate base, a carbanion in which the negative charge is on an *sp*-hybridized carbon atom is more stable than a carbanion of an sp^2- or sp^3-hybridized carbon atom.

Problem 3.9

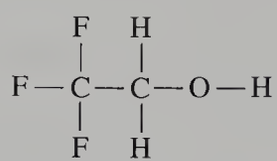
Based on periodic trends and structurally similar compounds, predict which is the stronger acid, CH_3OH or CH_3SH.

Problem 3.10

The pK_a values of ethanol and 2,2,2-trifluoroethanol are 15.9 and 12.4, respectively. What is responsible for this difference?



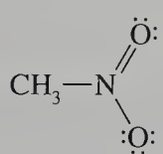
ethanol



2,2,2-trifluoroethanol

Problem 3.11

The pK_a of nitromethane is 10.2, whereas the pK_a of methane is approximately 49. Explain why nitromethane is so acidic.



3.5 Equilibrium and Thermodynamics

Thermodynamics deals with the energy changes associated with chemical reactions and physical transformations. The thermodynamic quantity that controls the degree to which a reaction proceeds is the **Gibbs free energy change** ($\Delta G°$) in going from the reactants to the products. The superscript symbol (°) indicates that the thermodynamic quantity is given for substances at 25 °C and 1 atm pressure. The Gibbs free energy of formation ($\Delta G_f°$) of a compound is the free energy change for the formation of the compound from the elements in their standard state at 25 °C (298 K). The Gibbs free energy is a state function. That is, its value is independent of how the substance is obtained.

The change in the Gibbs free energy for a reaction ($\Delta G°_{rxn}$) is the difference between the free energy of the products and the free energy of the reactants. It is independent of the pathway by which the process occurs.

$$\Delta G°_{rxn} = \Delta G_f°(\text{products}) - \Delta G_f°(\text{reactants})$$

When the reactants are of higher free energy than the products ($\Delta G°_{rxn} < 0$), the reaction is said to be **exergonic**. A reaction in which the reactants are of lower free energy than the products ($\Delta G°_{rxn} > 0$) is said to be **endergonic**. These terms should not be confused with exothermic and endothermic, which refer to $\Delta H°_{rxn}$.

Gibbs Free Energy, Enthalpy, and Entropy

Two thermodynamic state functions, enthalpy (H) and entropy (S), contribute to the free energy. The equation relating the three state functions is

$$G° = H° - TS°$$

We can express the free energy change for a chemical reaction at constant temperature and pressure in terms of the changes in enthalpy and entropy.

$$\Delta G°_{rxn} = \Delta H°_{rxn} - T\,\Delta S°_{rxn}$$

$$\text{where } \Delta H°_{rxn} = \Delta H_f°(\text{products}) - \Delta H_f°(\text{reactants})$$
$$\Delta S°_{rxn} = S_f°(\text{products}) - S_f°(\text{reactants})$$

The $\Delta H_f°$ is related to the stored energy in the bonds of the substance. The $\Delta H°_{rxn}$ is the net energy change resulting from the bonds formed and broken in a chemical reaction. In subsequent sections we will learn how to estimate $\Delta H°_{rxn}$ for reactions if the $\Delta H_f°$ values of reactants or products are not all known.

The standard entropy, $S°$, of a substance is a measure of the disorder or randomness of its constituent bonded atoms. The significance of $\Delta S°_{rxn}$ in controlling chemical reactions is discussed in Section 3.9. In subsequent sections we will learn how to estimate $\Delta S°_{rxn}$ for reactions.

Equilibrium Constant and Gibbs Free Energy

The equilibrium constant and the $\Delta G°_{rxn}$ for a reaction are related by the following expression.

$$\Delta G^\circ_{rxn} = -RT \ln K_{eq} = -2.303RT \log K_{eq}$$

R = 8.314 J kelvin^{-1} mole^{-1} (1.987 cal kelvin^{-1} mole^{-1})

T = absolute temperature in kelvins

When the free energy of the products is less than the free energy of the reactants, $\Delta G^\circ_{rxn} < 0$ and $K_{eq} > 1$. For the combustion of methane, with $\Delta G^\circ_{rxn} = -816.6$ kJ mole^{-1}, the equilibrium constant is 10^{143}, so the reaction goes to completion. The esterification reaction of acetic acid and ethanol, with $K = 4$, corresponds to $\Delta G^\circ_{rxn} = -1.7$ kJ mole^{-1} at 298 K.

Table 3.4 provides some values of K_{eq} and the corresponding ΔG°_{rxn} values as well as the percentage of product at equilibrium for a general reaction in which the reactant X is converted to Y. As ΔG°_{rxn} becomes more negative, we say that there is a stronger driving force for the reaction. For ΔG°_{rxn} values more negative than −17 kJ mole^{-1} (−4.1 kcal mole^{-1}), the reaction is quantitative for all practical purposes because less than 0.01% of the reactant remains at equilibrium.

TABLE 3.4
Relationship Between ΔG° (kJ mole^{-1}) and K at 25 °C

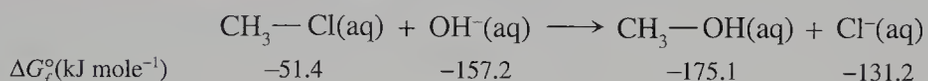
$$X \rightleftharpoons Y$$

ΔG°	K	% Y	ΔG°	K	% Y
0.00	1.0	50	−4.3	5.67	85
−0.50	1.22	55	−5.45	9.00	90
−1.0	1.50	60	−7.30	19.0	95
−1.5	1.86	65	−9.65	49.0	98
−2.1	2.33	70	−11	99	99
−2.7	3.00	75	−17	999.9	99.9
−3.4	4.00	80	−22	9999.9	99.99

In this text we will often assume that the heat of reaction (ΔH°_{rxn}) can be used to predict the equilibrium constant for a reaction. However, it is ΔG°_{rxn}, of which ΔH°_{rxn} is only a part, that determines the position of equilibrium and the direction of a reaction. The approximation that $\Delta G^\circ_{rxn} \approx \Delta H^\circ_{rxn}$ is valid only if ΔS°_{rxn} is small. The contributions of ΔH°_{rxn} and ΔS°_{rxn} will be discussed in subsequent sections.

Problem 3.12

Calculate ΔG°_{rxn} for the following substitution reaction using the ΔG°_f for the reactants and products.



ΔG°_f(kJ mole^{-1})	−51.4	−157.2	−175.1	−131.2

Sample Solution

Use the sum of the ΔG°_fs for both the reactants and products and the following relationship.

$$\Delta G^\circ_{rxn} = \Delta G^\circ(\text{products}) - \Delta G^\circ(\text{reactants})$$

$$\Delta G^\circ_{rxn} = \{(-175.1 - 131.2) - (-157.2 - 51.4)\} \text{ kJ mole}^{-1} = -97.7 \text{ kJ mole}^{-1}$$

The sum of the ΔG° for the products is more negative than the sum of the ΔG° for the reactants. Thus the reaction has $\Delta G^\circ_{rxn} < 0$.

Problem 3.13

The ΔG°_{rxn} for the addition reaction of HBr to ethylene at 25 °C is −50 kJ mole^{-1}. Calculate K_{eq} at this temperature.

$$\underset{\text{ethylene}}{CH_2{=}CH_2} + HBr \longrightarrow \underset{\text{bromoethane}}{CH_3{-}CH_2{-}Br}$$

Problem 3.14

Using the following ΔG°_{rxn} for the addition of HBr to propene to give two possible bromoalkanes, determine which product is the more stable.

$$\underset{\text{propene}}{CH_3{-}CH{=}CH_2} + HBr \longrightarrow \underset{\text{1-bromopropane}}{CH_3{-}CH_2{-}CH_2{-}Br} \qquad \Delta G^\circ_{rxn} = -31.9 \text{ kJ mole}^{-1}$$

$$\underset{\text{propene}}{CH_3{-}CH{=}CH_2} + HBr \longrightarrow \underset{\text{2-bromopropane}}{CH_3{-}CHBr{-}CH_3} \qquad \Delta G^\circ_{rxn} = -36.6 \text{ kJ mole}^{-1}$$

3.6 Enthalpy Changes in Chemical Reactions

The first law of thermodynamics states that the total energy of the universe is conserved in all chemical reactions. We can say that the total energy of a system—say, a flask in which a chemical reaction occurs—and its surroundings is a constant. Consider the general reaction

$$m\,A + n\,B \rightleftharpoons p\,X + q\,Y + \text{energy}$$

Because energy is conserved, the amount of energy flowing out of the system into the surroundings in the forward reaction exactly equals the amount of energy flowing from the surroundings into the system in the reverse reaction.

The heat energy released or absorbed in a reaction, measured at constant pressure, is the **enthalpy change**, ΔH°_{rxn}. Although kilojoule (kJ) is the preferred SI unit, some organic chemists still use kilocalorie (kcal) as an energy unit (1 kcal = 4.184 kJ). For an exothermic reaction, $\Delta H_{rxn} < 0$— that is, the system releases heat into the surroundings. For an endothermic reaction, $\Delta H_{rxn} > 0$—that is, the system absorbs heat from the surroundings.

Standard conditions refer to measurements made at 298 K and 1 atm. Enthalpy changes for reactions carried out at standard conditions are called standard enthalpy changes, ΔH°. The following conventions are used.

1. The standard enthalpy of formation (ΔH°_f) of a compound is the enthalpy change when the compound is formed in its standard state from the elements in their standard states. The superscript indicates that the reaction occurs under standard conditions.
2. The standard state of any element or compound is its most stable form at 298 K and 1 atm pressure.
3. The standard enthalpy of formation of any element in its standard state is 0 kJ mole^{-1}.

The standard enthalpy change for a general reaction is given by

$$\Delta H^\circ_{rxn} = [p\Delta H^\circ_f(X) + q\Delta H^\circ_f(Y)] - [m\Delta H^\circ_f(A) + n\Delta H^\circ_f(B)]$$

We can interpret the enthalpy change for a reaction in terms of the structure of the reactants and products. All substances contain stored chemical energy in their bonds. When a chemical bond forms, energy is released:the process is exothermic. Conversely, breaking a chemical bond requires energy: the process in endothermic. Therefore, the energy change for a chemical reaction reflects the energies of the bonds that are broken and formed. When reactants are converted to products, the stored chemical energies are not the same because the number and types of bonds are altered. If the products of a reaction contain less stored energy than the reactants, the net difference is released as heat energy, ΔH°_{rxn}. The contribution of the number and types of bonds broken and formed in a chemical reaction to the heat of reaction will be discussed in the next section.

3.7 Bond Dissociation Energies

The ΔH°_f values, which are required to calculate ΔH°_{rxn}, are not available for all compounds. In those cases, we can estimate ΔH°_{rxn} using the bond dissociation energies for the bonds made or broken in the reaction. The **bond dissociation energy** is the energy required, in the gas phase, to break a bond into two fragments, each having one half of the electrons present in the original bond. For a single bond, the general process is represented as

$$X{:}Y \longrightarrow X\cdot + \cdot Y \qquad \Delta H^\circ_{rxn} > 0$$

The enthalpy change for breaking covalent bonds is positive. In contrast, the enthalpy change when atoms combine to form bonds in molecules is negative. Recall that the first law of thermodynamics states that energy can neither be created or destroyed. Therefore, the energy released when a given bond forms exactly equals the energy required to break it. Consider the energy changes for breaking and forming the covalent bond in H—H.

$$H\cdot + \cdot H \longrightarrow H{:}H \qquad \Delta H^\circ_{rxn} = -434 \text{ kJ mole}^{-1}$$

$$H{:}H \longrightarrow H\cdot + \cdot H \qquad \Delta H^\circ_{rxn} = +434 \text{ kJ mole}^{-1}$$

The bond dissociation energy of a specific bond in a polyatomic molecule is not easily determined, and is rarely known more accurately than about ± 0.5 kJ mole^{-1}. The ΔH°_{rxn} for bond dissociation is usually given by the symbol DH°. A list of some bond dissociation energies is given in Table 3.5. The bond cleaved is indicated by a dash. For CH_3—H, the listed DH° value refers to the following process.

$$CH_3{-}H \longrightarrow CH_3\cdot + H\cdot \qquad DH^\circ = 438 \text{ kJ mole}^{-1}$$

Effect of Electronegativity

The bond dissociation energy increases with an increasing difference in the electronegativity of the bonded atoms. For example, the bond dissociation energies of carbon–halogen bonds increase in the order C—I < C—Br < C—Cl < C—F. This trend results from the polarization of the carbon–halogen bond and the attraction of

TABLE 3.5
Bond Dissociation Energies of Representative Compounds

Bond	*DH°(kJ mole^{-1})*	*Bond*	*DH°(kJ mole^{-1})*
H—H	435	CH_3—H	438
F—F	159	CH_3—F	451
Cl—Cl	242	CH_3—Cl	349
Br—Br	192	CH_3—Br	293
I—I	150	CH_3—I	234
		CH_3—OH	380
H—F	586		
H—Cl	431	CH_3CH_2—H	422
H—Br	366	CH_2=CH—H	452
H—I	297	HC≡C—H	523
H—OH	497		
		CH_3—CH_3	368
		CH_2=CH_2	610
		HC≡CH	830

electrons toward the halogen atom. When a carbon–halogen bond breaks so that one electron remains with each fragment, the electropositive element (carbon) must "recover" its electron from the electronegative element. As the electronegativity of the atom "losing" the electron increases, the bond dissociation energy increases.

Effect of Hybridization on Bond Energy

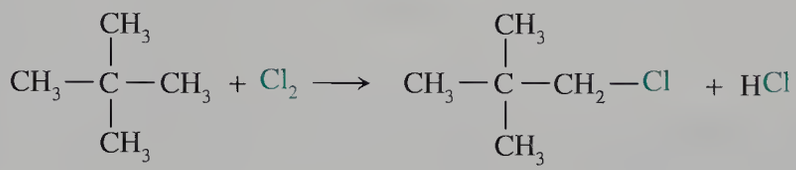
The bond energy of a C—H bond increases in the order $sp^3 < sp^2 < sp$, as we can see from the bond energies of ethane, ethylene, and acetylene given in Table 3.5. We have already discussed the reasons for this trend. The average distance of the electrons in the hybrid orbitals from the nucleus depends on the percent contributions of the *s* and *p* orbitals. The contribution of the *s* orbital is 25% in an sp^3 orbital and rises to 50% in an *sp* hybrid orbital. Because the sp^3 hybrid orbital has the smallest *s* character, the electrons in the orbital are farther from the nucleus, and the bond formed with this orbital is the weakest.

Effect of Multiple Bonds on Bond Energy

The bond energy between common atoms increases in the order single < double < triple. This trend partly reflects the effect of the closer approach of the σ bonding electrons to the nucleus as the percent *s* character in the hybrid orbitals increases. However, the substantial increase in the carbon–carbon bond strength is largely a consequence of the increased number of bonds joining the carbon atoms.

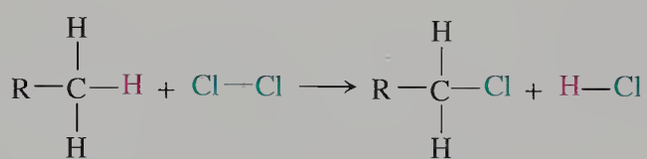
3.8 Estimating ΔH°_{rxn} from Bond Energies

The standard enthalpy change for a chemical reaction, ΔH°_{rxn}, can be approximated by considering the energy of the bonds that are cleaved or formed in the process. The exact bond energies are not known for complex molecules, but average bond energies can be estimated based on simple, structurally analogous compounds. Consider the substitution reaction of 2,2-dimethylpropane with chlorine.



2,2-dimethylpropane 1-chloro-2,2-dimethylpropane

In this reaction, a C—H bond is broken in a part of a molecule that resembles CH_4. Therefore, we approximate the *DH*° for the C—H bond in the compound by using the bond dissociation energy *DH*° for CH_3—H. Similarly, the C—Cl bond formed in the product resembles the C—Cl bond in CH_3—Cl, so we use the listed bond dissociation energy for CH_3—Cl. These approximations are summarized in the following equation, where the remainder of the molecule—the central carbon atom and its three attached CH_3 groups—is represented by R.



We recall that the net enthalpy change for a process that can be divided into two or more steps equals the sum of the enthalpy changes for the individual steps (this is Hess's law). The enthalpy changes for the individual bonds that are broken or formed are summed as follows.

Process	*DH° (kJ mole^{-1})*
break C—H bond	438
break Cl—Cl bond	242
make C—Cl bond	−349
make H—Cl bond	−431
	−100

Even though average bond dissociation energies are used in the calculation, the reaction is clearly predicted to be exothermic. The enthalpy change for the reaction is negative because the C—Cl and H—Cl bonds that form are collectively stronger than the C—H and Cl—Cl bonds that are broken. In general, reactions are enthalpically favored when the bonds made are stronger than the bonds broken.

The actual enthalpy change for a reaction may be somewhat different from the value calculated because bond energies do depend on structure. Thus the C—H bond energy of ethane is 422 kJ mole^{-1} as compared to 438 kJ mole^{-1} for methane. The effect of structure on bond energies will be discussed in Chapter 5.

Problem 3.15

Using bond energies, estimate the ΔH°_{rxn} for the following two reactions in the gas phase.

(a) $CH_3—OH + HCl \longrightarrow CH_3—Cl + H_2O$

(b) $CH_2=CH_2 + HBr \longrightarrow CH_3—CH_2—Br$

3.9 Entropy Changes in Chemical Reactions

The elusive concept of entropy is related to the order, or structure, of the system. The standard entropy at 25 °C (S°) is determined relative to the entropy of the substance at absolute zero in its perfect crystalline state, where the entropy of the elements is defined as zero. The units of entropy of a substance are J mole^{-1} deg^{-1} (or cal mole^{-1} deg^{-1}).

In a physical or chemical change, the entropy change ΔS° is positive if the final state is less ordered than the initial state. Conversely, the entropy change is negative if the final state is more ordered than the initial state. Like the change in enthalpy, the change in entropy is independent of the path by which the process occurs and depends only on the initial and final states of the system. Thus, the standard entropy change for a general equilibrium reaction may be written

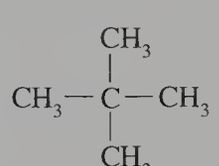
$$m\,A + n\,B \rightleftharpoons p\,X + q\,Y$$

$$\Delta S^\circ_{rxn} = [pS^\circ(X) + qS^\circ(Y)] - [mS^\circ(A) + nS^\circ(B)]$$

Entropy of Substances

Several general trends for the entropy of various substances are useful in discussing chemical reactions.

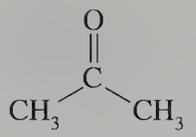
1. The entropy of a substance is lower in the solid state than in the liquid state, and much lower in the liquid state than in the gaseous state.
2. The entropy of a more symmetrical molecule is lower than the entropy of a less symmetrical molecule. For example, the entropy of 2,2-dimethylpropane, which has a spherical shape, is less than that of pentane, which has a cylindrical shape.



2,2-dimethylpropane
$S^\circ = 294$ J mole^{-1} deg^{-1}

pentane
$S^\circ = 338$ J mole^{-1} deg^{-1}

3. The entropy of a molecule in which free rotation around σ bonds is possible is larger than that of a molecule in which such rotation is restricted. For example, the entropy of acetone is larger than that of the isomeric molecule oxetane (trimethylene oxide). In acetone, the methyl groups may rotate freely about the σ bond to the carbonyl carbon atom. In oxetane, the ring restricts both the movement of the ring atoms and the position of the hydrogen atoms.

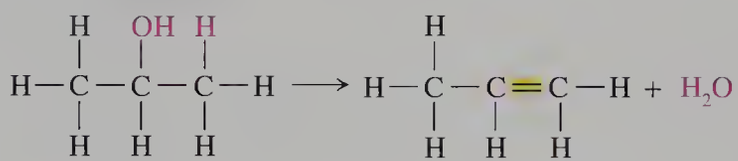


acetone
S° = 295 J mole^{-1} deg^{-1}

oxetane
S° = 274 J mole^{-1} deg^{-1}

Stoichiometry and ΔS°_{rxn}

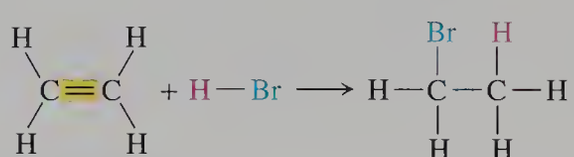
Although the individual S° values of the reactants and products contribute to the overall ΔS° for the reaction, the largest entropy changes are observed for chemical reactions in which the number of moles of product and reactant are different. For example, the number of moles of product is greater than the number of moles of reactant in an elimination reaction such as the dehydration of an alcohol.



1 mole reactant — 2 moles products

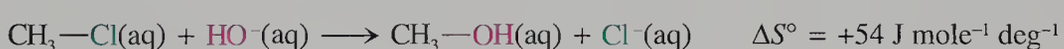
Since the number of moles of product is greater than the number of moles of reactant, there is more disorder in the distribution of atoms in the products than in the reactants, and we expect the entropy change for the reaction to be positive. An increase of 1 mole of product over reactant corresponds to approximately +125 J mole^{-1} deg^{-1}.

Now let's examine the addition reaction of HBr to ethylene, a reaction in which there are fewer moles of product than moles of reactants. The change in entropy for the reaction is expected to be approximately −125 J mole^{-1} deg^{-1}, based on a net decrease of 1 mole. The experimental value is −129 J mole^{-1} deg^{-1}



2 moles reactants — 1 mole product

When we estimate the entropy change for a reaction, we must consider the effect of the solvent. Solvent molecules may solvate the reactants and products to a different degree. Consider the substitution reaction of chloromethane by hydroxide ion in aqueous solution.



The entropy change is positive even though the numbers of moles of product and reactant are equal. In the aqueous phase, ions are solvated, which corresponds to more order. In this case, the hydroxide ions, which form strong hydrogen bonds to water, are more strongly solvated than chloride ions. Thus, as the reaction proceeds, some solvent molecules are "freed" and the disorder of the system increases. The change in order of the solvent molecules contributes to the positive entropy change.

3.10 Contributions of ΔH°_{rxn} and ΔS°_{rxn} to ΔG°_{rxn}

For most organic reactions, the value of ΔH°_{rxn} contributes more strongly to ΔG°_{rxn} than the $T\Delta S^\circ_{rxn}$ term does. For reactions in which the number of moles of reactants and products are the same and in which there is no significant change in the symmetry or rotational freedom, we know that ΔS°_{rxn} will be close to zero. Thus, the value of ΔH°_{rxn} is often a close approximation of ΔG°_{rxn}.

$$\Delta H^\circ_{rxn} \approx \Delta G^\circ_{rxn}$$

Consider the reaction of chlorine with methane, in which two molecules react to give two molecules of product. The $\Delta S^\circ_{rxn} = +2.9$ J mole^{-1} deg^{-1}. The standard entropy change is a small value because the numbers of moles of reactant and product are equal. The $-T\Delta S^\circ$ term at 298 K is -860 J mole^{-1} or -0.9 kJ mole^{-1}. Since ΔH°_{rxn} for the reaction is -102 kJ mole^{-1}, the ΔG°_{rxn} is -103 kJ mole^{-1}.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

$$\Delta G^\circ_{rxn} = \Delta H^\circ - T\Delta S^\circ_{rxn}$$

$$\Delta G^\circ_{rxn} = -102{,}000 \text{ J mole}^{-1} - (298 \text{ K})(2.9 \text{ J mole}^{-1} \text{ deg}^{-1})$$

$$= -103{,}000 \text{ J mole}^{-1} = -103 \text{ kJ mole}^{-1}$$

The contributions of enthalpy and entropy changes to the free energy change depend on temperature. The enthalpy component is more important at low temperatures, where the $T\Delta S^\circ$ term is small. On the other hand, the $T\Delta S^\circ$ term becomes more important at higher temperatures. Thus, if an increase in the degree of disorder is great, an endothermic process may be exergonic at a sufficiently high temperature. A reaction in which the products have greater order than the reactants has a negative entropy change and can occur only in an exothermic reaction. Such reactions become more favorable at a low temperature. To illustrate the effect of temperature on a reaction, consider the decomposition reaction of butane to give ethane and ethylene at 298 K and at 700 K. The reaction is endothermic, but occurs with a large positive entropy change.

$$CH_3CH_2CH_2CH_3 \longrightarrow CH_3CH_3 + CH_2{=}CH_2$$

$$\Delta H^\circ_{rxn} = 93.1 \text{ kJ mole}^{-1}$$

$$\Delta S^\circ_{rxn} = 140 \text{ J mole}^{-1} \text{ deg}^{-1}$$

At 298 K, the ΔH°_{rxn} term is more important than the $T\Delta S^\circ_{rxn}$ term, and the standard free energy change is positive.

$$\Delta G^\circ_{rxn} = \Delta H^\circ - T\Delta S^\circ_{rxn}$$

$$\Delta G^\circ_{rxn} = 93{,}100 \text{ J mole}^{-1} - (298 \text{ K})(140 \text{ J mole}^{-1} \text{ deg}^{-1})$$

$$= 51{,}400 \text{ J mole}^{-1} = 51.4 \text{ kJ mole}^{-1}$$

In contrast, the $T\Delta S^\circ$ term dominates at 700 K, and the standard free energy change is slightly negative.

$$\Delta G^\circ_{rxn} = \Delta H^\circ - T\Delta S^\circ_{rxn}$$

$$\Delta G^\circ_{rxn} = 93{,}100 \text{ J mole}^{-1} - (700 \text{ K})(140 \text{ J mole}^{-1} \text{ deg}^{-1})$$

$$= -4900 \text{ J mole}^{-1} = -4.9 \text{ kJ mole}^{-1}$$

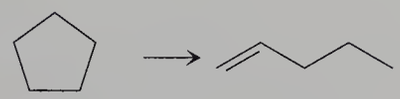
Problem 3.16

Predict the ΔS°_{rxn} for the complete fluorination of methane.

$$CH_4 + 4F_2 \longrightarrow CF_4 + 4HF$$

Problem 3.17

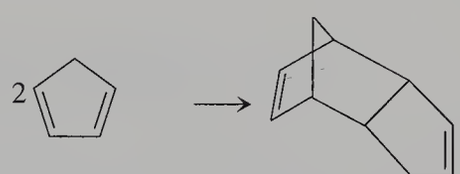
The ΔS°_{rxn} for the isomerization reaction of cyclopentane to produce 1-pentene is positive. Explain why.



cyclopentane 1-pentene

Problem 3.18

1,3-Cyclopentadiene readily dimerizes at room temperature to form dicyclopentadiene in an addition reaction known as the Diels–Alder reaction. For this reaction $\Delta G^\circ < 0$ and $\Delta H^\circ < 0$ at room temperature. However, upon heating to the boiling point, dicyclopentadiene decomposes to 1,3-cyclopentadiene. Explain why.



1,3-cyclopentadiene dicyclopentadiene

Sample Solution

The reaction as written converts 2 moles of reactant into 1 mole of product. Thus, we expect $\Delta S^\circ_{rxn} \approx -125$ J mole^{-1} deg^{-1}, and this term should contribute to make the reaction unfavorable. The ΔH° term is responsible for the overall favorable reaction. For the reverse reaction ΔH° is positive. However, ΔS° will be positive, and the reaction will become more favorable at a higher temperature, because the $-T\Delta S^\circ$ term will contribute to making $\Delta G^\circ < 0$.

Problem 3.19

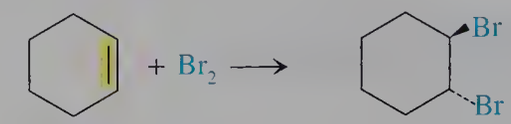
Using the indicated values for ΔH°_f and S°_f of the reactants and the product for the addition of HI to propene, calculate ΔG°_{rxn} at 25 and 225 °C. At which temperature is the reaction less favored? What factor is responsible for the change in the equilibrium constant for the reaction?

	$CH_3-CH=CH_2$ +	HI $\longrightarrow$	$CH_3-CHI-CH_3$
ΔH°_f (kJ mole^{-1})	11.7	−5.6	−82.1
S°_f (J mole^{-1} deg^{-1})	301.2	221.4	380.5

3.11 Kinetics of Reactions

Thermodynamics can predict whether or not a chemical reaction will occur and the position of the resulting equilibrium, but provides no information about the experimental conditions required for the reaction or the rate at which the reaction occurs. Let's consider reactions of several hydrocarbons with bromine to illustrate these points.

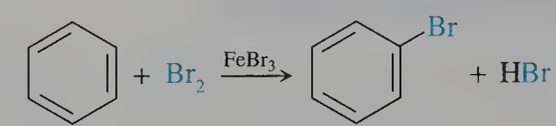
When a drop of bromine is added to a solution of cyclohexene at 25 °C, the dark red-orange color of the bromine disappears instantly in an exothermic reaction. The product of the reaction is 1,2-dibromocyclohexane, the result of an addition reaction.



cyclohexene 1,2-dibromocyclohexane

$\Delta H^\circ_{rxn} = -105 \text{ kJ mole}^{-1}$

Neither benzene nor cyclohexane reacts with bromine under the same reaction conditions. However, if iron(III) bromide is present, benzene reacts at a moderate rate at 50 °C. The reaction is exothermic. Cyclohexane does not react even under these conditions.

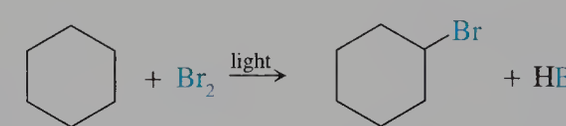


benzene bromobenzene

$\Delta H^\circ_{rxn} = -46 \text{ kJ mole}^{-1}$

Not only are different conditions required for the reaction with benzene but the reaction stoichiometry is different than the reaction with cyclohexene. A substitution reaction occurs for benzene, replacing hydrogen by bromine.

If a mixture of cyclohexane and bromine is irradiated, a rapid exothermic reaction occurs. Thus, although the reaction conditions are different, again a substitution reaction occurs and HBr is a by-product.



cyclohexane bromocyclohexane

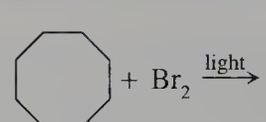
$\Delta H^\circ_{rxn} = -63 \text{ kJ mole}^{-1}$

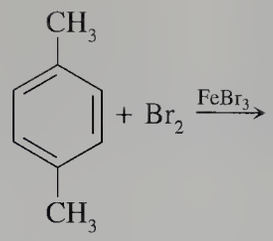
All three exothermic reactions are spontaneous. That is, $\Delta G_{rxn} < 0$ for each reaction. However, the required experimental conditions for each process are different.

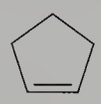
The study of the speed or rate of chemical reactions is called **kinetics**. Kinetic studies help us formulate the **mechanisms** of reactions that describe the sequence of bond cleavage and bond formation during a reaction and the energy associated with those steps. Once we unravel the sequence of steps that occur as reactants are converted into products for a few examples within a class of organic reactions, we can apply this information to many other reactions. The prediction of reaction mechanisms for new reactions, based on other reactions with well-established mechanisms, is a powerful tool in understanding organic chemistry.

Problem 3.20

Draw the product for each of the following reactions.

(a) 

(b)  + Br_2 $\xrightarrow{FeBr_3}$

(c)  + Br_2 $\longrightarrow$

3.12 Reaction Mechanisms

A reaction mechanism accounts for the structural changes that occur and the energy change associated with each structural change at every stage of the reaction. Such precise detail has been achieved for very few reactions. However, using the functional group concept and some "common sense", we can make reasonable guesses about the mechanisms of chemical reactions that are similar to other well-studied reactions.

Concerted and Multistep Reactions

In some reactions, bond breaking and bond formation occur simultaneously in a single step. Such processes are **concerted reactions**. A description of such a reaction mechanism resembles that of an ordinary chemical equation.

$$\underset{\text{reactant}}{A} \longrightarrow \underset{\text{product}}{X}$$

Many reactions occur in a series of steps. For example, the conversion of reactant A into product X may occur in two steps. An intermediate, which is not shown in the balanced chemical equation, forms and then reacts.

Step 1. An intermediate forms.

$$\underset{\text{reactant}}{A} \longrightarrow \underset{\text{intermediate}}{M}$$

Step 2. The intermediate is converted to product.

$$\underset{\text{intermediate}}{M} \longrightarrow \underset{\text{product}}{X}$$

In a multistep reaction, the individual steps usually have different rates. The overall rate of conversion of reactant into product can occur no faster than the slowest individual step, called the **rate-determining step**.

Types of Bond Cleavage

When a bond is broken so that one electron remains with each of the two fragments, the process is called **homolytic** cleavage. The fragments that contain unpaired electrons are **radicals**.

$$X{-}Y \longrightarrow X\cdot + \cdot Y$$

general example of homolytic bond cleavage

Homolytic cleavage of a bond to carbon produces a **carbon radical**, which is highly reactive because it has only seven electrons in its valence shell. In the general reaction shown below, Y represents an atom or a small number of atoms and R represents the remainder of the carbon-containing structure.

$$R{-}Y \longrightarrow R\cdot + \cdot Y$$

(a carbon radical)

When a bond is broken so that one fragment gains both bonding electrons, the process is called **heterolytic** cleavage. The fragment that gains an electron has a negative charge. The second fragment loses an electron and has a positive charge.

$$X{-}Y \longrightarrow X^+ + :Y^-$$

general example of heterolytic bond cleavage

Heterolytic cleavage of a bond to carbon can produce two different carbon species.

1. If the bond breaks so that its electrons remain with the carbon atom, a **carbanion** results. A carbanion has an octet of electrons. It can act as a Lewis base or nucleophile.

$$R{-}Y \longrightarrow R:^- + Y^+$$

(a carbanion)

2. If the bond breaks so that its electrons are lost by the carbon atom, a positively charged **carbocation** results. The carbocation has a sextet of electrons and is an electron-deficient species. It can act as a Lewis acid or electrophile.

$$R{-}Y \longrightarrow R^+ + :Y^-$$

(a carbocation)

The mode of heterolytic cleavage of a C—Y bond depends on the electronegativity of Y. There are two possibilities. If Y is a less electronegative element, such as a metal, the bond tends to break heterolytically to form a carbanion. If Y is a more electronegative element than carbon, a halogen atom, for example, the bond has the opposite polarity and tends to break heterolytically to form a carbocation.

$$\overset{\delta^-}{R}{-}\overset{\delta^+}{Li} \longrightarrow R:^- + Li^+$$

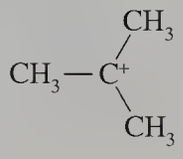
$$\overset{\delta^+}{R}{-}\overset{\delta^-}{Br} \longrightarrow R^+ + :\ddot{\underset{..}{Br}}:^-$$

3.13 Structure and Stability of Carbon Intermediates

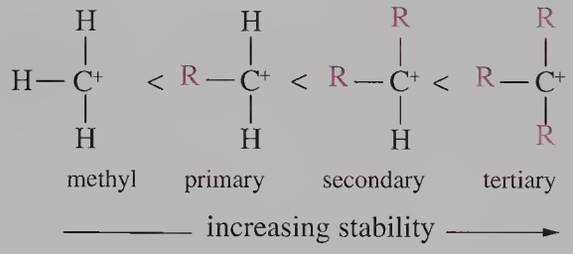
Carbon radicals, carbocations, and carbanions are trivalent species that react quickly with other substances to give stable products with tetravalent carbon atoms. We will consider two aspects of these intermediates: their relative stabilities and their relative reactivities. The term stability refers to a thermodynamic property. The term reactivity refers to the rate of a reaction. At this time we will consider only the stability of the intermediates, not their reactivity.

A carbocation has only six electrons in its valence shell and the carbon atom has a formal +1 charge. However, that charge is shared to some extent by the atoms bonded to the cationic center. This distribution of charge over several atoms can result from inductive or resonance effects, which are the same phenomena illustrated in our discussion of the stability of acids and their conjugate bases (Section 3.4).

Simple sp^3-hybridized groups, such as $-CH_3$, can donate electrons through the σ bond to the positively charged carbon atom. From a different viewpoint, the charged carbon atom withdraws electron density from the groups bonded to it. However, we usually focus on the contribution of the groups bonded to the electron-deficient center and say that the carbocation is stabilized by electron donation of groups such as $-CH_3$.



Reactive intermediates are classified according to the number of carbon atoms directly bonded to the trivalent carbon atom. A carbon atom that is bonded to one, two, or three other carbon-containing groups is called a **primary carbon**, **secondary carbon**, or **tertiary carbon** atom. These types of atoms are designated by 1°, 2°, and 3°. Carbocation stability increases with the number of carbon-containing groups bonded to it. With R representing a carbon-containing group, the order of stability is



The positively charged carbon atom in a carbocation is sp^2 hybridized. A carbocation, such as the methyl carbocation (CH_3^+), has a trigonal planar structure with H—C—H bond angles of 120°. We picture a carbocation with an unhybridized *p* orbital perpendicular to the plane of the C—H bonds. However, the *p* orbital does not contain electrons (Figure 3.1a).

Like carbocations, radicals are electron-deficient species. A carbon radical has seven electrons in the valence shell in contrast to six electrons for carbocations. Like carbocations, carbon radicals are stabilized by the inductive effect of groups bonded to the radical center. Because radicals are not as electron deficient as carbocations, the differences in stability of radicals are smaller than for carbocations. The order of carbon radical stability echoes the order of carbocation stability.

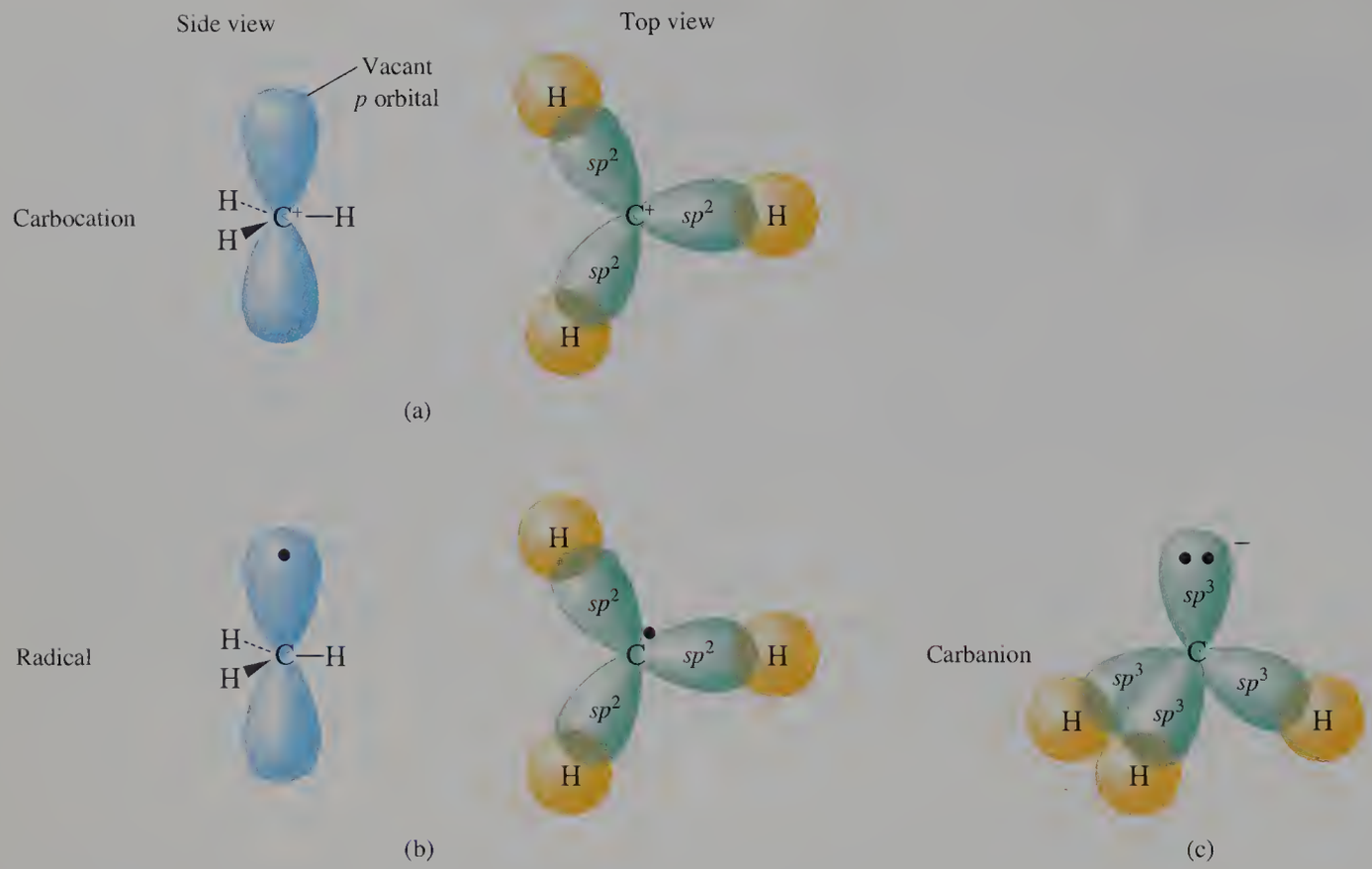
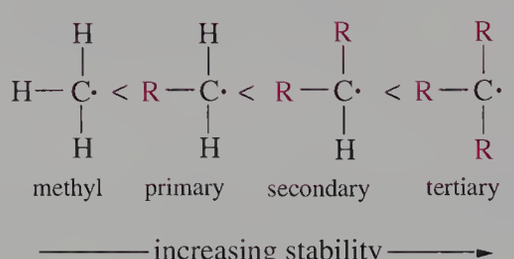
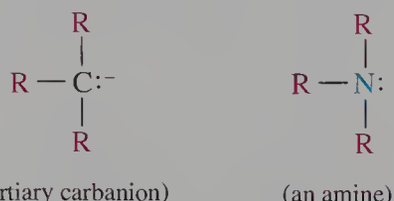


FIGURE 3.1 Structure of Reactive Intermediates



A carbon radical has a trivalent carbon atom that is sp^2 hybridized. The methyl radical ($CH_3\cdot$) has a planar structure with H—C—H bond angles of 120°. The trivalent carbon atom has an unhybridized *p* orbital that is perpendicular to the plane of the C—H bonds and contains the unpaired electron (Figure 3.1b).

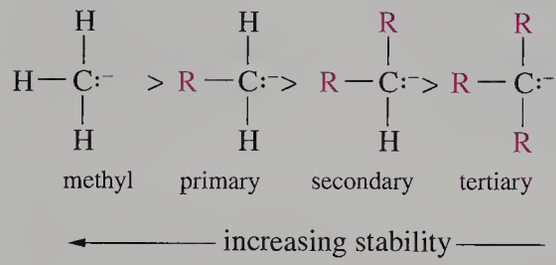
A carbanion has a negatively charged, trivalent carbon atom that has eight electrons in its valence shell. Thus, a carbanion is not electron deficient. It is isoelectronic with amines.



(a tertiary carbanion) (an amine)

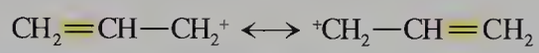
In contrast to carbocations and radicals, a carbanion is destabilized by electron-donating groups bonded to the anionic center because the center already has an octet

of electrons. Thus, the order of stability of carbanions is opposite that of carbocations and radicals.



The negatively charged carbon atom of a carbanion is sp^3 hybridized. Like the other sp^3 hybridized species we have considered, the four hybrid orbitals are directed toward the corners of a tetrahedron. One of the sp^3 hybrid orbitals contains an unshared pair of electrons (Figure 3.1c). As a result, the three groups bonded to the carbanionic center form a pyramidal molecule.

Carbocations, radicals, and carbanions can be stabilized by resonance. For example, if a carbon atom with a π bond is bonded to the trivalent carbon atom of the intermediate, the empty orbital of that carbon atom can interact with the p orbitals of the π bond. The result is a resonance-stabilized intermediate. The resonance forms of a simple stabilized carbocation intermediate are

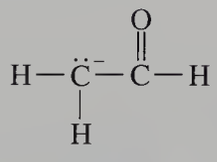


Problem 3.21

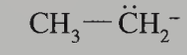
Trichloromethane ($CHCl_3$) is a stronger acid ($pK_a = 25$) than methane ($pK_a \approx 49$). Explain this difference considering the stability of the respective conjugate bases.

Problem 3.22

The conjugate base derived from ethanal (acetaldehyde) is more stable than the conjugate base of ethane. Explain why.



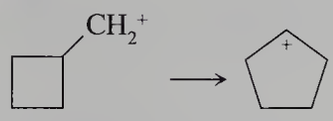
conjugate base of ethanal



conjugate base of ethane

Problem 3.23

Is the following rearrangement reaction of a carbocation spontaneous?



3.14 Bond Formation from Reactive Intermediates

Reactive intermediates can form two-electron covalent bonds in two ways. These processes are the reverse of the two bond-cleaving reactions.

1. Bond formation from fragments that each contain one electron is a **homogenic** process.

$$X\cdot + \cdot Y \longrightarrow X{-}Y$$

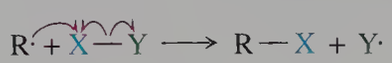
one electron provided from each fragment

2. Formation of a two-electron bond from oppositely charged fragments is a **heterogenic** process.

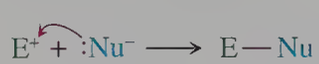
$$X^+ + Y{:}^- \longrightarrow X{-}Y$$

both electrons provided by one fragment

Homogenic reactions between two radicals are rare because these intermediates are so reactive that their concentration is extremely low. It is far more likely that they encounter another molecule and react by abstracting an atom to produce another radical. Thus, the most typical reaction of a free radical involves simultaneous homolytic bond cleavage and homogenic bond formation. A curved arrow using a single-barbed "fishhook" indicates the movement of one electron.



Heterogenic reactions are more common than homogenic reactions in organic chemistry. In organic reactions, a carbocation behaves as an electron-loving species called an **electrophile**. It seeks a negatively charged center to neutralize its positive charge and to complete a stable octet of electrons. On the other hand, a carbanion has an electron pair that causes it to react as a nucleus-loving species called a **nucleophile**. It seeks a positively charged center to neutralize its negative charge. Many organic reactions can be depicted by the following equation, in which E^+ represents an electrophile and Nu^- represents a nucleophile. The curved arrow notation shows the movement of a pair of electrons from the nucleophile to the electrophile.



3.15 Representative Mechanisms

The mechanism of a chemical reaction is not revealed by a balanced chemical equation. For example consider the following two substitution reactions.

$$CH_3{-}Cl + NaOH \longrightarrow CH_3{-}OH + NaCl$$

$$CH_3{-}H + Cl_2 \longrightarrow CH_3{-}Cl + H{-}Cl$$

In the first equation, a chlorine atom is replaced by a hydroxyl group. In the second equation, a hydrogen atom is replaced by a chlorine atom. The balanced equations look quite similar, but these processes occur by very different mechanisms. The first reaction takes place in one step, in which OH^- replaces Cl^- in a concerted process that occurs by heterolytic cleavage and heterogenic bond formation. The second reaction occurs in several steps and involves homolytic bond cleavage and homogenic bond formation.

Nucleophilic Substitution—A Polar Reaction

Reactions in which a nucleophile "attacks" a carbon atom and replaces another group are very common. The group displaced from the carbon center is called the **leaving group**, symbolized by L. A leaving group is often an electronegative atom or a group that can exist as a stable anion. R represents the remainder or the rest of the molecule.

$$Nu:^- + R{-}L \longrightarrow Nu{-}R + :L^-$$

The nucleophile has an unshared pair of electrons that forms a bond to the carbon residue. Thus, bond formation is a heterogenic process. The leaving group departs with an electron pair, and cleavage of the bond between the leaving group and carbon is a heterolytic process.

An example of a nucleophilic substitution process is the reaction of chloromethane with hydroxide ion.

$$OH^- + \overset{\delta^+}{C}H_3{-}\overset{\delta^-}{Cl} \longrightarrow CH_3{-}OH + Cl^-$$

In this reaction, the nucleophile approaches the carbon atom, which is made somewhat positive by the electronegative chlorine atom. The nucleophile has a nonbonding pair of electrons, which begins to bond to the carbon atom. As the nucleophile approaches the carbon atom, the bond between carbon and the chloride ion, a leaving group, weakens. The entire process is concerted because bond breaking and bond formation occur simultaneously.

Chlorination of an Alkane—A Radical Reaction

Now let's consider a reaction in which bonds break homolytically and form homogenically. Methane reacts with chlorine gas at elevated temperatures or in the presence of ultraviolet light as an energy source. In this reaction, a chlorine atom replaces a hydrogen atom.

$$CH_3{-}H + Cl_2 \longrightarrow CH_3{-}Cl + H{-}Cl$$

The mechanism of this reaction requires several steps.

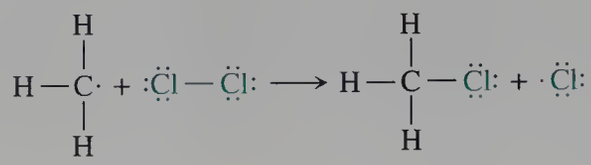
Step 1. A chlorine molecule absorbs either heat energy or light energy and the Cl—Cl bond breaks to give two chlorine atoms. They are electron-deficient, highly reactive radicals. This step starts the reaction and is called the **initiation step**.

$$:\ddot{Cl}{-}\ddot{Cl}: \longrightarrow :\ddot{Cl}\cdot + \cdot\ddot{Cl}:$$

Step 2. A chlorine atom abstracts a hydrogen atom from methane, breaking a C—H bond and making an H—Cl bond. This step, which continues the reaction by generating a new radical, is called a **propagation step**.

$$H{-}\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}{-}H + \cdot\ddot{Cl}: \longrightarrow H{-}\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}\cdot + H{-}\ddot{Cl}:$$

Step 3. A Cl—Cl bond breaks and a C—Cl bond forms. A radical reacts and another radical forms. This is also a propagation step.



The propagation steps, 2 and 3, repeat because one radical generates another in this sequence of reactions. The process continues as long as radicals and a supply of both reactants are present. Therefore, only a few chlorine atoms are required to initiate the reaction.

Problem 3.24

Bromine reacts with ethane by a free radical mechanism. Write the steps of this mechanism.

3.16 Factors That Influence Reaction Rates

A chemical reaction rate expresses a change in the concentration of the reactant or product per unit time. Concentration is usually expressed as molarity. Time is measured in seconds or minutes. In general, in this text we will only be concerned with changes in the reaction rate constants as the structures of a series of related compounds change.

The factors that affect the rate of a reaction are (1) the nature of the reactants, (2) the concentration of reactants, (3) temperature, and (4) the presence of substances called catalysts. We will briefly consider each of these factors to prepare for more detailed discussions in later chapters.

Effect of Structure on Reactivity

The structure of a reactant is the most important feature controlling the rate of a chemical reaction. For example, the addition reaction of ethylene (C_2H_4) with Br_2 occurs at a slower rate than the addition reaction of propene (propylene) with Br_2.

$$CH_2{=}CH_2 + Br_2 \longrightarrow Br{-}CH_2{-}CH_2{-}Br \qquad k_{rel} = 1$$

$$CH_3{-}CH{=}CH_2 + Br_2 \longrightarrow CH_3{-}CHBr{-}CH_2Br \qquad k_{rel} = 60$$

Although the same number and types of bonds are broken and formed in these two reactions, the rates of the reaction differ. We shall learn later that the CH_3— group of propene affects the reactivity of the π bond.

Effect of Concentration

As the concentration of reactants is increased, the reaction velocity increases because reactant molecules are more likely to collide and react. For a general reaction

$$a\,A + b\,B \longrightarrow \text{product}$$

where a and b are the coefficients of the balanced equation. We represent the rate

equation as rate $= k[A]^m[B]^n$, where the proportionality constant k is the **rate constant** and the exponents m and n represent the **order** of the reaction with respect to the reactants. Sometimes the values for the exponents in the rate expression are equal to the coefficients in the balanced equation ($a = m$ and $b = n$). However, we should not expect that equality. The coefficients are a consequence of the stoichiometry of the reaction. The exponents in the rate equation depend on the mechanism of the reaction. We shall return to this point later.

The exponents in a rate equation are determined experimentally, and they describe the effect of concentration on the rate of reaction. For example, in the substitution reaction of CH_3Cl and OH^-, the reaction rate increases when the concentration of either reagent increases. If we double the concentration of OH^-, the reaction rate increases by a factor of two; doubling the concentration of CH_3Cl also doubles the reaction rate. This means that the exponents in the rate equation both equal 1. When this is so, we say that the reaction is first order with respect to OH^- and first order with respect to CH_3Cl and is second order overall. This relationship is expressed by

$$\text{rate} = k[CH_3Cl][OH^-]$$

Not all substitution reactions are second order. Some reactions are first order in the reactant containing the leaving group, but are not affected by the concentration of the nucleophile. We will consider such reactions in Chapter 10.

Effect of Temperature

The rates of chemical reactions increase with a rise in temperature because the reactant molecules collide more frequently and with greater energy. However, not every collision between reactant molecules results in the formation of products. In most collisions the molecules simply bounce off each other. Collisions between molecules that result in a chemical reaction are called **effective collisions**. An effective collision in a chemical reaction occurs when the molecules have the proper orientation and have at least a certain amount of energy, called the **activation energy** (E_a). Molecules colliding with less than the activation energy rebound without reaction. The small fractions of molecules having the necessary activation energy at different temperatures are shown in Figure 3.2.

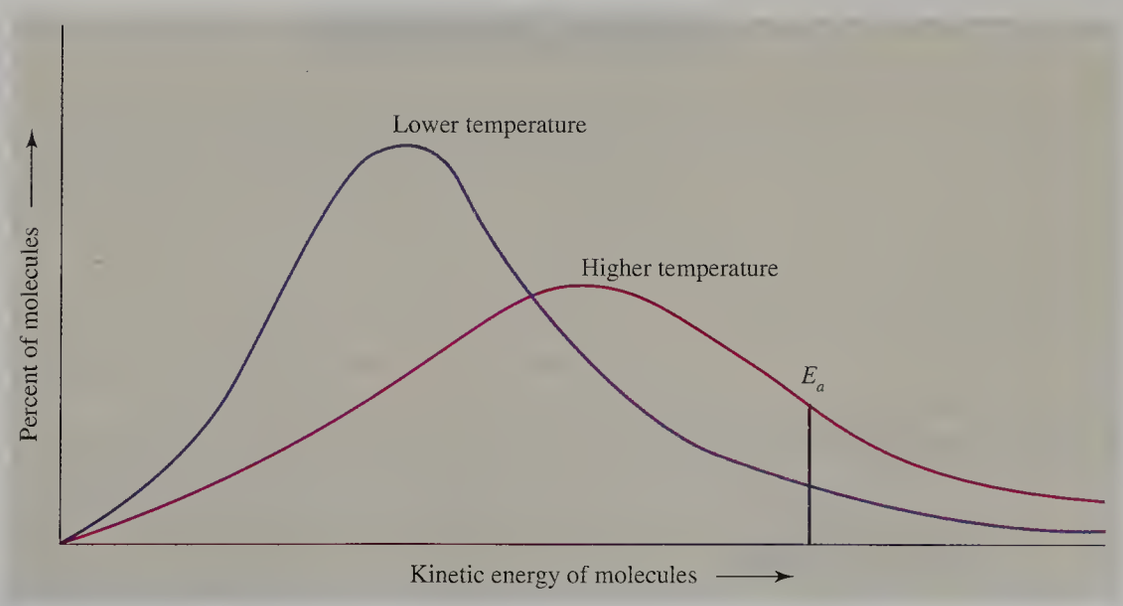


FIGURE 3.2 Distribution of Energies of Molecules and Temperature

An increase in temperature affects the rate constant of a reaction because the average kinetic energy of the molecules is directly proportional to the absolute temperature. As the kinetic energy increases, so does the number of collisions. However, more important is the larger fraction of molecules that have energy equal to or greater than the activation energy at higher temperatures (Figure 3.2). As a "rule of thumb," the rates of organic reactions increase between twofold and fourfold for each increase of 10 °C. If the rate is doubled for a 10 °C increase, a 30 °C change in temperature would increase the reaction rate by approximately $2^3 = 8$ times. The effect of temperature on the rate constant for the reaction of chloromethane with hydroxide is illustrated by data in Table 3.6.

TABLE 3.6
Effect of Temperature on Rates of a Substitution Reaction

Temperature (°C)	*Rate Constant ($L\ mole^{-1}\ sec^{-1}$)*
35	2.6×10^{-5}
45	8.5×10^{-5}
55	2.6×10^{-4}
65	7.8×10^{-4}

Effect of Catalyst

A **catalyst** is a substance that increases a reaction rate. A catalyst is said to catalyze the reaction, and its effect is known as catalysis. Catalysts are usually required only in small amounts. The catalyst is not consumed, even though it does interact with the reactant during the reaction. Although a catalyst increases the rate of a reaction, it does not change the equilibrium constant for the reaction because it does not change the standard free energies of either the reactants or products.

The addition reaction of ethylene and hydrogen occurs only at very high temperatures in the gas phase. However, in the presence of platinum suspended on the surface of carbon, a heterogeneous reaction occurs rapidly at room temperature. At the completion of the reaction, the catalyst is still active and can be used to catalyze further reaction if more reactants are added.

$$CH_2{=}CH_2 + H_2 \xrightarrow{Pt/C} CH_3{-}CH_3$$

Problem 3.25

The rate constant for the nucleophilic substitution reaction of CH_3Br with OH^- is 6.6×10^{-4} L $mole^{-1}$ s^{-1} at 310 K. Compare this value to the rate constant for the reaction of CH_3Cl with OH^- (Table 3.6). Which reaction is faster? What does this information indicate about the leaving group characteristics of Br^- and Cl^-?

Problem 3.26

Bromoethane reacts with cyanide ion according to the following equation. When the concentration of the cyanide ion is doubled, the rate of the reaction is doubled. When the concentration of bromoethane is tripled, the rate of the reaction is tripled. What is the kinetic order with respect to each reactant? What is the overall kinetic order of the reaction? Write the rate equation.

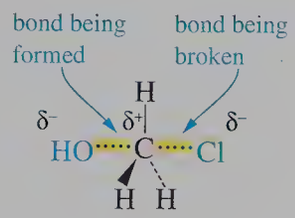
$$CH_3{-}CH_2{-}\ddot{Br}: + :C{\equiv}N:^- \longrightarrow CH_3{-}CH_2{-}C{\equiv}N: + :\ddot{Br}:^-$$

3.17 Reaction Rate Theory

The activation energy for a given reaction depends on the types of bonds broken and formed in the reaction. During a reaction, the arrangement of the atoms changes as bonds are distorted and eventually broken and new bonds form. When reactant atoms move close together, some repulsion results from the proximity of the electrons sur-

rounding each atom. As bonding patterns change during a reaction, each specific arrangement of atoms has an associated energy. The atomic arrangement whose structure has the maximum energy on the minimum energy pathway from reactants to products is the **transition state**.

The transition state in the nucleophilic substitution of hydroxide ion and chloromethane has both the hydroxide and chloride ions bonded to the carbon atom.



Dotted lines are used to represent bonds that are partially broken or partially formed. The carbon–chlorine bond breaks on one side of the transition state structure while the carbon–oxygen bond forms on the other side. Transition state structures represent species that cannot be isolated. The structure of the transition state for a reaction is inferred from kinetic data. Transition states are not intermediates. An intermediate is a species with a finite lifetime, and some intermediates can be isolated. An intermediate forms in one reaction, has a discrete structure, and then reacts in a second reaction.

Reaction Coordinate Diagrams

Reaction coordinate diagrams are used to indicate the energy of a chemical system relative to the structure of reacting species as they are converted from reactant to product (Figure 3.3). A reaction coordinate diagram has a vertical axis that shows the total free energy of the reacting system. However, $\Delta H°$ is often used instead, an approximation that works well if $\Delta S°$ is small. The horizontal axis qualitatively represents some change in the structure of the reacting species, such as the formation of a bond or the cleavage of a bond. The reaction coordinate diagram places the reactants on the left of the axis and proceeds to the products located at the right of the axis. Figure 3.3 includes diagrams for exothermic and endothermic reactions. The heat of reaction, $\Delta H°_{rxn}$—given by the difference in the $\Delta H°_{products}$ and $\Delta H°_{reactants}$—is shown for both types of reactions. Note that $\Delta H°_{rxn}$ is independent of the path by which the reaction occurs. It depends only on the difference in energy between the initial and final states.

The transition state is represented at the highest point on the graph. The difference between the energy of the reactants and the transition state is the activation energy ($E_a > 0$). Once the molecules reach this point, they may release energy and proceed to form products.

The activation energy and the temperature of the reaction control the speed of a reaction. A reaction that has a large activation energy is slow because only a small fraction of the molecules collide with sufficient energy to reach the transition state. The rate of the reaction increases when the temperature increases because the kinetic energy of molecules increases with increasing temperature. As a result, more molecular collisions occur with energy equal to or greater than the activation energy.

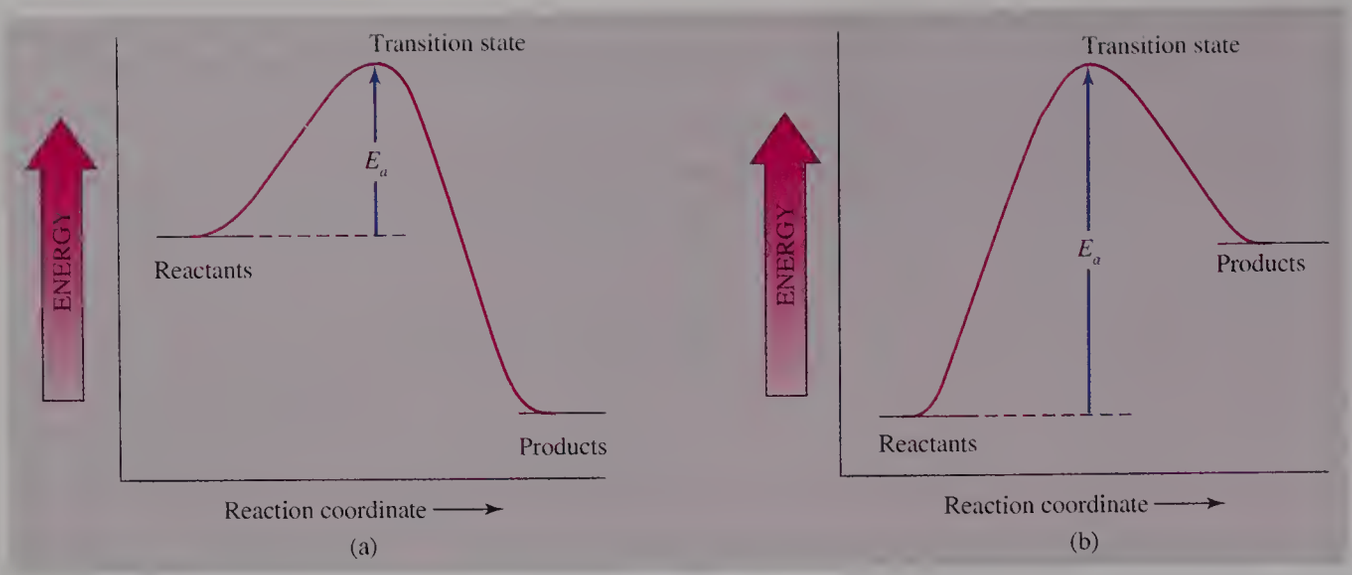


FIGURE 3.3 Reaction Coordinate Diagrams
Reaction coordinate profiles for (a) exothermic and (b) endothermic reactions. The activation energy that is required to give the transition state structure is positive in both cases.

Mechanisms and Reaction Coordinate Diagrams

A reaction coordinate diagram shows the energy associated with the sequence of events for single- or multiple-step reactions. The energies of the transition states and of any intermediates formed are of particular importance. The effect of variations in structure on these energies will form the basis for most of the reactions studied in this text.

First let's consider the reaction coordinate diagram for the substitution reaction of chloromethane with hydroxide ion. We recall that the kinetics of the reaction show it to be first order in each reactant and second order overall. These data are consistent with a single-step, concerted mechanism. As will be demonstrated in Chapter 10, the reactants must be oriented so that the nucleophile, the carbon atom, and the leaving group are collinear. In the transition state, both hydroxide and chloride are partially bonded to the carbon atom. The energy of the transition state is higher than the energy of the reactants and products because energy is required to partially break the carbon–chlorine bond and the total energy of carbon–oxygen bond formation has not yet been fully released (Figure 3.4). Other nucleophilic substitution reactions that occur in a single step have similar reaction coordinate diagrams. The differences are only in the ΔH°_{rxn} and E_a, which result from differences in the bond energy for the bond formed between carbon and the nucleophile and the bond energy for the bond broken between carbon and the leaving group.

Some reactions occur in two or more steps. For a general reaction involving two steps we write

$$\text{reactants} \rightleftharpoons \text{intermediate} \rightleftharpoons \text{products}$$

In this process, an intermediate that forms via a transition state for the first reaction subsequently reacts via a different transition state in a second reaction. An additional intermediate is required for each additional step in the reaction sequence. Thus, an n-step reaction sequence has n transition states and $n - 1$ intermediates.

Reaction coordinate diagrams are shown in Figure 3.5 for two general cases of two-step reactions. In the first case, the activation barrier for formation of the intermediate is of higher energy than the activation barrier for the reaction of the in-

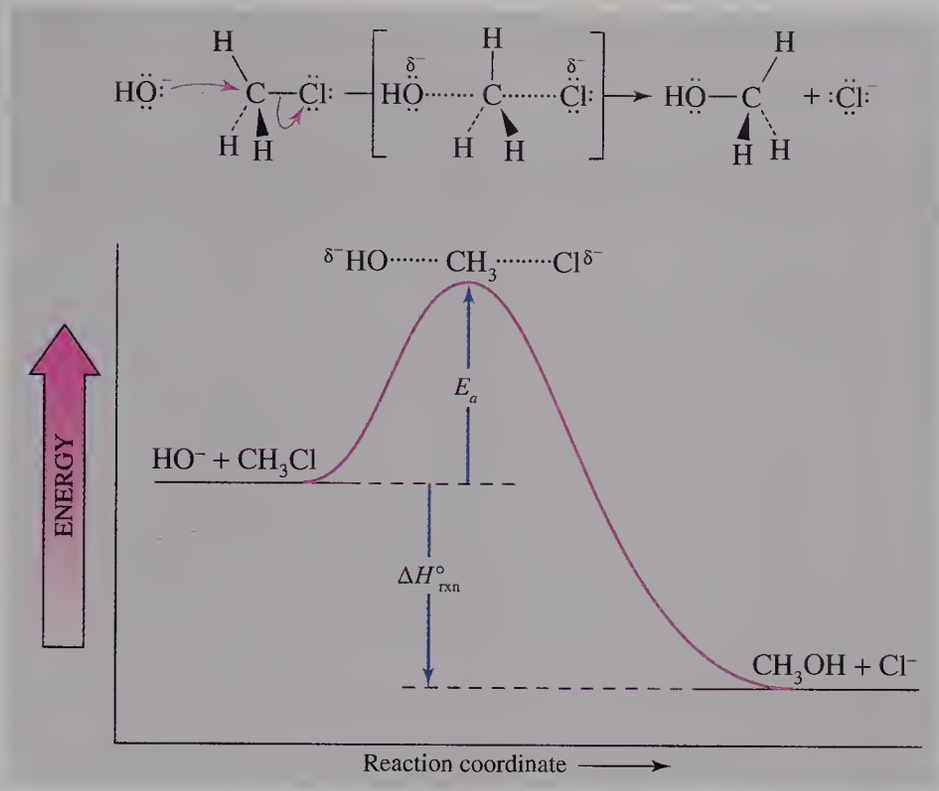
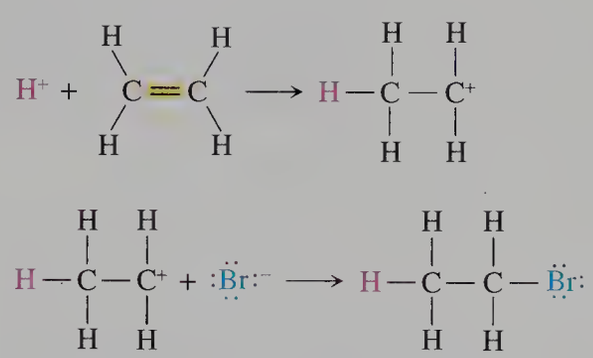


FIGURE 3.4 Transition State of a Substitution Reaction
The reaction of chloromethane with hydroxide ion occurs in a single-step process. The activation energy reflects the stability of the transition state relative to the stability of the reactants.

termediate (Figure 3.5a). This means that the rate constant for the first step is smaller than the rate constant for the second step. In the second case, the activation barrier for formation of the intermediate is of lower energy than the activation barrier for the reaction of the intermediate (Figure 3.5b). This means that the rate constant for the first step is larger than the rate constant for the second step.

Let's consider the addition reaction of ethylene and HBr. The reaction involves two steps.



In the first step, a proton acts an electrophile. It forms a bond to carbon using the π electrons of the double bond. As a consequence, an intermediate carbocation forms, which then reacts in a second step with the nucleophilic bromide ion. Each of the steps is shown in the reaction coordinate diagram in Figure 3.6.

In the first transition state, a hydrogen ion begins to bond to carbon as π electrons are removed from the double bond. The energy then decreases until an intermediate carbocation forms. In the second step, the carbocation starts to bond to the nucleophilic bromide ion. Note that the energy of the carbocation is lower than the energy of the two transition states. Finally, as the carbon–bromine bond becomes fully formed, the reaction coordinate diagram shows that the energy of the products is lower than the energy of the reactants.

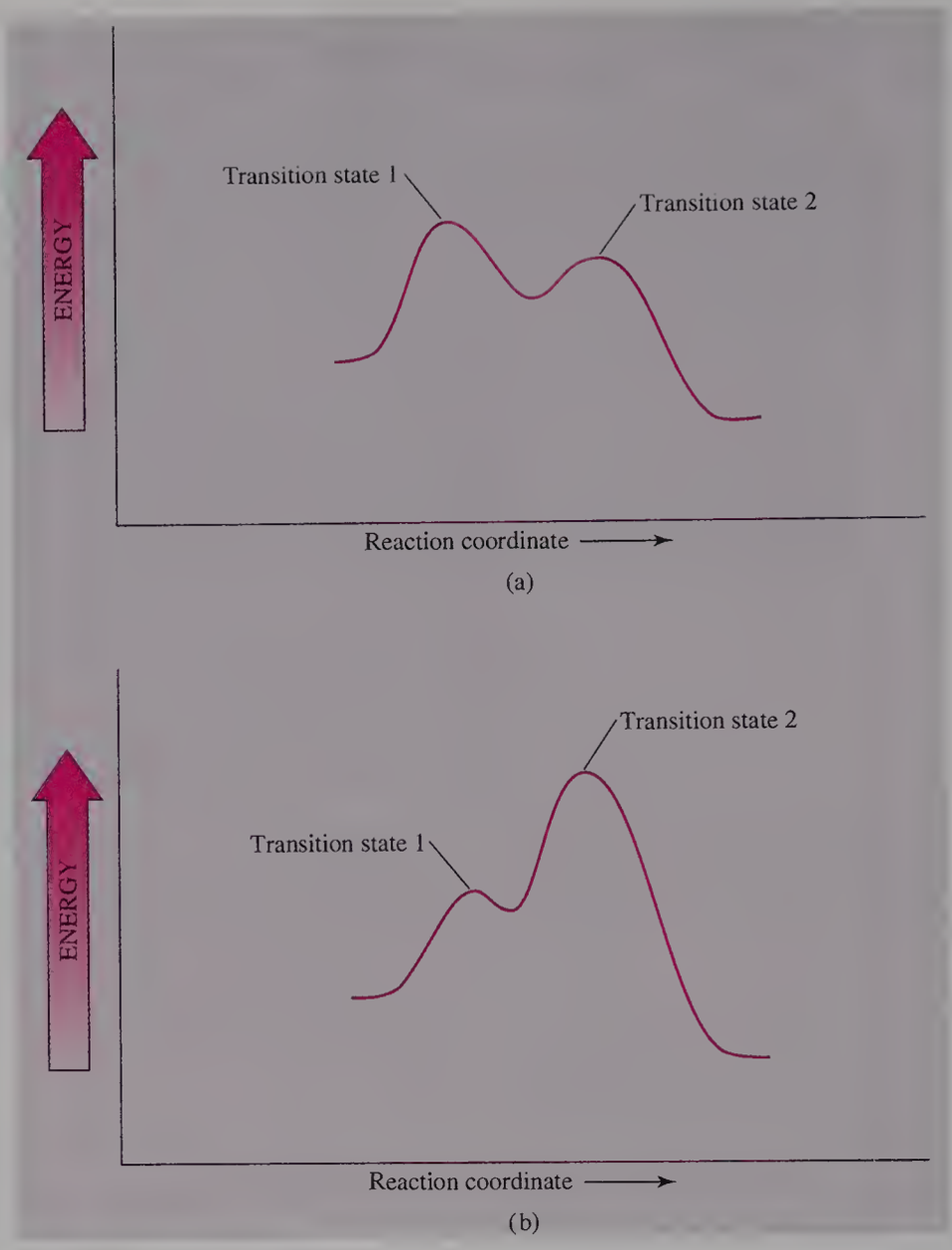


FIGURE 3.5 Reaction Coordinate Diagram for Multistep Reactions
(a) The first step has the higher activation energy and is the rate-determining step.
(b) The second step has the higher activation energy and is the rate-determining step. The rate of reaction of the first step is very much faster than the second step.

How Catalysts Function

A catalyst provides a path for the reaction that is different from the path of the uncatalyzed reaction. The path starts with the same reactants and concludes with the same products. The effect of a catalyst on the path of a reaction may involve additional steps. Consider the hypothetical reaction of A and B, a reaction with a high activation energy.

$$A + B \longrightarrow X$$

The high activation energy can be reached by only a few high-energy molecular collisions, and as a consequence the reaction is slow. However, in the presence of a catalyst, represented by C, the following reactions may occur.

$$\text{Step 1:} \quad A + C \longrightarrow A{-}C$$

$$\text{Step 2:} \quad A{-}C + B \longrightarrow X + C$$

The catalyst may combine with A in a reaction with a low activation energy. Similarly, the reaction of A—C with B may also have a low activation energy. Therefore,

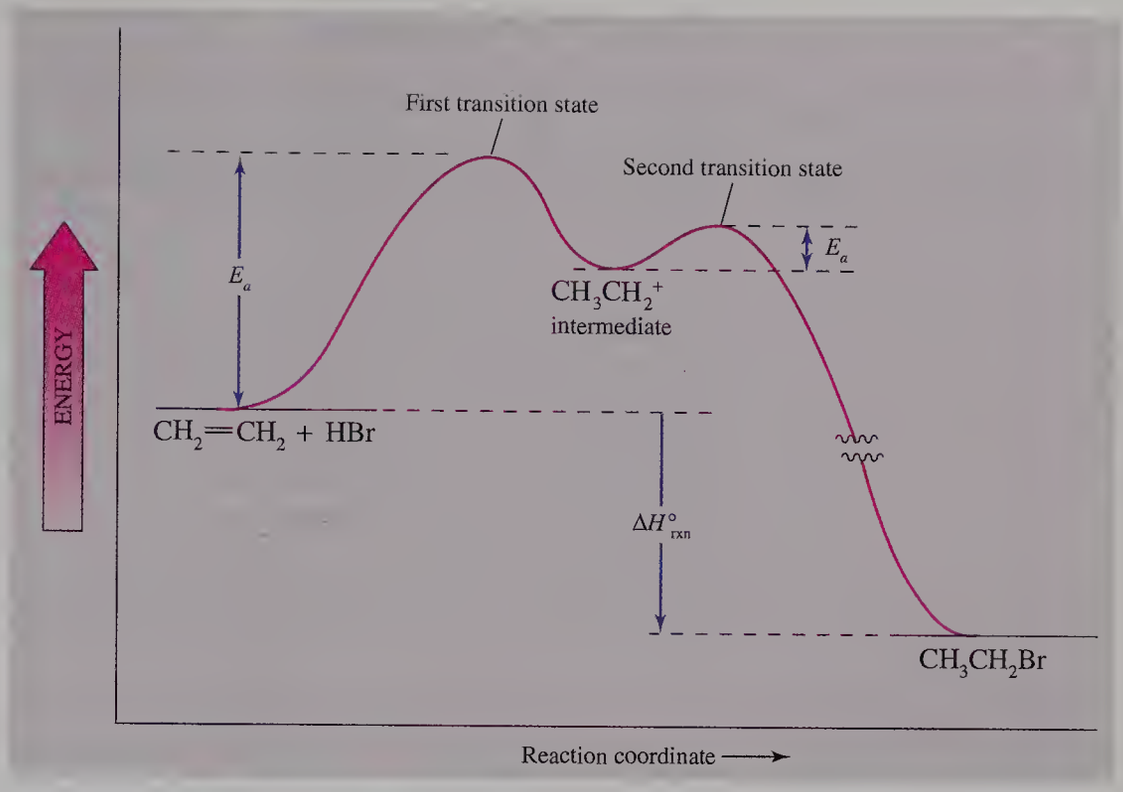
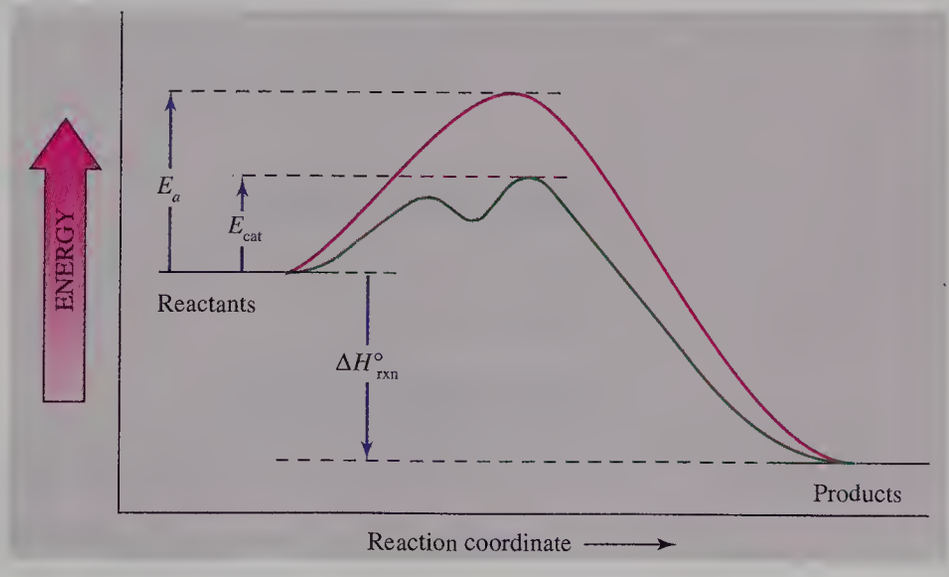


FIGURE 3.6 Reaction Mechanism of an Addition Reaction
The rate-determining step in the addition of HBr to ethylene is the attack of a proton on the electrons of the double bond to give a carbocation. The subsequent step occurs at a faster rate because the activation energy of the second step is lower than for the first step.

a larger fraction of molecules will be able to react faster via this catalyzed pathway than they could without the catalyst at the same temperature.

The path for the addition reaction of ethylene and hydrogen catalyzed by platinum on carbon has a different, lower activation energy than the uncatalyzed reaction. The metal catalyst used in the addition of hydrogen to ethylene functions by attaching both reactants to its surface. The hydrogen molecule dissociates into hydrogen atoms on the surface and each hydrogen atom successively bonds to the ethylene molecule. The catalyzed reaction rate is faster because the activation energy of each of the many steps is lower than for the step in the uncatalyzed reaction (Figure 3.7).

FIGURE 3.7 Effect of Catalyst on the Mechanism of a Reaction
The activation energy for a catalyzed reaction is smaller than the activation energy for reaction in the absence of a catalyst. The catalyzed reaction may involve a different number of steps.



Transition State Structure

How can we picture the structure of the transition state when it is merely a transient and part of a continuum of structures along a reaction pathway? We infer its structure based on what we know about the structure of the species that leads to it and the species formed from it. The species that produces it is the reactant. The species that forms may be the product or an intermediate, such as a carbocation formed in a multistep reaction.

Consider the generalized reaction coordinate diagrams shown in Figure 3.8 for strongly exothermic and endothermic reactions. In the strongly exothermic case, the energies of the transition state and the reactants are close to each other. As a consequence, the transition state occurs at a point not far along the reaction coordinate. For such a situation, the structure of the transition state resembles the structure of the reactant more than the structure of the product. This correlation is summarized by the **Hammond postulate**, which states that the structures of transition states most closely resemble those species most similar in energy. Thus, in general, we find that the structure of the transition state for an exothermic process is more reactant-like. It follows that the structure of the transition state for an endothermic process is more product-like.

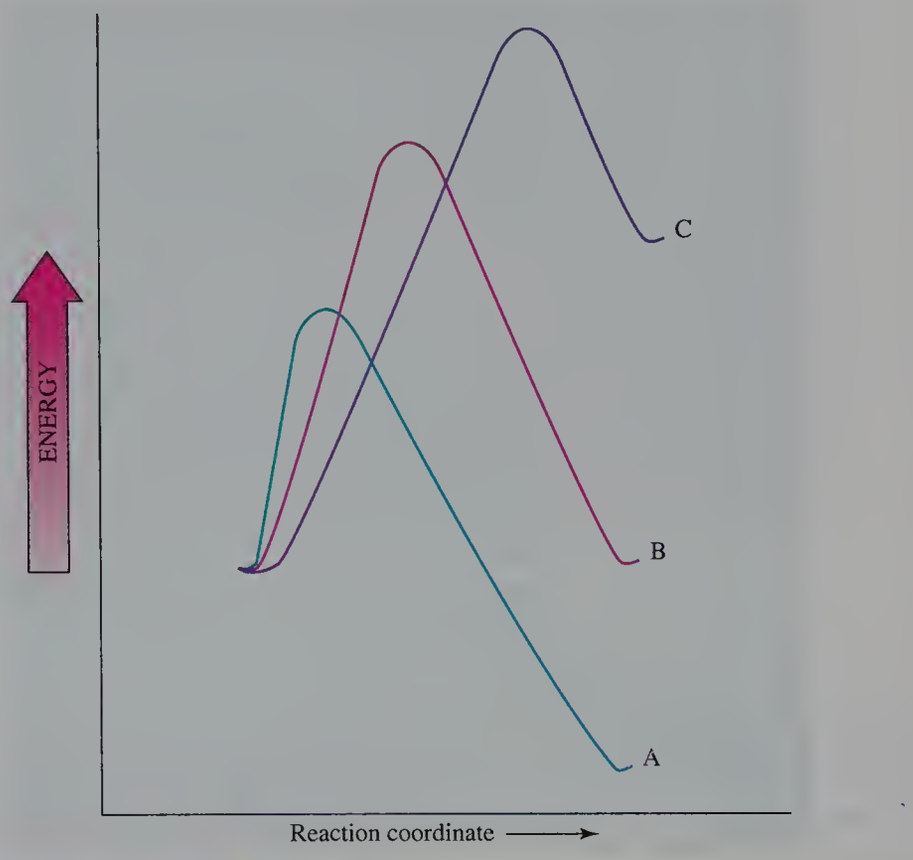


FIGURE 3.8 The Hammond Postulate
The location of the transition state along the reaction coordinate axis depends on the activation energy. Curve A for an exothermic process has an "early" transition state that is closer to the reactant side. Curve B is for a reaction with no difference in enthalpy between reactants and products. The transition state is in the middle. Curve C is for an endothermic process, which has a "late" transition state that is closer to the product side.

Problem 3.27

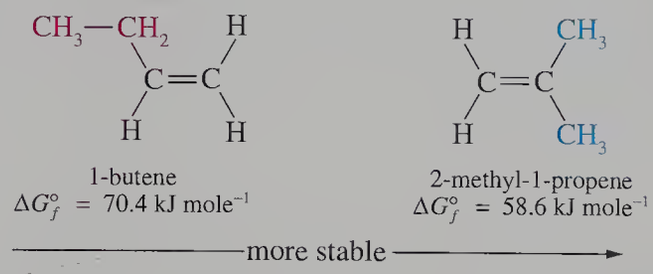
The rate constants for the nucleophilic substitution reaction with hydroxide ion with CH_3Cl and CH_3Br at 310 K are 3.2×10^{-5} and 6.6×10^{-4} L mole^{-1} s^{-1}, respectively. Which reaction has the larger E_a?

Problem 3.28

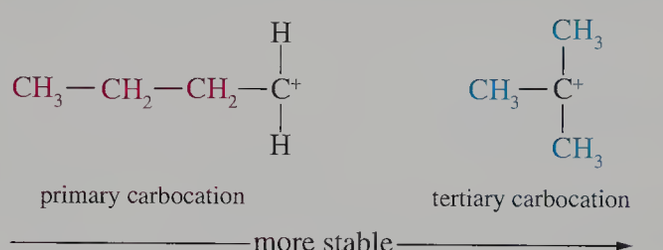
The hydrolysis reaction of ethyl ethanoate (ethyl acetate) in basic solution occurs in three steps. How many transition states are there? How many intermediates are involved?

3.18 Stability and Reactivity

Although we might think that the terms stability and reactivity are related, they are in fact not. Let's see how these two words differ in meaning. Stability is related to ΔG_f°, a thermodynamic state function. A compound with a more negative ΔG_f° than another compound is more stable. Thus, 2-methyl-1-propene is more stable than 1-butene.

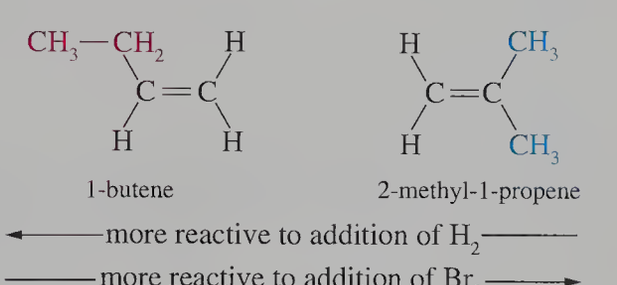


When we discuss changes in structure that "stabilize" a compound, we mean that its free energy is lowered. This term is used in describing reactants, products, and even intermediates. Thus, we learned in Section 3.13 that carbocations are intermediates in chemical reactions. Tertiary carbocations are stabilized by the three carbon groups bonded to the positive carbon atom. A primary carbocation is not as stabilized because there is only a single carbon group bonded to its positive carbon atom.



Now let's consider what is meant by the term reactivity. It reflects the energy of activation required for that substance to form a particular transition state. Thus, we must define a specific reaction in order to discuss reactivity. Reactivity is not directly related to stability but rather is the difference in the stability of the reactant and the stability of the transition state.

A substance may be more reactive than another substance with one reagent, and the order of reactivity may be reversed for some other reagent. For example, 1-butene is more reactive than 2-methyl-1-propene in the addition of H_2. However, the order of reactivity to the addition of bromine is reversed.



The reasons for the differences in reactivity are related to the different mechanisms for the two reactions. We use the rate data to picture transition state structures for each reaction.

EXERCISES

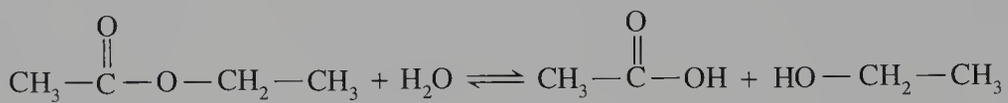
Equilibrium Constant Expressions

3.1 Write the equilibrium constant expression for the reaction of ethanal and methanol to give an acetal.

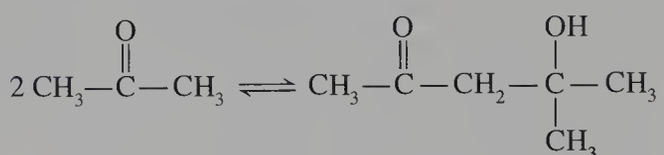
$$CH_3CHO + 2\,CH_3OH \rightleftharpoons CH_3CH(OCH_3)_2 + H_2O$$

3.2 Write the equilibrium constant expression for the reaction of acetylene to give cyclooctatetraene (C_8H_8).

3.3 How do the equilibrium constant expressions differ for the hydrolysis reaction of ethyl ethanoate and the esterification reaction of ethanol and ethanoic acid (Section 3.2)? What is the value of the equilibrium constant for the hydrolysis reaction?



3.4 At equilibrium, the yield of the condensation product of acetone is about 5%. Calculate the equilibrium constant for the reaction.



Acid–Base Equilibria

3.5 Without reference to tables of pK_a values, predict the position of the following equilibrium.

$$CH_3CH_2{-}S{-}H + CH_3{-}O^- \rightleftharpoons CH_3CH_2{-}S^- + CH_3{-}OH$$

3.6 Without reference to tables of pK_a values, predict the position of the following equilibrium.

$$CH_3CH_2CO_2H + CH_3O^- \rightleftharpoons CH_3CH_2CO_2^- + CH_3OH$$

3.7 The approximate pK_a values of CH_4 and CH_3OH are 49 and 16, respectively. Which is the stronger acid? Will the equilibrium position of the following reaction lie to the left or to the right?

$$CH_4 + CH_3O^- \rightleftharpoons CH_3^- + CH_3OH$$

3.8 The approximate pK_a values of NH_3 and CH_3OH are 36 and 16, respectively. Which is the stronger acid? Will the equilibrium position of the following reaction lie to the left or to the right?

$$CH_3OH + NH_2^- \rightleftharpoons NH_3 + CH_3O^-$$

Structure and Acid Strength

3.9 Write the structures of the two conjugate acids of hydroxylamine ($NH_2{-}OH$). Which is the more acidic?

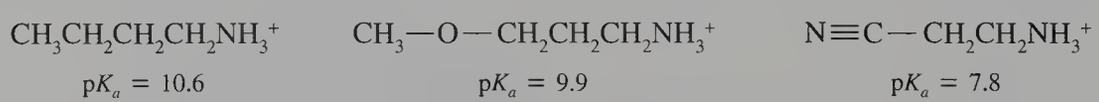
3.10 Write the structures of the two conjugate bases of hydroxylamine ($NH_2{-}OH$). Which is the more basic?

3.11 Which is the stronger acid, chloroethanoic acid ($ClCH_2CO_2H$) or bromoethanoic acid ($BrCH_2CO_2H$)? Why?

3.12 Which acid has the larger pK_a, chloroethanoic acid ($ClCH_2CO_2H$) or dichloroethanoic acid (Cl_2CHCO_2H)? Why?

3.13 Based on the pK_a values of substituted butanoic acids (Section 3.4), predict the pK_a of 4-chlorobutanoic acid.

3.14 Explain the trends in the pK_a values of the following ammonium ions.

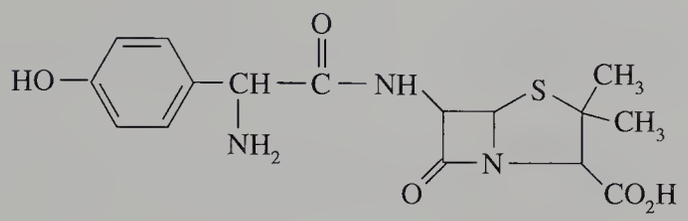


3.15 Explain why the hydrogen of the CH_3 of propene is more acidic than hydrogen of the CH_3 of propane.

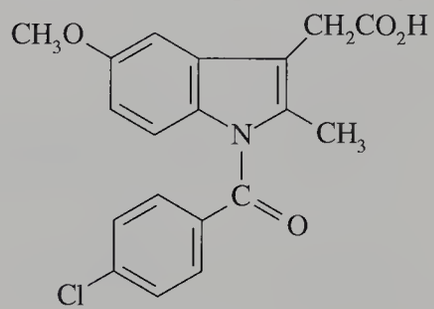
$$CH_3—CH_2—CH_3 \qquad CH_2=CH—CH_3$$

3.16 Ethanonitrile ($CH_3C{\equiv}N$) is a stronger acid than ethane. Explain why.

3.17 The pK_a of acetic acid ($CH_3—CO_2H$) is 4.8. Explain why the carboxylic acid group of amoxicillin (pK_a = 2.4), a synthetic penicillin, is more acidic than acetic acid, whereas the carboxylic acid group of indomethacin (pK_a = 4.5), an anti-inflammatory analgesic used to treat rheumatoid arthritis, is of comparable acidity.

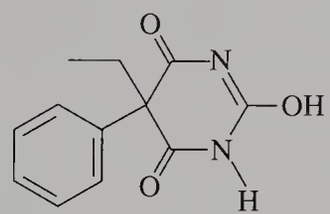


amoxicillin



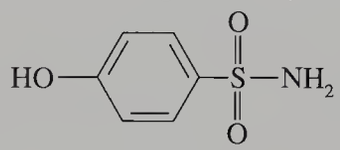
indomethacin

3.18 The pK_a of the OH group of phenobarbital is 7.5, whereas the pK_a of CH_3OH is 16. Explain why phenobarbital is significantly more acidic.



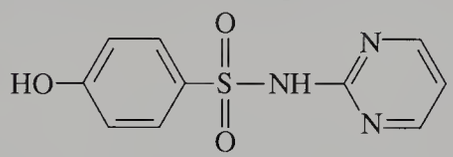
phenobarbital

3.19 The N—H bond of ammonia is not very acidic (pK_a = 33). However, the pK_a for the N—H bond of sulfanilamide, a sulfa drug, is 10.4. Suggest a reason for the higher acidity of sulfanilamide.



sulfanilamide

3.20 The pK_a of sulfadiazine, a sulfa drug, is 6.5. Why is this compound more acidic than sulfanilamide?



sulfadiazine

Equilibrium Constant and Free Energy

3.21 A reaction has $K = 1 \times 10^{-5}$. Are the products more or less stable than the reactants? Is the reaction exergonic or endergonic?

3.22 Which reaction would be exergonic, one with K = 100 or one with K = 0.01?

3.23 Could a reaction have K = 1? What relationship would exist between the free energies of the reactants and products as shown in the reaction coordinate diagram?

3.24 Which reaction is exergonic, one with $\Delta G^\circ_{rxn} = +15$ kJ mole^{-1} or one with $\Delta G^\circ_{rxn} = -15$ kJ mole^{-1}?

3.25 The ΔG°_{rxn} for the following substitution reaction is +2 kJ mole^{-1}. What is K at 25 °C?

$$CH_3SH + HBr \rightleftharpoons CH_3Br + H_2S$$

3.26 The equilibrium constant at 25 °C for the following isomerization reaction is 4.9. What is ΔG°_{rxn}?

$$CH_3-CH_2-CH_2-CH_3 \rightleftharpoons CH_3-\underset{\displaystyle CH_3}{\overset{|}{CH}}-CH_3$$

Bond Dissociation Energy

3.27 Using bond dissociation energies, calculate ΔH°_{rxn} for each of the following reactions.

(a) $CH_3CH_3 + Br_2 \longrightarrow CH_3CH_2Br + HBr$ **(b)** $CH_3CH_2OH + HBr \longrightarrow CH_3CH_2Br + H_2O$

(c) $CH_2{=}CH_2 + H_2O \longrightarrow CH_3CH_2OH$

3.28 Using bond dissociation energies, calculate ΔH°_{rxn} for each of the following reactions.

(a) $CH_3{-}O{-}CH_3 + HBr \longrightarrow CH_3OH + CH_3Br$ **(b)** $CH_3CH_2SH + NH_3 \longrightarrow CH_3CH_2NH_2 + H_2S$

(c) $HC{\equiv}CH + 2\,H_2 \longrightarrow CH_3CH_3$

Estimation of ΔS°_{rxn}

3.29 The following series of reactions is used as an industrial synthesis of vinyl chloride, a compound used in the production of polyvinyl chloride (PVC). Estimate the ΔS°_{rxn} for each step.

$$CH_2{=}CH_2 \xrightarrow{Cl_2} Cl{-}CH_2{-}CH_2{-}Cl \xrightarrow{heat} CH_2{=}CH{-}Cl + HCl$$

3.30 The following two reactions are used as an industrial synthesis of methanol. Estimate the ΔS°_{rxn} for each step.

$$CH_4 + H_2O \xrightarrow{700\ ^\circ C} CO + 3\,H_2$$

$$CO + 2\,H_2 \xrightarrow{400\ ^\circ C} CH_3OH$$

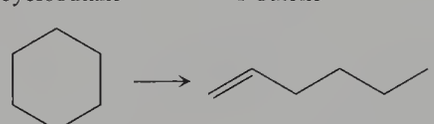
3.31 Consider the ΔS° values for the substitution reaction converting ethane to chloroethane and the addition reaction converting ethene to chloroethane. Explain the difference.

$$CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl \qquad \Delta S^\circ = +2\ \text{J mole}^{-1}\ \text{deg}^{-1}$$

$$CH_2{=}CH_2 + HCl \longrightarrow CH_3{-}CH_2{-}Cl \qquad \Delta S^\circ = -129\ \text{J mole}^{-1}\ \text{deg}^{-1}$$

3.32 Consider the ΔS° values for the following two isomerization reactions. Why are the values positive? Why do the two values differ?

cyclobutane 1-butene $\qquad \Delta S^\circ = 43.4\ \text{J mole}^{-1}\ \text{deg}^{-1}$



cyclohexane 1-hexene $\qquad \Delta S^\circ = 88.5\ \text{J mole}^{-1}\ \text{deg}^{-1}$

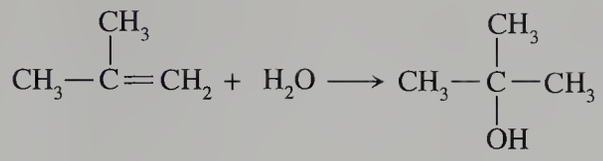
Gibbs Free Energy, Enthalpy, and Entropy

3.33 Calculate ΔG°_{rxn} for the following elimination reaction at 225 °C.

$$CH_3CHICH_3 \longrightarrow CH_3CH{=}CH_2 + HI$$

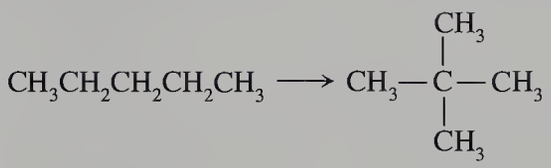
	CH_3CHICH_3	$CH_3CH{=}CH_2$	HI
ΔH°_f (kJ mole^{-1})	−82.0	11.7	−5.6
S° (J mole^{-1} deg^{-1})	380	306	221.2

3.34 Calculate ΔG°_{rxn} for the following addition reaction at 25 °C.



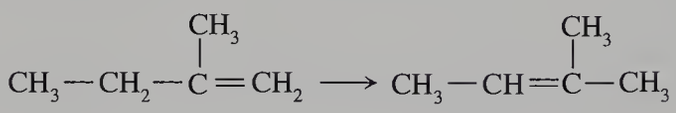
ΔH_f° (kJ mole^{-1})	−16.9	−285.2	−358.5
S° (J mole^{-1} deg^{-1})	293.0	69.8	193.3

3.35 Calculate ΔG°_{rxn} for the following isomerization reaction at 400 °C.



ΔH_f° (kJ mole^{-1})	−149.5	−167.8
S° (J mole^{-1} deg^{-1})	349	306

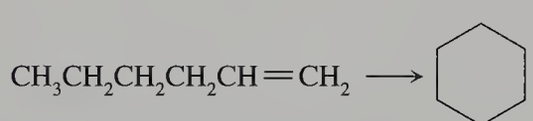
3.36 Calculate the ΔG°_{rxn} for the following isomerization reaction at 100 °C.



ΔH_f° (kJ mole^{-1})	−35.9	−42.2
S° (J mole^{-1} deg^{-1})	341	338

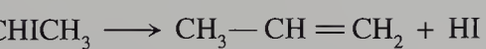
Estimation of K_{eq} and Thermodynamic Quantities

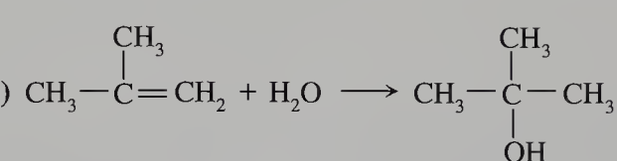
3.37 The ΔH°_{rxn} values for the formation of HCl from H_2 and Cl_2 and the formation of cyclohexane from 1-hexene differ by about 12.5 kJ mole^{-1}. However, the equilibrium constants at 25 °C differ by a factor of 10^7. Which reaction has the larger equilibrium constant? Why?

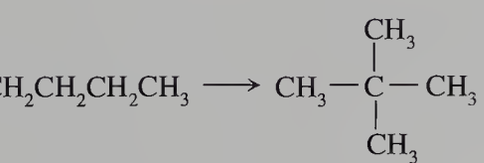


3.38 The ΔH°_{rxn} for the addition of hydrogen to ethylene is −134 kJ mole^{-1}. At approximately 800 °C, the equilibrium constant for the reaction is 1. What is ΔS°_{rxn}?

3.39 Indicate why K_{eq} cannot be estimated for the following reactions based only on ΔH°_{rxn}. For which reaction would the approximation that ΔH°_{rxn} is equal to ΔG°_{rxn} be closest to correct?

(a) 

(b) 

(c) 

3.40 Assuming that ΔS°_{rxn} is zero, calculate the equilibrium constant for each of the following reactions based on the ΔH°_{rxn} values.

(a) $CH_3—C{\equiv}C—CH_3 \longrightarrow CH_3—CH_2—C{\equiv}C—H$

$\Delta H^\circ_f = 144.9$ kJ mole^{-1} $\Delta H^\circ_f = 164.9$ kJ mole^{-1}

(b) $CH_3—CH_2—\underset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 \longrightarrow CH_3—CH{=}\underset{\displaystyle CH_3}{\overset{|}{C}}—CH_3$

$\Delta H^\circ_f = -35.9$ kJ mole^{-1} $\Delta H^\circ_f = -42.2$ kJ mole^{-1}

(c) $CH_3—CH_2—CH_2—Cl \longrightarrow CH_3—\underset{\displaystyle Cl}{\overset{|}{C}}H—CH_3$

$\Delta H^\circ_f = -129.4$ kJ mole^{-1} $\Delta H^\circ_f = -140.3$ kJ mole^{-1}

Bond Cleavage and Intermediates

3.41 Write the structure of the radical formed by abstraction of a hydrogen atom by a chlorine atom for each of the following compounds.

(a) CH_3CH_3 (b) CH_3Cl (c) CH_2Cl_2

3.42 Write the structures of all possible radicals formed by abstraction of a hydrogen atom by a chlorine atom for each of the following compounds.

(a) $CH_3—CH_2—CH_3$ (b) $CH_3—CH_2—CH_2—CH_3$ (c) $CH_3—\underset{\displaystyle CH_3}{\overset{|}{C}}H—CH_3$

3.43 The oxygen–chlorine bond of methyl hypochlorite ($CH_3—O—Cl$) can cleave heterolytically. Based on the electronegativity values of chlorine and oxygen, predict the charges on the cleavage products.

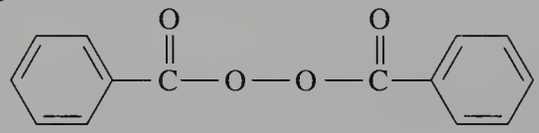
3.44 2-Chloropropane reacts with the Lewis acid $AlCl_3$ to give $AlCl_4^-$ and a carbon intermediate. What is the intermediate? What type of bond cleavage occurs?

$CH_3—\underset{\displaystyle Cl}{\overset{|}{C}}H—CH_3$

2-chloropropane

3.45 Hydrogen peroxide ($H—O—O—H$) reacts with a proton to give a conjugate acid, which undergoes heterolytic oxygen–oxygen bond cleavage to yield water. What is the second product?

3.46 Benzoyl peroxide is used in creams to control acne. It is an irritant that causes proliferation of epithelial cells. It undergoes a homolytic cleavage of the oxygen–oxygen bond. Write the structure of the product, indicating all of the electrons present on the oxygen atoms.



benzoyl peroxide

Stability of Reactive Intermediates

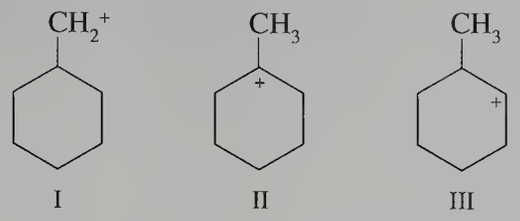
3.47 Arrange the following intermediates in order of increasing stability.

$CH_3—CH_2—\dot{C}H—CH_3$ I

$CH_3—\underset{\displaystyle CH_3}{\overset{|}{C}}H—CH_2\cdot$ II

$CH_3—\underset{\displaystyle CH_3}{\overset{|}{\dot{C}}}—CH_3$ III

3.48 Arrange the following intermediates in order of increasing stability.



I II III

3.49 The carbon–bromine bond of 1-bromopropane requires more energy to cleave heterolytically than does the carbon–bromine bond of 2-bromopropane. Explain why.

$CH_3CH_2CH_2Br$	$CH_3CHBrCH_3$
1-bromopropane	2-bromopropane

3.50 The carbon–chlorine bond of 3-chloropropene requires less energy to cleave heterolytically than does the carbon–chlorine bond of 1-chloropropane. Explain why.

$CH_2{=}CHCH_2Cl$	$CH_3CH_2CH_2Cl$
3-chloropropene	1-chloropropane

3.51 Chloroform ($CHCl_3$) reacts with a strong base in an unusual elimination reaction to give dichlorocarbene (CCl_2). Write the Lewis structure for this species. What features of the chlorine atoms might stabilize this carbene compared to CH_2?

3.52 Draw the Lewis structure of OH^+. How does it differ from OH^-? Is OH^+ a nucleophile or an electrophile?

Activation Energy and Rates of Reaction

3.53 Consider the following information about two reactions. Which reaction will occur at the faster rate at a common temperature?

Reaction	ΔH°_{rxn}	E_a
A ⟶ X	−120 kJ mole^{-1}	+100 kJ mole^{-1}
B ⟶ Y	−100 kJ mole^{-1}	+120 kJ mole^{-1}

3.54 Consider the information given in Exercise 3.53. Which reaction is the more exothermic?

3.55 Consider the activation energies for the following steps in free radical reactions. Which reaction occurs at the faster rate?

$$CH_4 + F\cdot \longrightarrow CH_3\cdot + HF \qquad E_a = 5 \text{ kJ mole}^{-1}$$

$$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl \qquad E_a = 16 \text{ kJ mole}^{-1}$$

3.56 Consider the activation energies for the following nucleophilic substitution reactions. Which reaction occurs at the faster rate?

$$CH_3{-}I + Cl^- \longrightarrow CH_3{-}Cl + I^- \qquad E_a = 104 \text{ kJ mole}^{-1}$$

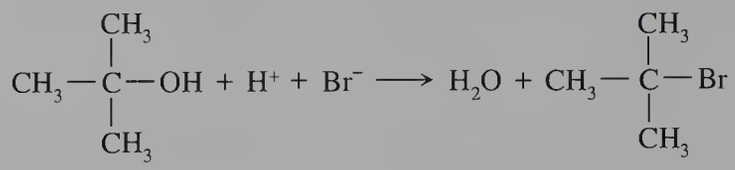
$$CH_3{-}I + Br^- \longrightarrow CH_3{-}Br + I^- \qquad E_a = 96 \text{ kJ mole}^{-1}$$

Kinetic Order of Reactions

3.57 Sodium cyanide reacts with chloroethane by the following equation. When the concentration of cyanide ion is tripled, the reaction rate triples. When the concentration of chloroethane doubles, the reaction rate doubles. What is the overall kinetic order of the reaction? Write the rate equation for the reaction.

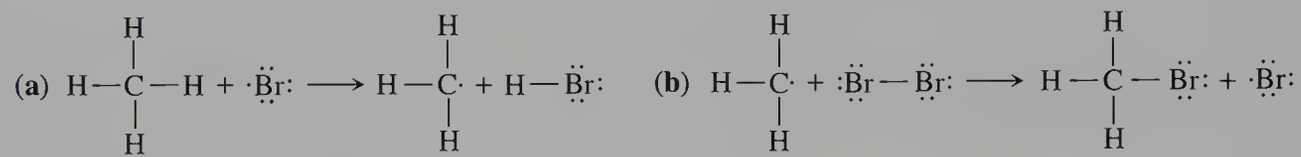
$$CH_3{-}CH_2{-}Cl + {}^-{:}C{\equiv}N: \longrightarrow CH_3{-}CH_2{-}C{\equiv}N: + Cl^-$$

3.58 Reaction of *tert*-butyl alcohol with concentrated HBr gives *tert*-butyl bromide. When the concentration of the alcohol is doubled, the reaction rate doubles. When the concentration of acid is tripled, the reaction rate triples. If more bromide ion in the form of sodium bromide is added, the rate is unaffected. What is the kinetic order with respect to each reactant? What is the overall kinetic order of the reaction?

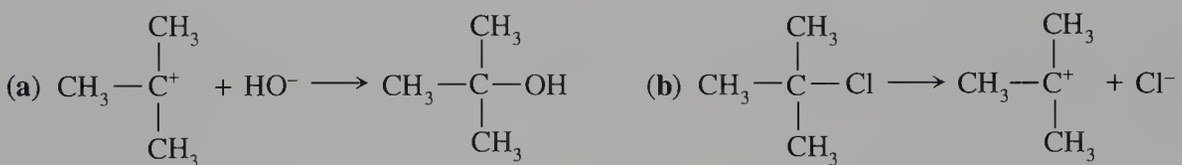


Mechanisms of Reactions

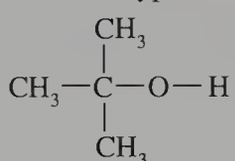
3.59 Identify the processes of bond cleavage and bond formation for each of the following reactions.



3.60 Identify the processes of bond cleavage and bond formation for each of the following reactions.



3.61 The following alcohol acts as a base with a strong acid. The resulting conjugate acid produces water and an intermediate. Write the structure of the intermediate. What type of bond cleavage occurs?



3.62 Dimethyl ether ($CH_3—O—CH_3$) can be prepared by adding a strong base such as NaH to methanol (CH_3OH) and then adding iodomethane (CH_3I) to the reaction mixture. Write plausible steps for this reaction.

3.63 Bromine adds to the double bond of ethylene ($CH_2=CH_2$). The reaction occurs via an intermediate that results from the heterolytic cleavage of Br_2. Write a plausible two-step mechanism for the reaction.

3.64 Write the propagation steps for the reaction of Br_2 with CH_4 to give CH_3Br.

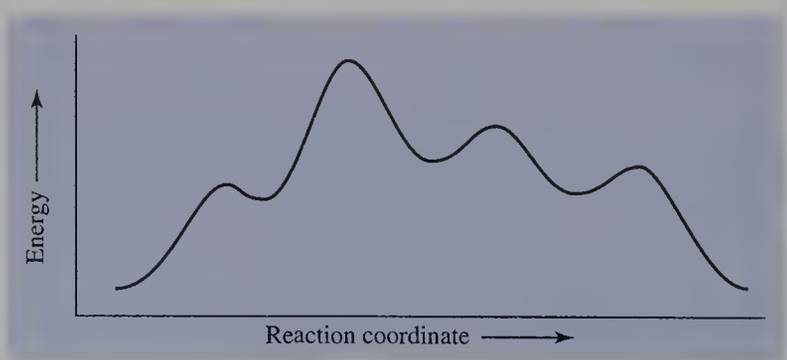
Reaction Coordinate Diagrams

3.65 Distinguish between an intermediate and a transition state.

3.66 A reaction occurs in three steps. How many transition states are there? How many intermediates form?

3.67 Draw a reaction coordinate diagram for a two-step exothermic reaction with a rate-determining second step.

3.68 How many intermediates are involved in a reaction represented by the following reaction coordinate diagram.



3.69 The E_a for the abstraction of a hydrogen atom from CH_4 by a chlorine atom is 17 kJ mole^{-1}. The $\Delta H°$ for the reaction is 4 kJ mole^{-1}. Draw the reaction coordinate diagram for this reaction. What is the activation energy for the following reaction?

$$CH_3\cdot + H{-}Cl \longrightarrow CH_4 + Cl\cdot$$

3.70 Based on the following data for the two propagation steps for the free radical bromination of methane, draw a complete reaction coordinate diagram.

	E_a (kJ mole^{-1})	$\Delta H°$ (kJ mole^{-1})
$CH_4 + Br\cdot \longrightarrow CH_3\cdot + HBr$	+75	+67
$CH_3\cdot + Br_2 \longrightarrow CH_3{-}Br + Br\cdot$	+4	−101

Hammond Postulate

3.71 The $\Delta H°_{rxn}$ for the abstraction of each of the possible hydrogen atoms of propane by a bromine atom are indicated below. Based on the data and the fact that the starting materials are the same, what might be surmised about the relative energies of activation for the two reactions? Do the transition states more closely resemble the reactants or the products?

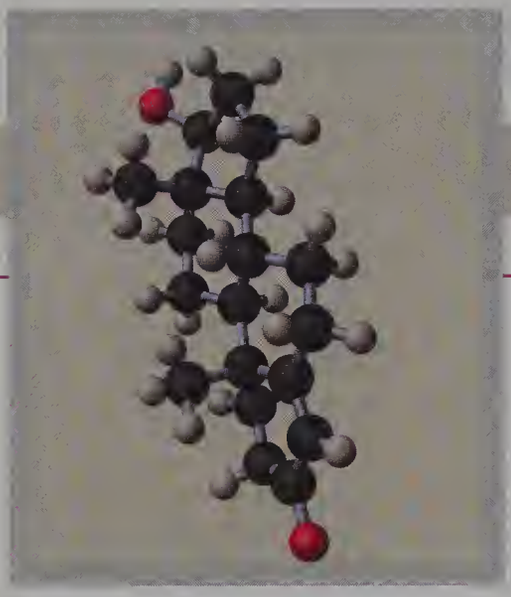
$$CH_3{-}CH_2{-}CH_3 + Br\cdot \longrightarrow CH_3{-}CH_2{-}CH_2\cdot + HBr \qquad \Delta H°_{rxn} = 42 \text{ kJ mole}^{-1}$$

$$CH_3{-}CH_2{-}CH_3 + Br\cdot \longrightarrow CH_3{-}\dot{C}H{-}CH_3 + HBr \qquad \Delta H°_{rxn} = 29 \text{ kJ mole}^{-1}$$

3.72 The $\Delta H°_{rxn}$ for the abstraction of each of the possible hydrogen atoms of propane by a chlorine atom is indicated below. Based on the data and the fact that the starting materials are the same, what might be surmised about the relative energies of activation for the two reactions? Do the transition states more closely resemble the reactants or the products?

$$CH_3{-}CH_2{-}CH_3 + Cl\cdot \longrightarrow CH_3{-}CH_2{-}CH_2\cdot + HCl \qquad \Delta H°_{rxn} = -20 \text{ kJ mole}^{-1}$$

$$CH_3{-}CH_2{-}CH_3 + Cl\cdot \longrightarrow CH_3{-}\dot{C}H{-}CH_3 + HCl \qquad \Delta H°_{rxn} = -33 \text{ kJ mole}^{-1}$$



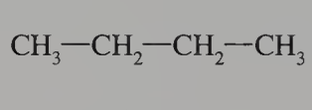
4

Alkanes and Cycloalkanes: Structure and Properties

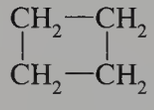
4.1 Classes of Hydrocarbons

Now that we have reviewed some chemical principles and have seen how these principles apply to the study of organic chemistry, we can consider the chemistry of particular classes of organic compounds. We begin with compounds that contain only hydrogen and carbon, **hydrocarbons**. They occur as mixtures in natural gas, petroleum, and coal.

Hydrocarbons are categorized according to the types of bonds between the carbon atoms. Hydrocarbons that have only carbon–carbon single bonds are **saturated**; those that contain carbon–carbon multiple bonds are **unsaturated**. Saturated hydrocarbons can be further divided into alkanes and cycloalkanes. **Alkanes** have carbon atoms bonded in chains. **Cycloalkanes** have carbon atoms bonded to form a ring.



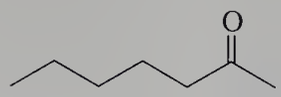
butane
(an alkane)



cyclobutane
(a cycloalkane)

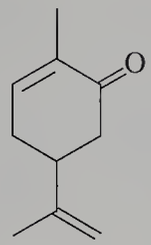
Compounds in which one or more functional groups are attached to one or more chains of carbon atoms are called **acyclic** compounds, meaning *not cyclic*. Compounds that contain rings of carbon atoms, and which may also contain functional groups, are **carbocyclic** compounds, commonly called cyclic compounds. However, some cyclic compounds contain at least one atom other than carbon in the ring. The noncarbon ring atoms are called **heteroatoms**. Cyclic compounds containing one or more heteroatoms are called **heterocyclic** compounds.

An acyclic compound



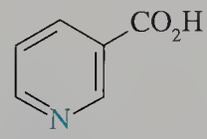
2-heptanone
(in oil of cloves)

A cyclic compound



carvone
(in spearmint oil)

A heterocyclic compound



nicotinic acid
(a B vitamin)

4.2 Normal and Branched Alkanes

Alkanes contain sp^3-hybridized carbon atoms bonded either to other carbon atoms or to hydrogen atoms. Hydrocarbons with a continuous chain of carbon atoms are **normal alkanes**. An example of a normal alkane is octane. Normal alkanes are usually drawn with the carbon chain in a horizontal line.

$$CH_3—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3$$

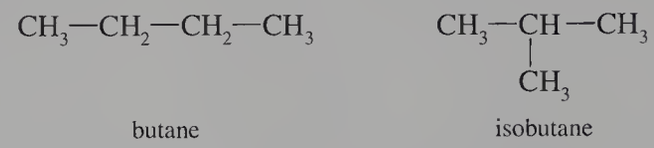
octane
(a normal alkane)

The names and condensed structural formulas of normal alkanes with one to twenty carbon atoms are given in Table 4.1. The first four compounds have common names. The names of the higher molecular weight compounds are derived from Greek numbers that indicate the number of carbon atoms. Each name has the suffix *-ane*, which identifies the compound as an alkane.

TABLE 4.1
Names of Normal Alkanes

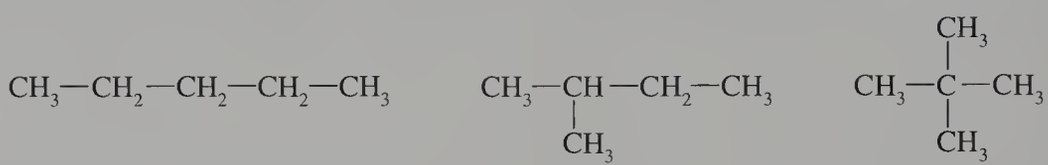
Number of carbon atoms	*Name*	*Molecular formula*
1	methane	CH_4
2	ethane	C_2H_6
3	propane	C_3H_8
4	butane	C_4H_{10}
5	pentane	C_5H_{12}
6	hexane	C_6H_{14}
7	heptane	C_7H_{16}
8	octane	C_8H_{18}
9	nonane	C_9H_{20}
10	decane	$C_{10}H_{22}$
11	undecane	$C_{11}H_{24}$
12	dodecane	$C_{12}H_{26}$
13	tridecane	$C_{13}H_{28}$
14	tetradecane	$C_{14}H_{30}$
15	pentadecane	$C_{15}H_{32}$
16	hexadecane	$C_{16}H_{34}$
17	heptadecane	$C_{17}H_{36}$
18	octadecane	$C_{18}H_{38}$
19	nonadecane	$C_{19}H_{40}$
20	eicosane	$C_{20}H_{42}$

Hydrocarbons that have carbon atoms bonded to more than two other carbon atoms are called **branched alkanes**. The carbon atom bonded to three or four other carbon atoms is the branching point. The carbon atom attached to the main chain at the branching point is part of an **alkyl group**. For example, isobutane is the simplest branched alkane, with three carbon atoms in the main chain and one branch, a $-CH_3$ (methyl) group.



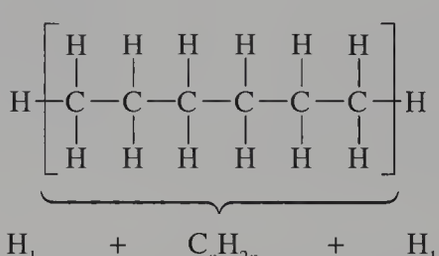
butane isobutane

Isopentane and neopentane are isomers of pentane. Isopentane is a branched alkane with four carbon atoms in the main chain and one branching methyl group. Neopentane has three carbon atoms in the chain with two additional methyl groups bonded to the central carbon atom.



pentane isopentane neopentane

Both normal and branched alkanes have the general molecular formula C_nH_{2n+2}. For example, the molecular formula of hexane is C_6H_{14}. Each carbon atom in this normal alkane, where $n = 6$, has at least two hydrogen atoms bonded to it, accounting for the $2n$ in the general formula. Each of the two terminal carbon atoms has another hydrogen atom bonded to it, accounting for the +2 in C_nH_{2n+2}.



$H_1 + C_nH_{2n} + H_1$

Alkanes form a **homologous series** in which each member differs from the preceding one by one methylene unit, $-CH_2-$. Methane is the first member of the homologous series of alkanes ($n = 1$). Hexane is the sixth member ($n = 6$).

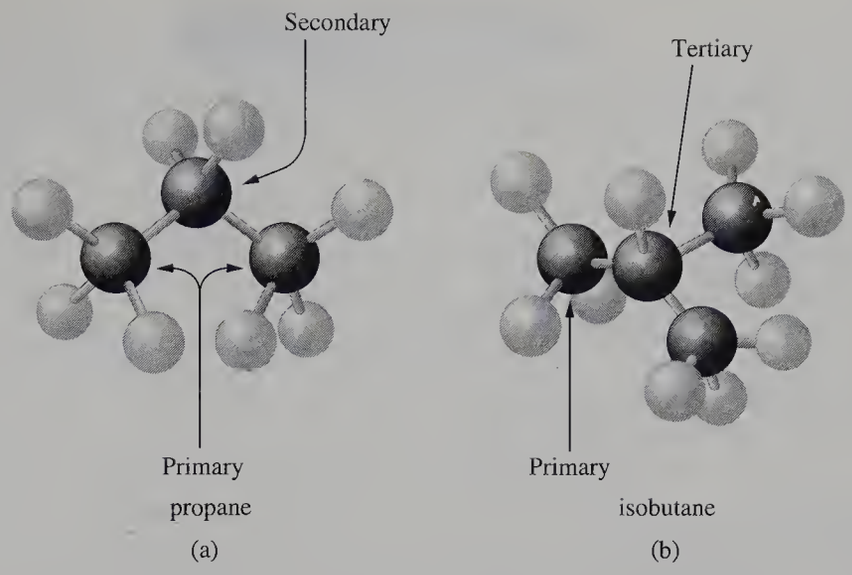
Classification of Carbon Atoms

It is convenient to classify parts of a hydrocarbon structure according to the number of carbon atoms directly bonded to a specific carbon atom. This classification will be used to describe the reactivity of functional groups attached at the various carbon atoms in a structure.

A carbon atom bonded to only one other carbon atom is called a **primary carbon atom**. It is designated by the symbol 1°. The carbon atom at each end of a chain of carbon atoms is primary. For example, ethane and propane each have two primary carbon atoms. In contrast, the middle carbon atom in propane is not primary because it is bonded to two other carbon atoms (Figure 4.1a).

A carbon atom bonded to two other carbon atoms is a **secondary carbon atom**. It is designated by the symbol 2°. For example, the middle carbon atom of propane

FIGURE 4.1
Classification of Carbon Atoms
(a) The terminal carbon atoms of propane are primary; they are directly bonded to only one other carbon atom. The internal carbon atom is secondary; it is bonded to two carbon atoms.
(b) The terminal carbon atoms of isobutane are primary; they are directly bonded to only one other carbon atom. The internal carbon atom is tertiary; it is bonded to three carbon atoms.



is secondary. A carbon atom bonded to three other carbon atoms is a **tertiary carbon atom**, symbolized 3°. For example, isobutane has one tertiary and three primary carbon atoms (Figure 4.1b). A carbon atom bonded to four other carbon atoms is called a **quaternary carbon atom**.

Problem 4.1

One of the components of the wax of a cabbage leaf is a normal alkane containing 29 carbon atoms. What is the molecular formula of the compound?

Problem 4.2

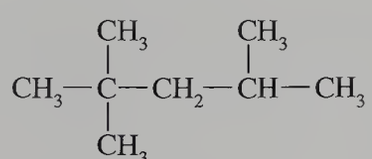
The following compound is a sex attractant released by the female tiger moth. Classify the carbon atoms in this compound as 1°, 2°, or 3°.

Sample Solution

The 14 carbon atoms that are in CH_2 units are secondary because each is bonded to two other carbon atoms. The carbon atoms in the CH_3 units at each end of the chain and the CH_3 unit at the branch point are all primary because each is bonded to only one other carbon atom. The carbon atom of the CH unit near the left side of the structure is tertiary. It is bonded to three other carbon atoms.

Problem 4.3

The octane number is a scale used to rate gasoline. The octane number of the following compound, called isooctane, is 100. Classify the carbon atoms of this compound.

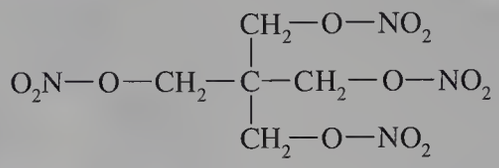


Sample Solution

The carbon atoms in all five CH_3 groups are primary. The carbon atom bonded to three CH_3 groups near the left side of the structure is also bonded to a CH_2 unit. This carbon atom is quaternary. The CH_2 and CH carbon atoms are secondary and tertiary, respectively.

Problem 4.4

Pentaerythritol tetranitrate is used to reduce the frequency and severity of angina attacks. Classify the carbon atoms in this compound as 1°, 2°, 3°, or 4°.



4.3 Nomenclature of Alkanes

There are two isomeric C_4H_{10} alkanes, called butane and isobutane, and three isomeric C_5H_{12} alkanes, called pentane, isopentane, and neopentane. It is easy to learn their names. However, as the number of carbon atoms in an alkane increases, the number of isomers increases exponentially (Table 4.2). Many of these possible isomers have never been found in petroleum or produced in a chemistry laboratory, but each could be made in the laboratory. A system for naming the many isomeric alkanes is clearly needed.

TABLE 4.2
Number of Isomers of the Alkanes

Molecular formula	*Number of isomers*
CH_4	1
C_2H_6	1
C_3H_8	1
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{20}H_{42}$	336,319
$C_{30}H_{62}$	4,111,846,763
$C_{40}H_{82}$	62,491,178,805,831

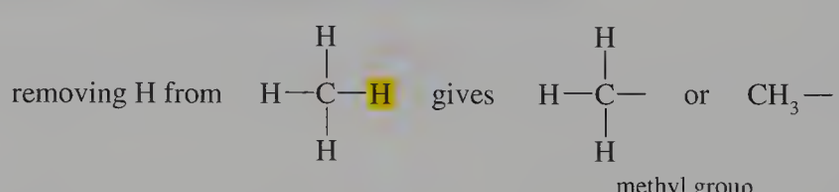
IUPAC Rules

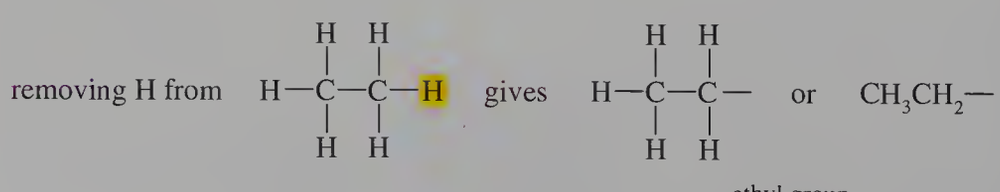
Organic compounds are named by the rules set forth by the International Union of Pure and Applied Chemistry (IUPAC). When these rules are followed, a unique name describes each compound. The IUPAC (systematic) name is constructed of three parts: prefix, parent, and suffix.

prefix — parent — suffix

The **parent** is the longest continuous carbon chain in a molecule. The **suffix** identifies the functional group of most classes of organic compounds. For alkanes, the **suffix** is *-ane* when the longest chain contains only carbon–carbon single bonds and when no functional groups are present. The **prefix** indicates the identity and location of alkyl groups. Some functional groups, such as the halogens, are also identified in the prefix. For example, in halogenated alkanes the prefixes chloro- and bromo- identify chlorine and bromine, respectively.

An alkane that has "lost" one hydrogen atom is called an **alkyl** group. Alkyl groups are named by replacing the *-ane* ending of an alkane by *-yl*. The parent name of CH_4 is methane, and CH_3— is a methyl group. The parent name of C_2H_6 is ethane and CH_3CH_2— is an ethyl group. In some texts the shorthand Me and Et are used to represent methyl and ethyl, respectively.

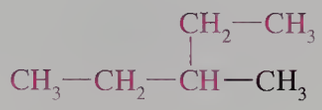




The general shorthand representation of an alkyl group is R—, which stands for the "rest" or "remainder" of the molecule.

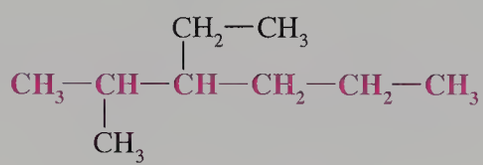
The names of alkanes specify the length of the carbon chain and the location and identity of alkyl groups attached to it. The IUPAC rules for naming alkanes are as follows.

1. The longest continuous chain of carbon atoms is the parent. The names of alkanes, which consist of a stem and the suffix *-ane*, are listed in Table 4.1. The longest chain is not always immediately apparent.

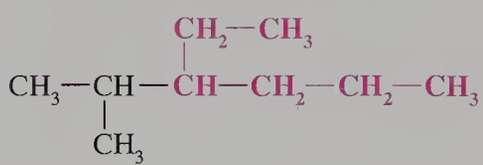


There are five carbon atoms in the longest carbon chain, not four carbon atoms.

If two possible chains have the same number of carbon atoms, the parent is the one with the larger number of branch points.

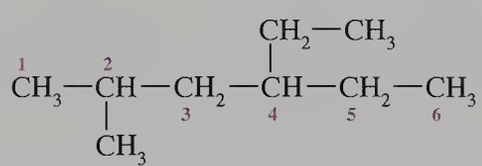


The compound should be considered a six-carbon parent chain with two branches, a methyl and an ethyl group.



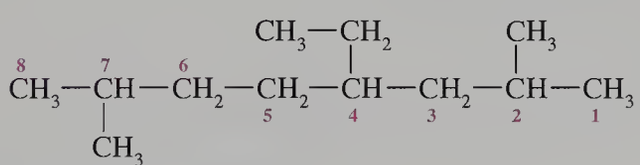
The six-carbon parent chain with only a single three-carbon alkyl group is not a correct choice.

2. Number the carbon atoms in the longest continuous chain starting from the end of the chain nearer the first branch.



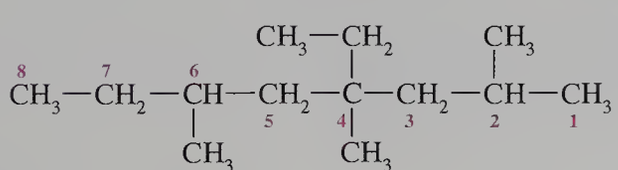
This substituted hexane has a methyl group at C-2 and an ethyl group at C-4, not an ethyl group at C-3 and a methyl group at C-5.

If branching occurs at an equal distance from each end of the chain, number from the end nearer the second branch.



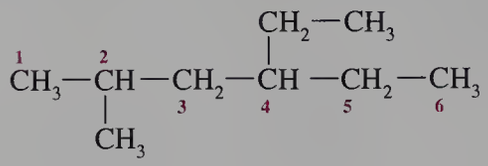
The ethyl group is closer to the right side of the molecule.

3. Each branch or substituent has a number indicating its location on the parent chain. When two substituents are located on the same carbon atom, each must be assigned the same number.



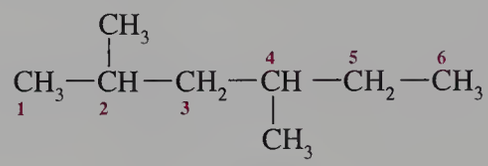
This octane has methyl groups on the C-2, C-4, and C-6 atoms and an ethyl group on the C-4 atom.

4. The number for the position of each alkyl group is placed immediately before the name of the group and is joined to the name by a hyphen. Alkyl groups are listed in alphabetical order.



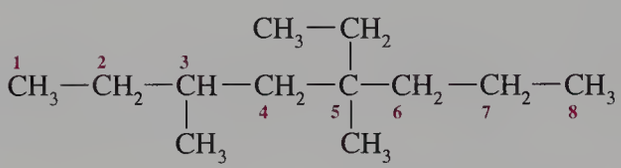
This is 4-ethyl-2-methylhexane, not 2-methyl-4-ethylhexane.

Two or more groups of the same type are indicated by the prefixes di-, tri-, etc. The numbers indicating the locations of branches are separated by commas.



This is 2,4-dimethylhexane.

5. The prefixes di-, tri-, tetra, etc., do not alter the alphabetical ordering of the alkyl groups.



This is 5-ethyl-3,5-dimethyloctane, not 3,5-dimethyl-5-ethyloctane.

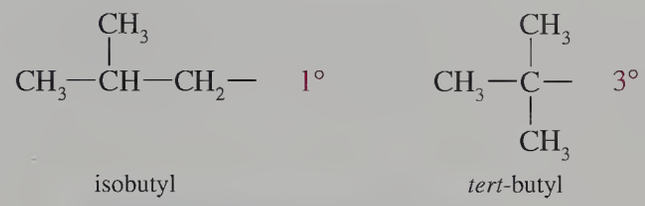
Names of Alkyl Groups

There is only one alkyl group derived from either methane or ethane. However, several isomeric alkyl groups are usually possible for a longer chain of carbon atoms, depending on which carbon atom "loses" a hydrogen atom. For example, propane has two 1° carbon atoms and a 2° carbon atom. If a primary carbon atom loses a hydrogen atom, a primary alkyl group, *propyl*, is produced. Propyl and other primary alkyl groups derived from normal alkanes are **normal alkyl groups**. If propane loses a hydrogen atom at its 2° carbon atom, a secondary alkyl group, known as the *isopropyl* group, results. The abbreviations of propyl and isopropyl are Pr and i-Pr, respectively.

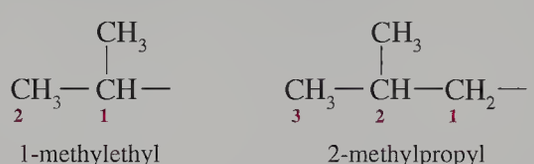
propyl isopropyl

Next, let's look at the alkyl groups that can be derived from the two isomers of butane, C_4H_{10}. These alkyl groups all have the formula C_4H_9. Two alkyl groups are derived from butane and two from isobutane. If butane loses a hydrogen atom at a primary carbon atom, a primary *n-butyl* group results. If, on the other hand, butane loses a hydrogen atom at a secondary carbon atom, a secondary alkyl group called the *sec-butyl* group forms.

If a primary carbon atom of isobutane loses a hydrogen atom, a primary alkyl group called the *isobutyl* group forms. If isobutane loses a hydrogen atom from the tertiary carbon atom, a tertiary alkyl group called the *tert-butyl* (or *t*-butyl) group forms. Thus, there are four isomeric C_4H_9— alkyl groups.



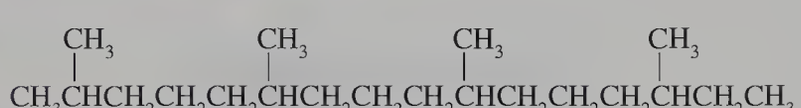
Complex alkyl groups are named using an IUPAC procedure similar to that used to name alkanes. They are named using the longest continuous chain beginning at the carbon atom that would be bonded to the main chain. For example, the IUPAC name for an isopropyl group is 1-methylethyl and the IUPAC name for an isobutyl group is 2-methylpropyl.



The names of complex alkyl groups are enclosed within parentheses to set them off from the names of other alkyl groups and the name of the parent chain. Consequently 4-isopropylheptane is also 4-(1-methylethyl)heptane. The nonsystematic names for the alkyl groups containing three and four carbon atoms are commonly used, and the IUPAC rules allow for their continued use.

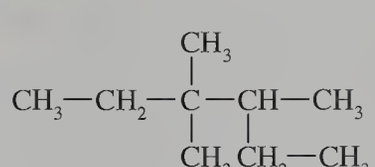
Problem 4.5

Name the following compound, which is produced by the alga *Spirogyra*.



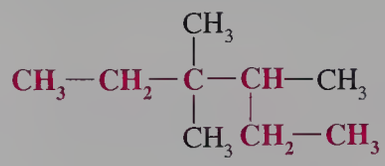
Problem 4.6

Name the following compound.



Sample Solution

First identify the longest continuous chain and use that number of carbon atoms as the parent name.



The parent name is hexane. There are three methyl groups attached—two at the third carbon atom from the left side and one at the third carbon from the right. Although no rule is specifically given above, the principle of selecting lowest numbers for branches provides a criterion for selecting the correct name. This trimethylhexane must be numbered from the left to give 3,3,4 rather than from the right to give 3,4,4. The IUPAC name is 3,3,4-trimethylhexane.

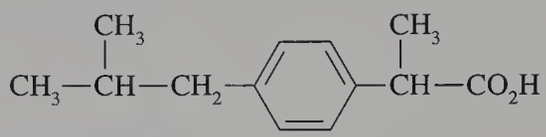
Problem 4.7

Write the structures of each of the following compounds.

(a) 3,3-dimethylhexane (b) 4-ethyl-3-methyloctane (c) 4-(1-methylethyl)octane

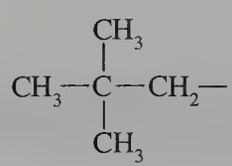
Problem 4.8

Identify the alkyl group on the left of the benzene ring in ibuprofen, an analgesic present in Nuprin, Advil, and Motrin.



Problem 4.9

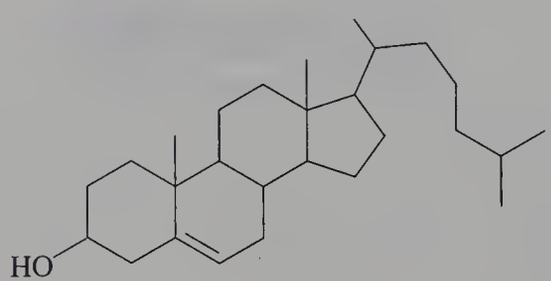
The common name for the five-carbon alkyl group with a quaternary carbon atom is neopentyl. What is its systematic name?



neopentyl

Problem 4.10

Name the alkyl group, containing eight carbon atoms, bonded to the five-membered ring of cholesterol.



4.4 Heats of Formation and Stability of Alkanes

We recall that the standard **heat of formation** of a compound, ΔH_f°, is the enthalpy change for a reaction in which one mole of the compound in its standard state is made from the elements in their standard states. The heats of formation of some alkanes are given in Table 4.3. None of these values have been determined by direct measurement of reactions forming the compounds from carbon and hydrogen. Rather, indirect methods that add ΔH° values for other reactions according to Hess's law have been applied.

TABLE 4.3
Heats of Formation of Alkanes

Alkane	ΔH_f° *(kJ mole^{-1})*	*Methylalkane*	ΔH_f° *(kJ mole^{-1})*
methane	−74.48		
ethane	−83.35		
propane	−104.68		
butane	−126.78	2-methylpropane	−134.18
pentane	−146.94	2-methylbutane	−153.55
hexane	−166.94	2-methylpentane	−174.68
		3-methylpentane	−172.0
heptane	−187.65	2-methylhexane	−194.72
		3-methylhexane	−191.3
octane	−208.82	2-methylheptane	−215.35
		3-methylheptane	−212.5
nonane	−228.86	2-methyloctane	−235.85
		3-methyloctane	−233.7
decane	−249.55	2-methylnonane	−256.52
		3-methylnonane	−254.4

We can use the heats of formation of organic compounds to compare their relative stabilities and to calculate the enthalpy changes for their reactions. For example, the ΔH_f° of pentane is −146.94 kJ mole^{-1} (−35.12 kcal mole^{-1}) and that of the isomeric 2-methylbutane is −153.55 kJ mole^{-1} (−36.70 kcal mole^{-1}).

$$5\ C(\text{graphite}) + 6\ H_2(\text{gas}) \longrightarrow CH_3CH_2CH_2CH_2CH_3 \qquad \Delta H_f^\circ = -146.94\ \text{kJ mole}^{-1}$$

$$5\ C(\text{graphite}) + 6\ H_2(\text{gas}) \longrightarrow (CH_3)_2CHCH_2CH_3 \qquad \Delta H_f^\circ = -153.55\ \text{kJ mole}^{-1}$$

These data show that 2-methylbutane is more stable than pentane by about 6.6 kJ mole^{-1} (Figure 4.2). The conclusion is valid because we are comparing the two compounds to the same number of moles of elements in their standard states. Now consider the standard heats of formation of hexane and pentane. The standard heat of formation of hexane (−166.94 kJ mole^{-1}) is more negative than that of pentane (−146.94 kJ mole^{-1}), but we cannot directly compare their relative stabilities because different numbers of moles of elements are required to form the two compounds.

Because we know the standard heats of formation of pentane and 2-methylbutane, we can use Hess's law to calculate ΔH_{rxn}° for the isomerization reaction of pentane to form 2-methylbutane. We write the equation for the formation of 2-methylbutane and the reverse of the equation for the formation of pentane. (When a chemical equation is reversed, the sign of ΔH° changes.) Adding these equations yields the equation for the isomerization of pentane to 2-methylbutane. The ΔH° for the reaction is obtained by summing the ΔH° values for the indicated reactions.

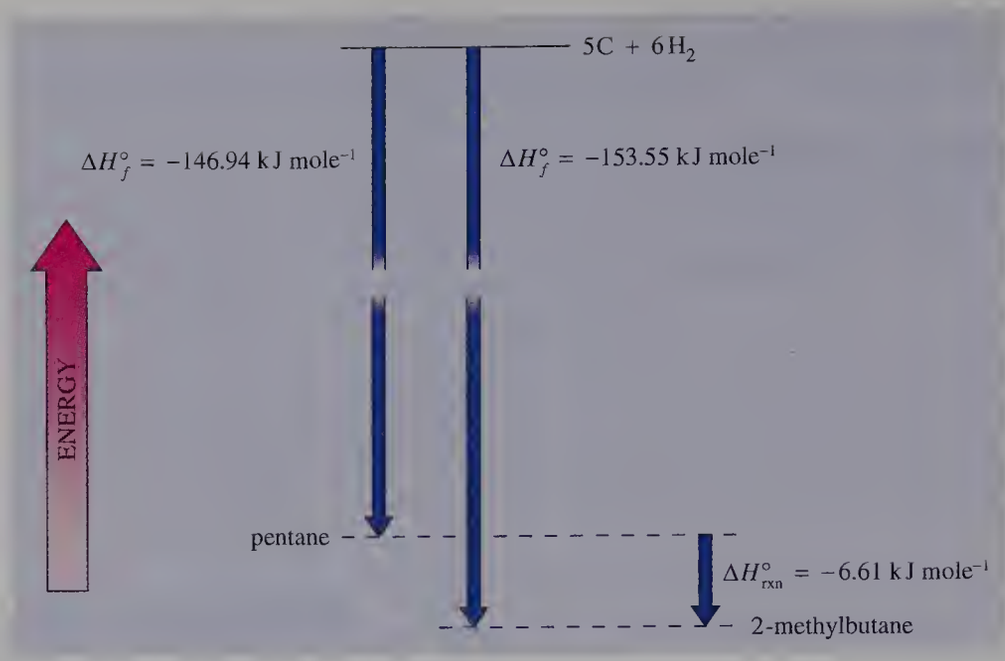


FIGURE 4.2 Relative Stability of Isomeric Alkanes

$$\begin{array}{lll} 5\ C(\text{graphite}) + 6\ H_2(\text{gas}) \longrightarrow (CH_3)_2CHCH_2CH_3 & \Delta H^\circ = -153.55\ \text{kJ mole}^{-1} \\ CH_3CH_2CH_2CH_2CH_3 \longrightarrow 5\ C(\text{graphite}) + 6\ H_2(\text{gas}) & \Delta H^\circ = +146.94\ \text{kJ mole}^{-1} \\ \hline CH_3CH_2CH_2CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 & \Delta H^\circ = -6.61\ \text{kJ mole}^{-1} \end{array}$$

We can use the same method to determine the standard entropy change for a reaction. The S° values for pentane and 2-methylbutane are 349.45 and 343.63 J mole^{-1} deg^{-1}, respectively. Thus, ΔS°_{rxn} for this isomerization reaction is −5.82 J mole^{-1} deg^{-1} (−1.4 cal mole^{-1} deg^{-1}). Once we have ΔH°_{rxn} and ΔS°_{rxn} for a reaction, we can calculate the standard free energy change using the relationship

$$\Delta G^\circ_{rxn} = \Delta H^\circ_{rxn} - T\Delta S^\circ_{rxn}$$

$$\Delta G^\circ_{rxn} = -6610\ \text{J mole}^{-1} - (298\ \text{K})(-5.82\ \text{J mole}^{-1}\ \text{deg}^{-1})$$

$$= -4880\ \text{J mole}^{-1} = -4.88\ \text{kJ mole}^{-1}$$

Accordingly, the ΔH°_{rxn} is the major contributor to ΔG°_{rxn}. Although ΔS°_{rxn} contributes to ΔG°_{rxn}, it is common practice to discuss the relative stabilities of isomeric hydrocarbons using their heats of formation. The data in Table 4.3 show that branched isomers are more stable than normal alkanes by about 7 kJ mole^{-1}.

Heats of Formation in a Homologous Series

When we examine Table 4.3, we notice that the heats of formation of adjacent members of the series of normal alkanes differ by approximately the same amount. The average difference, −20.6 kJ mole^{-1}, reflects the fact that the molecular formulas of the alkanes in the series differ from one another by one $—CH_2—$ unit. Thus, the −20.6 kJ mole^{-1} reflects the following change.

$$C(s) + H_2(g) \longrightarrow —CH_2— \qquad \Delta H^\circ = -20.6\ \text{kJ mole}^{-1}$$

Problem 4.11

The heat of formation of 2,2-dimethylpropane is –168.1 kJ mole^{-1}. Compare the stability of this compound with those of its two isomers. What is responsible for the difference?

Problem 4.12

The heats of formation of 2-methylpentane and 3-methylpentane are –174.68 and –172.0 kJ mole^{-1}, respectively. Based on these data, calculate the heat of reaction for the isomerization of 2-methylpentane to form 3-methylpentane.

Problem 4.13

Using the heat of formation of decane, predict the heat of formation of dodecane ($C_{12}H_{26}$).

Sample Solution

The heat of formation of decane (Table 4.3) is –249.55 kJ mole^{-1}. There are two additional CH_2 units in dodecane. Each additional CH_2 unit changes the heat of formation in a homologous series of alkanes by –20.6 kJ mole^{-1}. The heat of formation is $-249.55 + 2(-20.6) = -290.8$ kJ mole^{-1}.

Problem 4.14

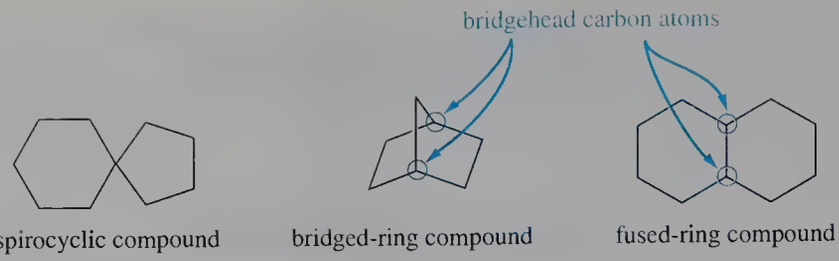
The heat of formation of 3-methylnonane is –254.4 kJ mole^{-1}. Predict the heat of formation of 3-methyltridecane.

4.5 Cycloalkanes

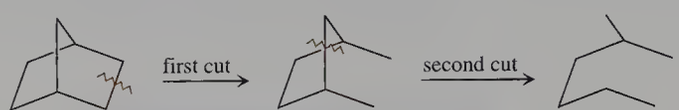
Cycloalkanes with one ring have the general formula C_nH_{2n}. Cycloalkanes have two fewer hydrogen atoms than alkanes because one carbon–carbon bond in the ring replaces two carbon–hydrogen bonds in the acyclic alkane. Cycloalkanes are usually drawn as simple polygons. The sides of the polygon represent the carbon–carbon bonds, and it is understood that each corner of the polygon is a carbon atom attached to two hydrogen atoms.

cyclopropane cyclobutane cyclopentane cyclohexane

Two or more rings can be part of the same molecule without sharing any common atoms. However, rings in a molecule can also share one or more common atoms. Compounds in which one carbon atom is shared between two rings are called **spirocyclic**. These compounds are relatively rare in nature. Compounds in which two nonadjacent carbon atoms are shared by two rings are called **bridged-ring** compounds. The shared carbon atoms are called **bridgehead carbon** atoms. These compounds are moderately prevalent in nature. Cyclic compounds in which two bridgehead atoms are bonded directly to each other are called **fused-ring** compounds. These compounds are very common in nature. For example, steroids (Section 4.8) contain four fused rings. Examples of compounds with shared carbon atoms are



Each of the examples shown contains two rings; they are **bicyclic** hydrocarbons. The spirocyclic and fused-ring compounds obviously have two rings, but the bridged-ring compound appears to have three rings, not two. We can find out how many rings are present in a ring system by determining the minimum number of "cuts" necessary to produce an acyclic compound. The number of cuts defines the number of rings. If two cuts are needed, the compound is a bicyclic hydrocarbon. For the bridged-ring compound, one "cut" gives a structure with only one ring (monocyclic). A second cut gives an acyclic structure. Therefore, the compound is bicyclic.

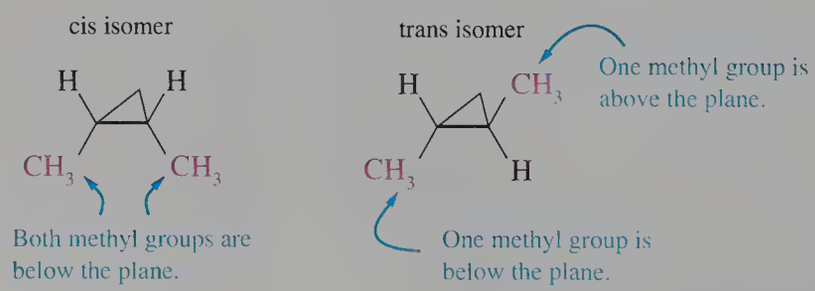


Geometric Isomerism

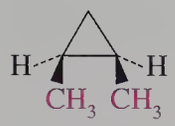
In Section 2.7, we saw that compounds can exist as isomers with different carbon skeletons, different functional groups, and different functional group locations. These isomers have different sequential arrangements of atoms. At that time we also learned that two compounds with the same connectivity of atoms can have different arrangements of atoms in space. This type of isomerism is **stereoisomerism**. Stereoisomers can exist in several ways in various classes of compounds. For example, cycloalkanes can exist as stereoisomers called **geometric isomers**.

To understand geometric isomers, first recall that rotation around the carbon–carbon bonds of alkanes gives different spatial arrangements called conformations. In contrast, rotation around the carbon–carbon bond of cycloalkanes is either restricted or, in the case of cyclopropane, impossible. Hence, cycloalkanes have two sides: a "top" and a "bottom".

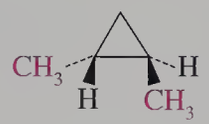
Consider the "top" and "bottom" of cyclopropane, whose three carbon atoms are in a single plane. A group can be bonded either "above" or "below" the plane of the ring. If we attach two methyl groups on adjacent carbon atoms on the same side of the ring, the substance is called a **cis** isomer; it is *cis*-1,2-dimethylcyclopropane. If the two methyl groups are attached on the opposite sides of the ring, the compound is the **trans** isomer. Consequently, 1,2-dimethylcyclopropane exists as both cis and trans geometrical isomers. (Note that when used as prefixes in names of compounds, *cis* and *trans* are italicized.)



In the structures shown below, the cyclopropane ring is viewed in the plane of the page. Wedge-shaped lines denote bonds above the plane of the ring, and dashed lines show bonds below the plane of the ring.



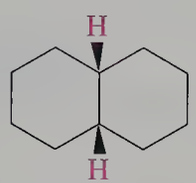
cis isomer



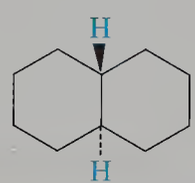
trans isomer

Cis and trans geometric isomers have different physical properties. One geometric isomer cannot be converted into the other without breaking a bond.

Geometric isomerism also occurs in polycyclic compounds in which the rings are linked either cis or trans. For example, the steroid ring system contains four fused rings (Section 4.8). The following bicyclic hydrocarbons, called decalins, are part of the structure of steroids. The decalin ring junction can have hydrogen atoms on the same side or opposite sides. When they are on the same side, the molecule is *cis*-decalin. When they are on opposite sides, the molecule is *trans*-decalin.



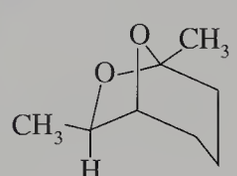
cis-decalin



trans-decalin

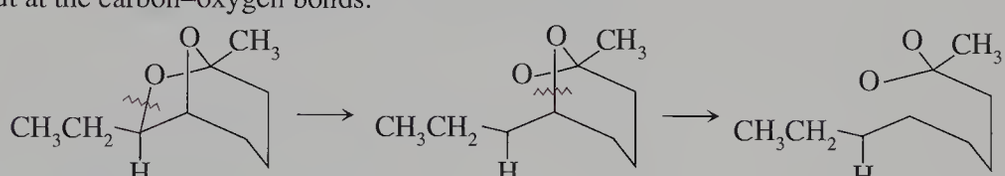
Problem 4.15

Classify brevicomin, the sex attractant of a species of pine beetle, according to the number of rings that it contains.



Sample Solution

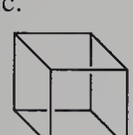
Select one site to "cut" a ring and then continue at other sites until no rings remain. Let's cut at the carbon–oxygen bonds.



Two cuts are required. Thus the compound is bicyclic.

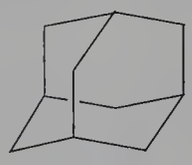
Problem 4.16

Cubane, classified as a pentacyclic hydrocarbon, appears to have six rings. Using "cuts", show that the compound is pentacyclic.

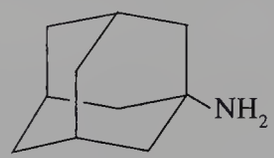

cubane

Problem 4.17

Adamantane has a carbon skeleton also found as part of the structure of diamond. Amantadine, which contains an amino group bonded to the adamantane structure, is useful in the prevention of infection by influenza A viruses. What are the molecular formulas of adamantane and amantadine? How many rings are in each molecule?



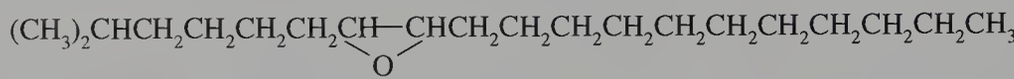
adamantane



amantadine

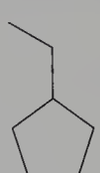
Problem 4.18

Disparlure, the sex attractant pheromone of the female gypsy moth, has the following general structure. Are geometric isomers possible for this structure?

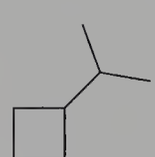


4.6 Nomenclature of Cycloalkanes

Cycloalkanes are named by the IUPAC system using the prefix *cyclo-*. When only one position contains a functional group or alkyl group, only one compound is possible, and therefore no number is necessary. For example, ethylcyclopentane and isopropylcyclobutane are the names of the following molecules.



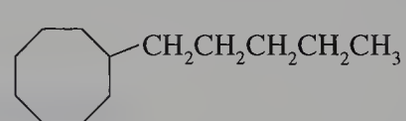
ethylcyclopentane



isopropylcyclobutane

If the alkyl chain has more carbon atoms than the cycloalkane ring, the compound is named as a **cycloalkylalkane**. For example, a compound that has a pentyl group bonded to a cyclopropane ring is named as a cycloalkylalkane because there are more carbon atoms in the alkyl group than in the ring. In contrast, a compound that has a pentyl group bonded to a cyclooctane ring is named as an alkylcycloalkane because there are more carbon atoms in the ring than in the alkyl group.

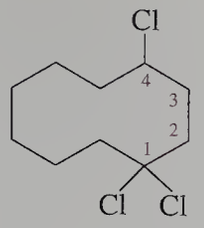
1-cyclopropylpentane



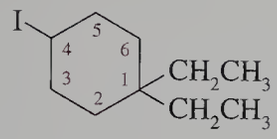
pentylcyclooctane

When a cycloalkane ring is linked to two or more groups, their positions are indicated by numbers. One of the groups is selected to be at position 1, and the ring is numbered in a clockwise or counterclockwise direction to give the lower number to the position with a second group attached to the ring, as in 1,1,4-trichlorocyclodecane. Groups are cited alphabetically, as in 1,1-diethyl-4-iodocyclohexane. The "e" of the diethyl group has precedence over the "i" of the

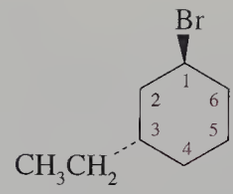
iodo group. Geometric isomers have the prefix *cis-* or *trans-*.



1,1,4-trichlorocyclodecane

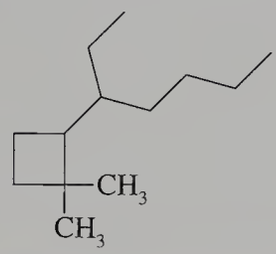


1,1-diethyl-4-iodocyclohexane



trans-1-bromo-3-ethylcyclohexane

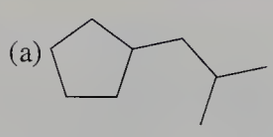
For compounds named as cycloalkylalkanes, the ring is itself a substituent, and C-1 is defined as the atom that is the point of attachment to the alkane.

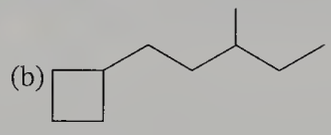


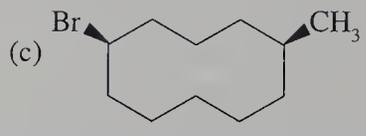
3-(2,2-dimethylcyclobutyl)heptane

Problem 4.19

What are the names of the following compounds?







4.7 Stability of Cycloalkanes

In Section 4.4, we saw that we can use standard heats of formation to compare the stabilities of isomeric normal alkanes and branched alkanes. We can also use heats of formation data to compare the relative stabilities of the cycloalkanes. Table 4.4 lists the heats of formation of cycloalkanes.

TABLE 4.4
Heats of Formation of Cycloalkanes

Cycloalkane	ΔH_f° *(kJ mole^{-1})*	ΔH_f° *(per CH_2) (kJ mole^{-1})*	*Strain energy (kJ mole^{-1})*
cyclopropane	+53.3	+17.8	115
cyclobutane	+28.4	+7.1	111
cyclopentane	−77.10	−15.4	26
cyclohexane	−123.19	−20.5	0
cycloheptane	−118.1	−16.9	26
cyclooctane	−124.4	−15.9	40
cyclononane	−132.6	−14.7	53
cyclodecane	−154.3	−15.4	52
cycloundecane	−179.4	−16.3	47
cyclododecane	−230.1	−19.2	17
cyclotridecane	−246	−18.9	22
cyclotetradecane	−301	−17.1	13
cyclopentadecane	−323	−21.5	14
alkane (reference)		−20.6	0

Table 4.4 also lists the heat of formation per CH_2 unit in cycloalkanes, obtained by dividing the heat of formation by the number of carbon atoms in the compound. We recall that the heats of formation of alkanes that differ from one another by one CH_2 unit differ by –20.6 kJ mole^{-1}. The heat of formation per CH_2 group for cyclohexane is –20.5 kJ mole^{-1}, not much different from the value observed for the alkanes. The heats of formation per CH_2 group for most cycloalkanes are similar, ranging from –15 to –20 kJ mole^{-1}, with the conspicuous exceptions of cyclopropane and cyclobutane. The standard heats of formation of the latter two compounds are positive, whereas more stable compounds usually have negative standard heats of formation.

Let's examine the bonding in cyclopropane to see why its heat of formation is positive rather than negative. Because cyclopropane has a positive standard heat of formation, its carbon–carbon bonds are not as strong as those in alkanes or in cycloalkanes having five or more carbon atoms. We recall that Linus Pauling's principle of maximum orbital overlap (Section 1.13) states that the strongest bonds form when two orbitals achieve maximum overlap. Maximum overlap occurs when orbitals are strongly directed toward each other along the internuclear axis. The linear overlap of sp^3 hybrid orbitals results in tetrahedral C—C—C bond angles in alkanes and in most cycloalkanes. Strong sp^3–sp^3 carbon–carbon σ bonds are not possible in cyclopropane, a planar molecule whose C—C—C bond angle is 60°—far from the tetrahedral bond angle of 109°. Therefore, the electron density in the carbon–carbon bonds is distributed in an arc that lies outside the area described by the internuclear axis (Figure 4.3). These "bent" bonds are weaker than other carbon–carbon σ bonds.

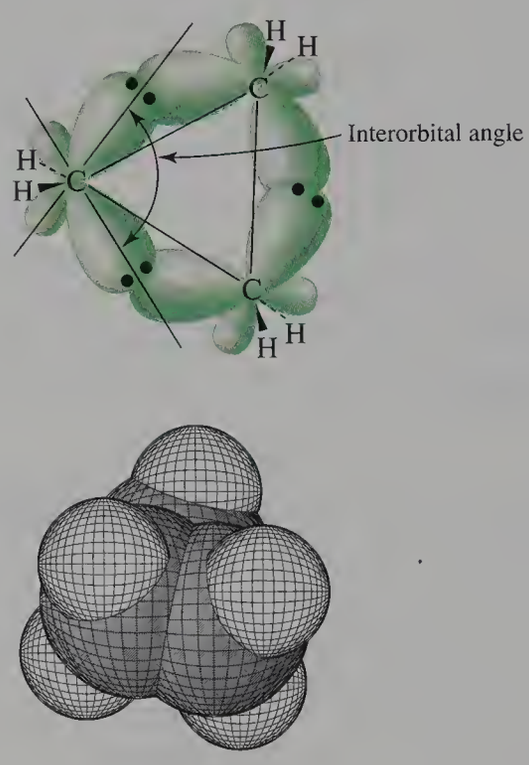


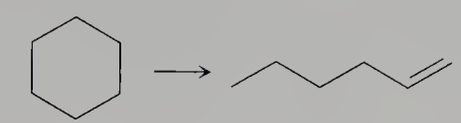
FIGURE 4.3 Structure of Cyclopropane
Cycloalkanes that do not have internuclear angles of 109.5° cannot have efficient overlap of the hybrid orbitals. The internuclear bond angle of cyclopropane is 60°. However, the interorbital angle is larger. As a result, the electron density lies "outside" the bond axis and is called a bent bond.

Because orbital overlap in cyclopropane is poor, cyclopropane is less stable per CH_2 unit than cycloalkanes in which effective overlap of sp^3 hybrid orbitals can occur. This instability is termed **ring strain**. Ring strain is calculated by multiplying the number of carbon atoms (n) by –20.6 kJ mole^{-1}, the "strain-free" heat of formation value for a CH_2 unit, and subtracting this quantity from the experimental heat of formation. The strain energy of cyclopropane is approximately 115 kJ mole^{-1}. The strain energies of cycloalkanes are given in Table 4.4. These values represent the "extra" energy contained in the molecule as a result of strain.

$$\Delta H_f^\circ - n(-20.6 \text{ kJ mole}^{-1}) = \text{strain energy}$$

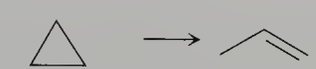
Let's compare the strain energies of cyclobutane and cyclopropane. Cyclobutane has an internuclear angle of 90°, closer to the tetrahedral angle than the 60° internuclear bond angle in cyclopropane. Thus, the carbon–carbon bonds in cyclobutane are not as bent as in cyclopropane and should be less strained. But when we look at the ring strain of the two compounds, we find that the total strain energy of cyclobutane is only slightly smaller than the strain energy of cyclopropane. However, there are four strained carbon–carbon bonds in cyclobutane rather than three. To take this difference into account, we divide the total ring strain by the number of carbon–carbon bonds. When we do this, we find that the ring strain per bond is 38 kJ mole^{-1} for cyclopropane and 27 kJ mole^{-1} for cyclobutane. Therefore, the strain energy per bond is greater in cyclopropane than in cyclobutane. For cycloalkanes with more than six carbon atoms, the strain energy per bond ranges from 1 to 5 kJ mole^{-1} and averages about 2 kJ mole^{-1}.

The heats of reaction of cycloalkanes are affected by ring strain. Consider the isomerization of cycloalkanes to form an isomeric acyclic unsaturated compound.



cyclohexane 1-hexene

$\Delta H^\circ = +81.14$ kJ mole^{-1}



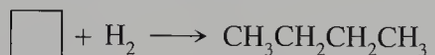
cyclopropane propene

$\Delta H^\circ = -32.6$ kJ mole^{-1}

The isomerization reaction of cyclopropane is more exothermic than the related isomerization reaction of cyclohexane. The difference, 113.7 kJ mole^{-1}, corresponds to the strain energy of the cyclopropane ring calculated from heat of formation data. Thus, we conclude that any reaction in which a strained ring is ruptured is more exothermic than the rupture of a compound with no ring strain.

Problem 4.20

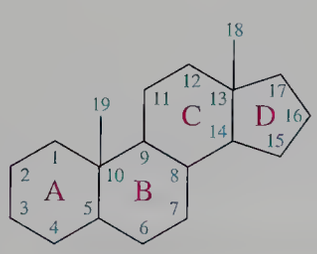
The ΔH°_{rxn} for the following reaction is −155.2 kJ mole^{-1}. Without referring to the tabulated heats of formation, estimate the ΔH°_{rxn} for the analogous reaction of cyclohexane to produce hexane.



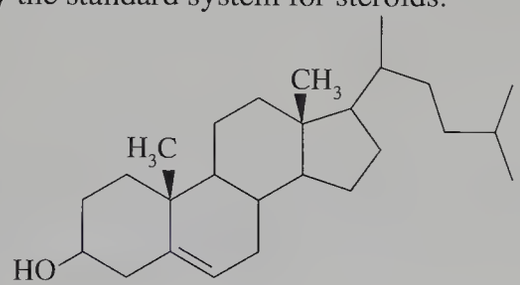
$\Delta H^\circ_{rxn} = -155.2$ kJ mole^{-1}

4.8 Steroids

Steroids are tetracyclic compounds that contain three six-membered rings and a five-membered ring. These compounds contain a variety of functional groups, such as hydroxyl, carbonyl, and carbon–carbon double bonds. Each ring is assigned a letter, and the carbon atoms are numbered by the standard system for steroids.



steroid ring system



cholesterol

The structural formulas of multiple-ring compounds are usually shown by the bond-line method. Each juncture of two or more lines represents a carbon atom. Because each carbon atom must have four covalent bonds, any "missing" bonds are implied to be hydrogen atoms. Groups projecting above and below the plane of the page are shown as wedges and dashed lines, respectively.

Cholesterol is the biosynthetic precursor of other steroid hormones. It is converted to progesterone by shortening the chain attached at the C-17 position (ring D). Progesterone is converted to corticosteroids and sex hormones (Figure 4.4).

Corticosteroids are produced in the adrenal cortex. They are of two types: *glucocorticoids* and *mineralocorticoids*. Glucocorticoids help to control the concentration of blood glucose. Cortisol (Figure 4.4) promotes the formation of the storage carbohydrate glycogen in the liver. Mineralocorticoids affect the electrolyte balance of body fluids, and hence the water balance. Aldosterone, secreted by the adrenal cortex, is the most active of the mineralocorticoids.

The testes of the male and the ovaries of the female produce steroidal sex hormones that control the growth and development of reproductive organs, the development of secondary sex characteristics, and the reproductive cycle. The female sex hormones are **estrogens**. They are also produced in the adrenal cortex. However, the major source of male and female sex hormones is the gonads. Progesterone and two

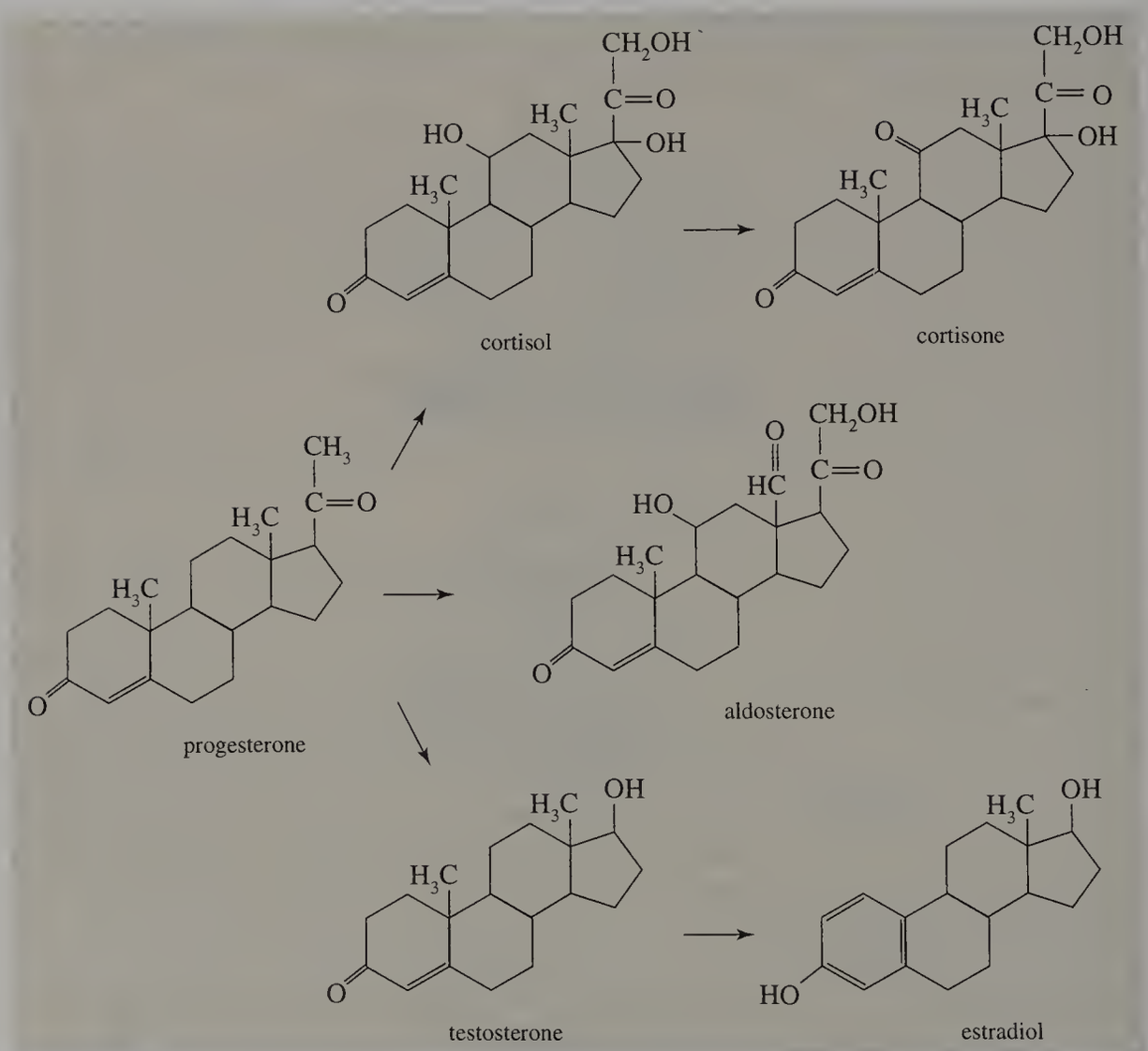


FIGURE 4.4
Progesterone and Derived Steroid Hormones

estrogens, estrone and estradiol, both produced in the ovaries, control the menstrual cycle. Estrogen secretion causes growth of the lining of the uterus and the ripening of the ovum. Progesterone secretion prevents other ova from ripening after ovulation, and maintains the fertilized egg after implantation. The estrogens cause the growth of tissues in female sexual organs. Although estrogens are secreted in childhood, the rate increases by 20-fold after puberty. The fallopian tubes, uterus, and vagina all increase in size. The estrogens also initiate growth of the breasts and the breasts' milk glands.

Male sex hormones are **androgens**. The most important androgen is testosterone (Figure 4.4), which stimulates production of sperm by the testes and promotes the growth of the male sex organs. Testosterone is also responsible for muscle development

Testosterone has two biological roles: androgenic activity (sex characteristic-determining) and anabolic activity (muscle-building). It would be medically useful if drugs could be developed that had anabolic activity without androgenic activity. Such drugs would help repair muscles of severely debilitated individuals. Efforts in this research area have improved the ratio of anabolic to androgenic activity, but no compound has been synthesized that is completely free of androgenic activity.

4.9 Physical Properties of Alkanes and Cycloalkanes

Alkanes have densities between 0.6 and 0.8 g cm^{-3}, so they are less dense than water (Table 4.5). For example, gasoline, which is largely a mixture of alkanes, floats on water. Pure alkanes are colorless, tasteless, and nearly odorless. Gasoline, however, has an odor and some color because dyes are added by refiners to indicate its source and composition. Gasoline also contains compounds with a benzene ring, called aromatic compounds, which have characteristic odors.

Alkanes contain only carbon–carbon and carbon–hydrogen bonds. Because carbon and hydrogen have similar electronegativity values, the C—H bonds are essentially nonpolar. Thus, alkanes are nonpolar. Their physical properties result from weak London forces.

Solubility of Alkanes

Alkanes are not soluble in water, a polar substance. The two substances do not meet the usual criterion of solubility: "like dissolves like". Water molecules are too strongly attracted to one another by hydrogen bonds to allow nonpolar alkanes to slip between them and dissolve.

Alkanes are solvents for nonpolar organic materials such as fats and oils. Alkane vapors, such as those of gasoline, cause severe damage to lung tissue by dissolving the fatty material in cell membranes. Body oils maintain the "moisture" of human skin. Long-term contact between low molecular weight alkanes and skin removes skin oils and can cause soreness and blisters. For this reason, contact with alkane solvents such as paint thinner or paint remover should be avoided.

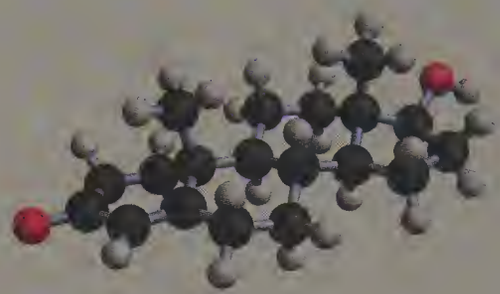
Boiling Points of Alkanes

The boiling points of the normal alkanes increase with increasing molecular weight and increased branching (Table 4.5). As the molecular weight increases, London forces increase because more atoms are present to increase the surface area of the molecules. The more numerous points of contact between neighboring molecules strengthen London forces.

Anabolic Steroids in Sports

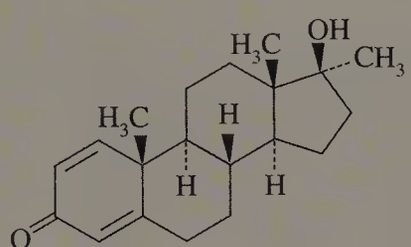
Athletes began to use anabolic steroids about 1950 to build muscle mass faster, and the abuse of these compounds rapidly became widespread. As recently as 1985, it was estimated that 90% of competitive weight lifters and body builders were using anabolic steroids. In the 1972 summer Olympics, about two-thirds of the track and field athletes had used anabolic steroids.

The anabolic steroids stanozolol and Dianabol are legally available only by prescription. Illegal and uncontrolled use of these compounds has severe consequences. The side effects in men include overly aggressive behavior, testicular atrophy, impotence, enlarged prostate, and cancer of the liver. In women, significant virilization occurs, resulting in clitoral enlargement, breast diminution, baldness, beard growth, deepened voice, and increased risk of cancer.

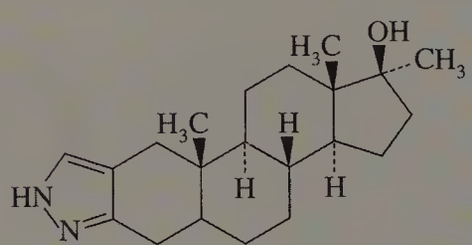


testosterone

Despite the well-known risks, these synthetic substances continue to be used by many athletes to promote muscle development. Steroid use is banned by most athletic unions. It is now standard practice during athletic competitions to test urine samples for the presence of synthetic anabolic steroids.



Dianabol

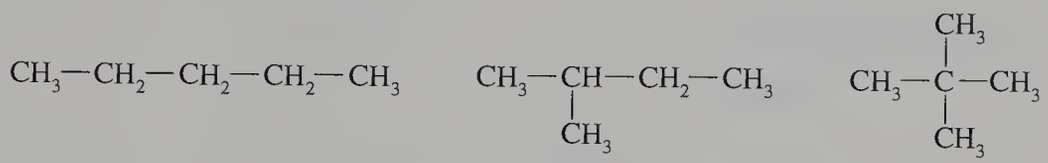


stanozolol

TABLE 4.5
Physical Properties of Some Alkanes and Cycloalkanes

Hydrocarbon	*Boiling point (°C)*	*Density (g/mL)*
methane	–164.0	
ethane	–88.6	
propane	–42.1	
butane	–0.5	
pentane	36.1	0.6262
hexane	68.9	0.6603
heptane	98.4	0.6837
octane	125.7	0.7025
nonane	150.8	0.7176
decane	174.1	0.7300
cyclopropane	–32.7	
cyclobutane	12.0	
cyclopentane	49.3	0.7457
cyclohexane	80.7	0.7786
cycloheptane	118.5	0.8098
cyclooctane	148.5	0.8349

Increased branching decreases the boiling points of isomeric alkanes. Normal alkanes can have efficient contact between chains, and the molecules can "stack" together. Branching in alkanes increases the distance between molecules, and the chains of carbon atoms are less able to come close to one another. Also, branched alkanes are more compact and have a smaller surface area than normal alkanes. The order of boiling points of the isomeric C_5H_{12} compounds illustrates this phenomenon.



pentane
bp 36 °C

isopentane
bp 28 °C

neopentane
bp 10 °C

Properties of Cycloalkanes

The physical properties of a series of cycloalkanes of increasing molecular weight are similar to those of a series of alkanes: as their molecular weights increase, their densities and boiling points also increase (Table 4.5). The boiling points of the cycloalkanes are higher than those of the alkanes containing the same number of carbon atoms.

4.10 Conformations and Properties

In Chapter 1, we learned that ethane can exist in various spatial arrangements, called **conformations**, which result from rotation of the CH_3 groups around the carbon–carbon σ bond. When the CH_3 units rotate around the C—C internuclear axis, the positions of the hydrogen atoms change with respect one another, but the connectivities of the carbon–carbon or carbon–hydrogen bonds remain the same. Thus, various conformations have different shapes, but are not structural isomers.

The study of the chemical and physical properties of different conformations of organic compounds is called **conformational analysis**. The Norwegian chemist O. Hassel and the Briton D. H. R. Barton were among the first organic chemists to recognize that conformations affect the properties of organic compounds. Hassel investigated the physical properties of the preferred conformations of small molecules. Barton showed how conformations affect chemical reactivity, especially in steroids. In 1969 they were awarded the Nobel Prize in chemistry for their pioneering work.

To understand the relationship between structure and physical properties, we need to know how structural differences change the conformations of molecules and which conformations predominate at equilibrium. To understand the relationship between structure and chemical reactivity, we must know the energy difference between the most stable conformation and the conformation required to bring atoms into proximity for reaction. If a substantial conformational change is required to "prepare" a molecule for reaction, then the energy associated with that change increases the E_a for the reaction.

In subsequent sections we will study the conformations of small organic molecules, such as ethane, propane, butane, and cyclohexane. At first glance, this might seem to be an unpromising topic. But once we understand the conformations of small molecules, we will be able to apply conformational concepts to much larger molecules, such as proteins. The conformation of a protein accounts for its highly specific biological function. A change in the biologically active conformation of a protein

often destroys its biological function. Thus, an understanding of the conformations of small molecules paves the way for understanding the behavior of vastly more complex structures.

4.11 Conformations of Ethane

Consider the models of ethane shown in Figure 4.5. The hydrogen atoms are in a different spatial relation to one another in the two structures. These two structures are conformations (or **conformers**) of ethane that can be interconverted by rotation around the carbon–carbon σ bond.

Ethane can exist in an infinite number of conformations. The conformation in which the hydrogen atoms and the bonding electrons are the farthest away from one another has the lowest energy. This conformation is said to be **staggered**. The conformation in which the hydrogen atoms are closest to each other has the highest energy. This conformation is said to be **eclipsed**. In the eclipsed conformation, each C—H bond on one carbon atom lines up with a C—H bond on another carbon atom, as the moon sometimes eclipses the sun. Any other intermediate conformation is a **skew** conformation. Sawhorse representations of the conformations of ethane are shown in Figure 4.5. These representations are three-dimensional and show the carbon–carbon bond as well as all of the C—H bonds. An alternate two-dimensional drawing called the Newman projection formula is often easier to draw.

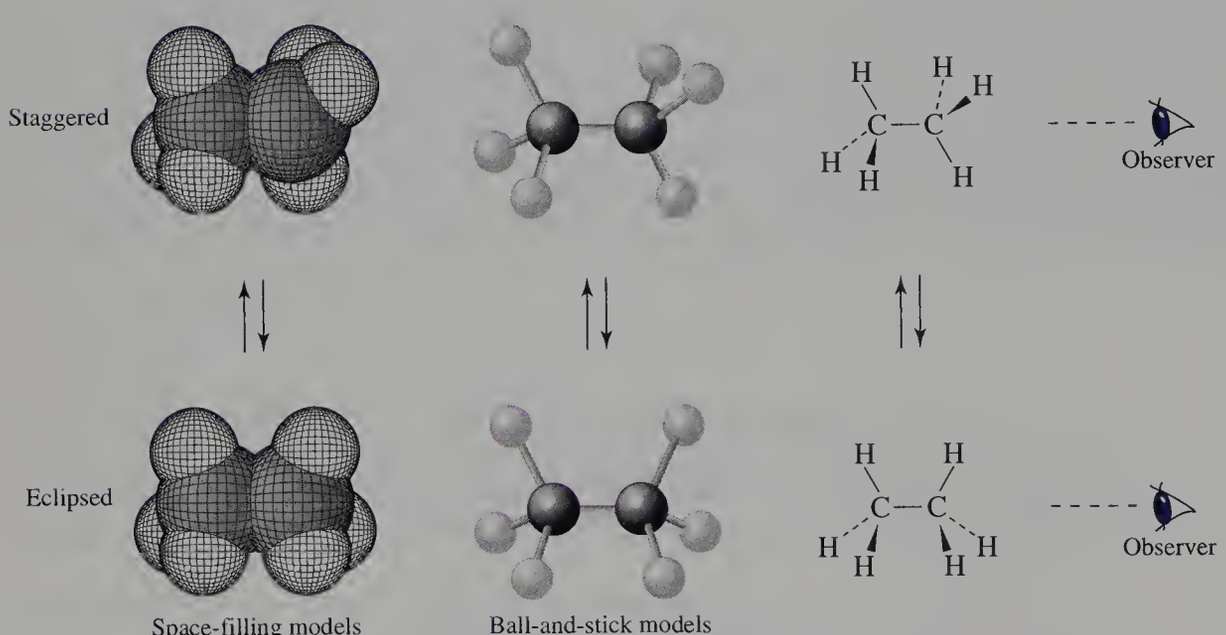
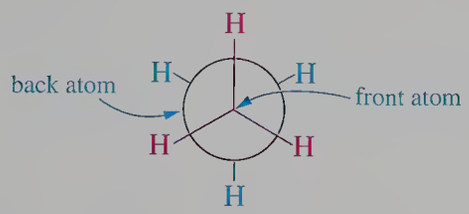


FIGURE 4.5
Conformations of Ethane
Rotation of the methyl group on the right by 60° converts a staggered conformation into an eclipsed conformation. Viewing the carbon–carbon bond end-on in the eclipsed conformation, the observer would see only the carbon atom and the three hydrogen atoms on the right. The left carbon atom and its three hydrogen atoms would be hidden.

Newman Projection Formulas

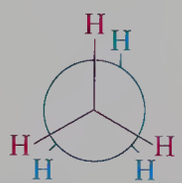
Newman projection formulas of structures concentrate on the two carbon atoms around which rotation may occur. The two atoms are viewed end-on. The "front" atom

is represented by a point with three bonds. The "back" atom is represented by a circle with three bonds that reach only to the perimeter of the circle. Although there is a bond between the two carbon atoms, it is hidden because it is located along the viewing axis.



Newman projection of staggered ethane conformation

A Newman projection of the eclipsed conformation of ethane shows only the three C—H bonds of the front carbon atom. The bonds and hydrogen atoms at the back are hidden by the front eclipsing bonds and hydrogen atoms. However, the bonded hydrogen atoms of the back carbon atom can be shown by viewing the conformation slightly off the bond axis so that all bonds can be seen.



Newman projection of eclipsed ethane conformation

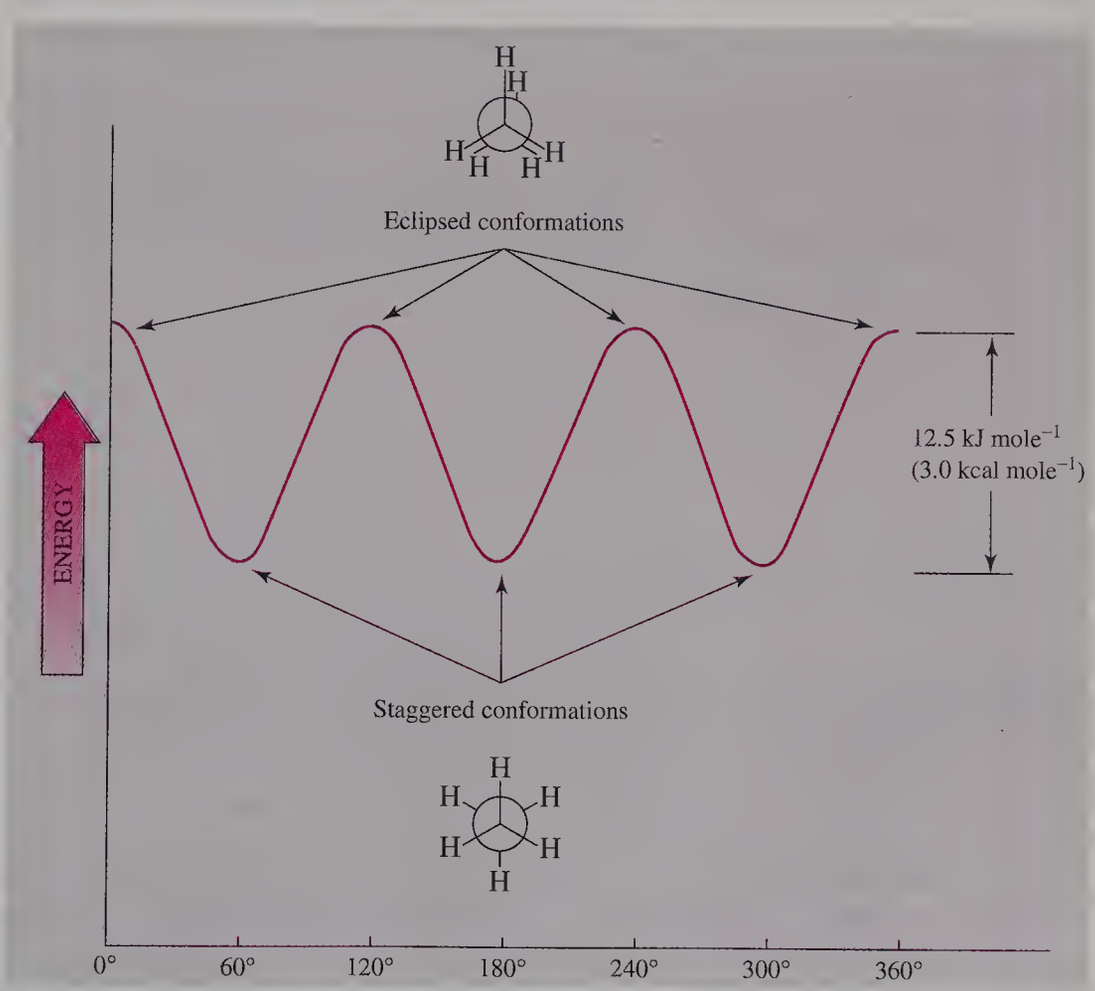
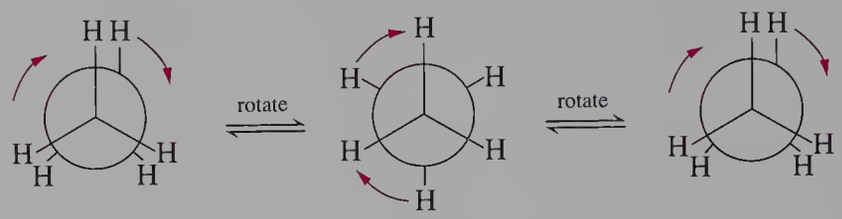


FIGURE 4.6 Rotational Barrier for Conformations of Ethane
Rotation about the carbon–carbon bond of ethane in 60° increments starting from an eclipsed conformation gives a series of alternating eclipsed and staggered conformations. The eclipsed conformation is 12.5 kJ mole^{-1} higher in energy than the staggered conformation.

Barrier to Rotation

Conformations interconvert by rotation around σ bonds. When the eclipsed conformation of ethane is rotated by 60° around the C—C axis, the staggered conformation is produced. Continued rotation by another 60° gives a new eclipsed conformation equivalent to the first.



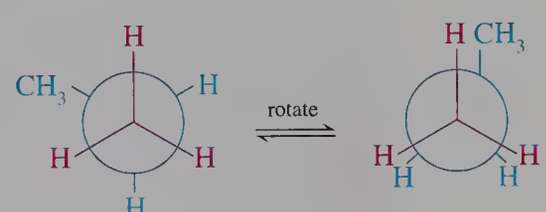
Continued rotation results in a series of staggered and eclipsed conformations. A plot of potential energy versus the angle of rotation for a complete 360° rotation around the C—C bond is shown in Figure 4.6. The energy difference between the staggered and eclipsed conformations is 12.5 kJ mole^{-1} (3.0 kcal mole^{-1}).

The eclipsed conformation has a higher energy because of **torsional strain** due to the repulsion between the bonded electrons in the C—H bonds as they approach and pass each other in the eclipsed conformation. Hence, there is a small barrier to rotation. Dividing the energy difference between the staggered and eclipsed conformations by 3, we obtain the energy of a hydrogen–hydrogen eclipsing interaction, 4.2 kJ mole^{-1} (1.0 kcal mole^{-1}).

The difference in energy between eclipsed and staggered conformations is small, and there is enough thermal energy at room temperature to allow rapid interconversion among these conformations. Consequently, we say that rotation around the C—C bond is virtually free or unrestricted.

4.12 Conformations of Propane

All acyclic alkanes exist as mixtures of conformations. The different conformations result from rotation around every carbon–carbon bond. Consider propane, which can exist in both eclipsed and staggered conformations.



staggered conformation eclipsed conformation

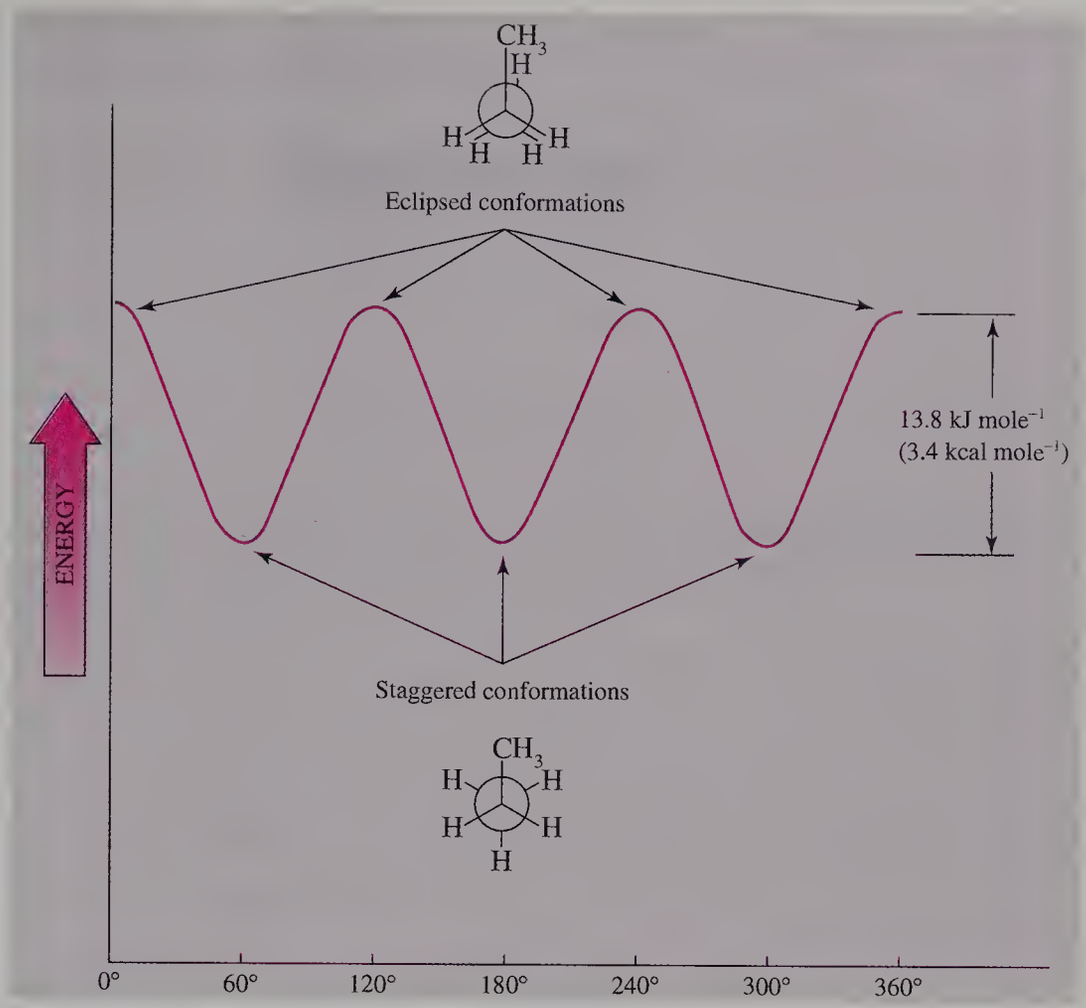
Figure 4.7 shows the energy of propane as rotation occurs around a carbon–carbon bond. As in ethane, the eclipsed conformation has the higher energy. The energy difference is 13.8 kJ mole^{-1} (3.4 kcal mole^{-1}). The eclipsed conformation of propane has two hydrogen–hydrogen eclipsing interactions and one hydrogen–methyl group eclipsing interaction. Because each of the two hydrogen–hydrogen eclipsing interactions is 4.2 kJ mole^{-1}, we conclude that the hydrogen–methyl interaction is 5.4 kJ mole^{-1} (1.4 kcal mole^{-1}).

When two or more atoms are forced into close proximity, they repel each other. They experience **van der Waals repulsion,** which occurs as the electrons associated with each atom start to occupy a common space. The effective size of atoms is given by the **van der Waals radii** (Table 4.6), which are related to how close atoms can

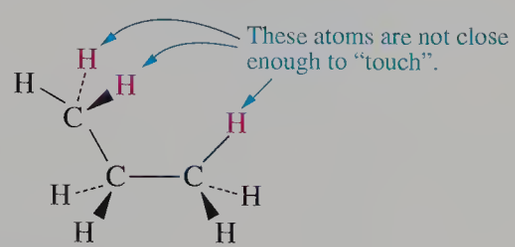
TABLE 4.6
Van der Waals Radii

Group	*Radius (pm)*
CH_3	200
CH_2	200
Br	195
Cl	180
F	135
H	120

FIGURE 4.7 Rotational Barrier for Conformations of Propane
Rotation about the carbon–carbon bond of propane in 60° increments starting from an eclipsed conformation gives a series of alternating eclipsed and staggered conformations. The eclipsed conformation is 13.8 kJ mole^{-1} higher in energy than the staggered conformation.



come without severe repulsion. Van der Waals repulsion is also called **steric hindrance**, and the energy of that interaction is **steric strain**. In the eclipsed conformation of propane, the indicated hydrogen atoms are not close enough to produce any substantial van der Waals repulsion.



It is useful to have some idea of when van der Waals repulsion affects the stability of a conformation. Consider a planar arrangement of five atoms in which all bond angles are 109°, the tetrahedral angle.

Atoms 1 and 5 are close enough to form a bond. Hence, their electron clouds are close enough for van der Waals repulsion between nonbonded atoms. The magnitude of the repulsion depends on the effective size of the atoms and the bond angles and bond lengths for the five-atom system. In the eclipsed conformation of propane, two sets

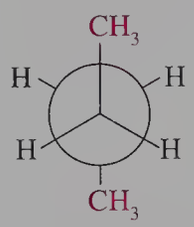
of hydrogen atoms, which are not bonded to each other, are in a 1,5 relationship. However, all of the atoms are not in a plane, and the steric repulsion is less than it would be if all five atoms were coplanar.

Problem 4.21

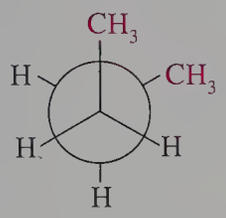
Predict the energy difference between the eclipsed and staggered conformations of 2-methylpropane around the C-1 to C-2 bond.

4.13 Conformations of Butane

The most stable conformation of butane has a zigzag arrangement of the carbon–carbon bonds in which all bonds are staggered. When butane is viewed along the C-2 to C-3 bond in a Newman projection, we find that the two methyl groups in one staggered conformation are the maximum distance apart in an **anti conformation**. A second staggered conformation, called the **gauche conformation**, is also possible.



anti conformation



gauche conformation

The angle between a front bond and a back bond in a Newman projection is called the **torsional angle** or **dihedral angle**, θ. In the gauche conformation of butane, the methyl groups lie at a 60° dihedral angle. In the anti conformation, the dihedral angle between the methyl groups is 180°.

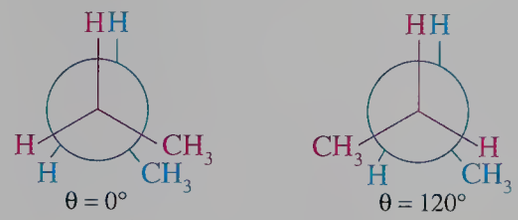
The two staggered conformations of butane differ in energy by 3.8 kJ mole^{-1} (0.9 kcal mole^{-1}). The anti conformation is more stable, and at 298 K, the ratio of anti to gauche conformation is about 2:1. The anti and gauche conformations interconvert about 10^8 times per second at room temperature.

Since there is no torsional strain in the two staggered conformations of butane, and the dihedral angle between each set of bonded pairs is 60°, why do the energies of the two conformations differ? In the gauche conformation the two methyl groups lie at a 60° angle, and the resulting van der Waals repulsion causes steric strain. We can understand why van der Waals repulsion occurs in the gauche conformation by using the simple atom-counting process described previously for the eclipsed conformation of propane. Consider a planar arrangement of six atoms in which all bond angles are the tetrahedral angle, 109°.

In this arrangement, atoms 1 and 6 would have to occupy the same region of space! Although the atoms in the gauche conformation of butane are not in a common plane, they are close enough to experience significant van der Waals repulsion. Melvin Newman of The Ohio State University summarized this situation in his "rule of 6", which qualitatively correlates the chemical properties of organic molecules with their conformations. The rule of 6 states that if a group of atoms is in proximity, such as in a common plane

or in a gauche conformation, an atom at site "1" is sterically strained by an atom at site "6". Furthermore, this strain increases as the number of atoms identified as "6" increases.

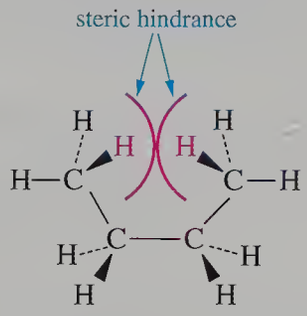
The two staggered conformations of butane are more stable than the two possible eclipsed conformations, which are present to only a limited extent.



eclipsed conformations of butane

Let's consider the eclipsed conformation having a dihedral angle of 120°. This conformation has one hydrogen–hydrogen eclipsing interaction and two hydrogen–methyl eclipsing interactions. Thus, the energy is greater than that of the anti conformation by $4.2 + 2 \times 5.4 = 15$ kJ mole^{-1}.

The eclipsed conformation with $\theta = 0°$ has two sets of hydrogen–hydrogen eclipsing interactions and one methyl–methyl interaction. The total energy of this conformation is estimated as 21 kJ mole^{-1} (5.0 kcal mole^{-1}) greater than the anti conformation. Because the two hydrogen–hydrogen eclipsing interactions account for 8.4 kJ mole^{-1}, we calculate a value of 12.6 kJ mole^{-1} (3.0 kcal mole^{-1}) for the methyl–methyl eclipsing interaction. This value is substantially larger than the 4.2 and 5.4 kJ mole^{-1} for the hydrogen–hydrogen and the hydrogen–methyl eclipsing interactions. When the dihedral angle is 0°, all four carbon atoms lie in a plane. The hydrogen atoms on the two terminal methyl groups have severe van der Waals repulsion.



A plot of potential energy of the various conformations of butane as a function of dihedral angle is shown in Figure 4.8. The maxima of the graph correspond to the eclipsed conformations and the minima to the staggered conformations.

Problem 4.22

Draw Newman projections of the staggered and eclipsed conformations of 1,2-dibromoethane. Qualitatively rank them by energy.

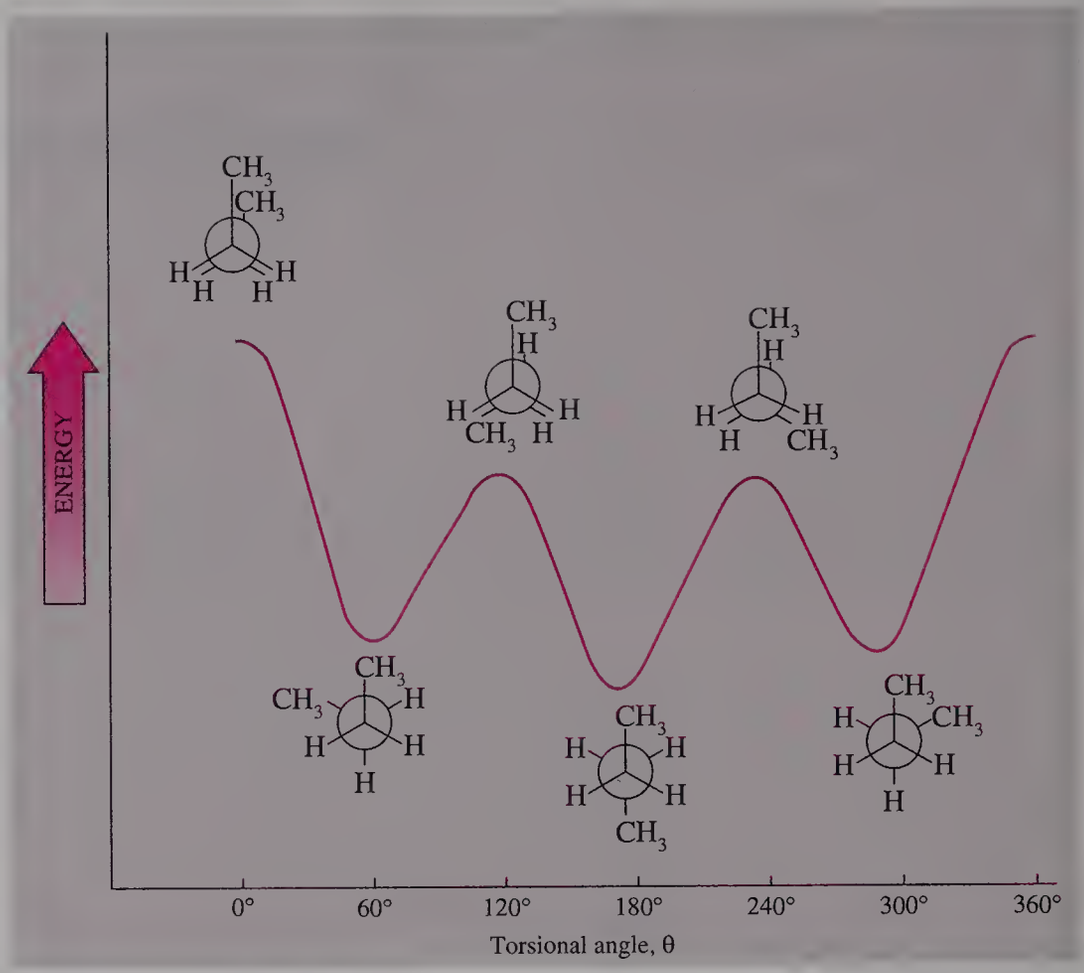
4.14 Conformations of Acyclic Compounds

We can expand our discussion of the relative energies of the conformations of ethane, propane, and butane to the energies of the conformations of the higher alkanes. We now know that

1. The lowest energy conformations have a staggered arrangement for all bonds.

FIGURE 4.8 Rotational Barrier for Conformations of Butane

Rotation about the central carbon–carbon bond of butane starting from a methyl–methyl eclipsed conformation gives two nonequivalent eclipsed and two nonequivalent staggered conformations. The gauche conformation is 3.8 kJ mole^{-1} higher in energy than the anti conformation.



2. Staggered conformations with $\theta = 180°$ are more stable that those with $\theta = 60°$.
3. The energy of eclipsing increases in the order hydrogen–hydrogen < hydrogen–alkyl < alkyl–alkyl.

The energies associated with each of the possible interactions in the conformations of alkanes are summarized in Table 4.7.

TABLE 4.7
Energy of Interactions in Hydrocarbons

Interaction	*Major cause*	*Energy (kJ mole^{-1})*
eclipsed H/H	torsional	4.2
eclipsed H/CH_3	torsional	5.4
eclipsed CH_3/CH_3	torsional + steric	12.6
gauche CH_3/CH_3	steric	3.8
gauche H/H (reference)		0

In normal alkanes, the conformation with all carbon–carbon bonds in anti arrangements is the lowest energy. However, normal alkanes also exist in higher en-

Conformations and Biological Activity

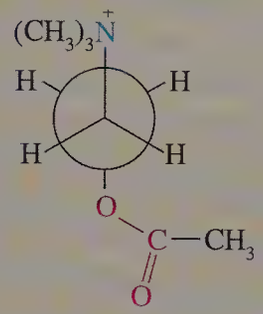
The conformational flexibility of small biomolecules determines how they bind with proteins called receptors. This interaction plays a significant role in regulating physiological processes. An understanding of small molecule–receptor binding interactions is required to design drugs that mimic the response of physiologically active biomolecules or that inhibit the activity of receptor proteins.

Consider the neurotransmitter acetylcholine, which contains a CH_2—CH_2 unit around which rotation may occur.

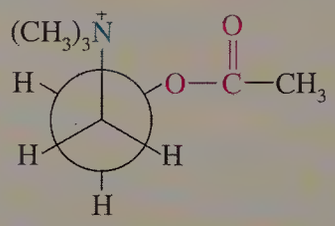
$$CH_3CO_2—CH_2CH_2—\overset{+}{N}(CH_3)_3$$

acetylcholine

Different conformations of acetylcholine interact with different biological receptors. For example, the anti conformation of acetylcholine interacts with the muscaric receptor of postganglionic parasympathetic nerves. The gauche conformation interacts with the nicotinic receptors at ganglia and neuromuscular junctions.



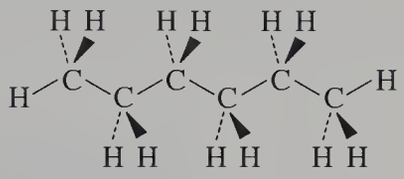
anti conformation



gauche conformation

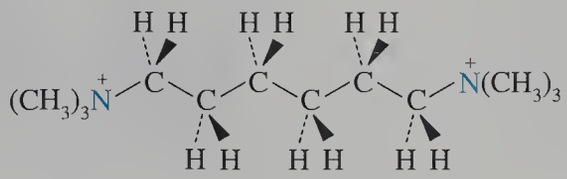
The physiological properties of different conformations of biologically active molecules have been studied by examining the properties of geometric isomers of structurally related compounds. These compounds, which are cyclic, have functional groups placed in a variety of three-dimensional relationships.

ergy conformations with gauche arrangements at one or more points in their chains. We will usually represent acyclic compounds in their most stable conformation.



most stable conformation, all anti

The conformations of substituted alkanes are affected by the functional groups. Charged groups attract each other if they have opposite charges and repel each other if they have like charges. For example, hexamethonium, a substance that blocks nerve transmission at neuromuscular junctions by binding the acetylcholine receptor, has ammonium ions at C-1 and C-6. The two positively charged nitrogen atoms stay as far apart as possible, considerably stabilizing the all-anti conformation.



4.15 Conformations of Cycloalkanes

Many naturally occurring compounds in plants and animals contain cyclic structures. For example, steroids are polycyclic structures consisting of five- and six-membered rings made up of only carbon atoms. Carbohydrates are heterocyclic compounds containing one oxygen atom in a ring along with four or five carbon atoms. Rings of this type are components of the nucleotides that make up DNA and RNA. We will emphasize six-membered rings because they are so abundant in nature.

Cyclopropane

Cyclopropane has only three carbon atoms, so it is a planar molecule. We recall that it is strained because the "bent" carbon–carbon bonds overlap poorly. The total ring strain in cyclopropane is 115 kJ mole^{-1} (27.5 kcal mole^{-1}). This strain energy is not exclusively angle strain, which results from weaker bonds formed by less efficient overlap of the hybrid orbitals of the ring carbon atoms. Other kinds of strain also contribute to the total ring strain. Cyclopropane has six hydrogen atoms. Three lie above the plane of the ring of carbon atoms and three lie below. These hydrogen atoms eclipse their neighboring hydrogen atoms on adjacent carbon atoms, introducing torsional strain. Cyclopropane has six pairs of hydrogen–hydrogen eclipsed interactions. We recall that a hydrogen–hydrogen eclipsing interaction in ethane is 4.2 kJ mole^{-1} (kcal mole^{-1}) . Although the bond angles are not the same in cyclopropane as in ethane, we can estimate that the total torsional strain energy is $6 \times 4.2 = 25.2$ kJ mole^{-1} (6.0 kcal mole^{-1}). Because the total strain energy is 115 kJ mole^{-1}, about three-quarters of the total strain energy is due to bond angle strain.

Cyclobutane

Let's begin our discussion of the conformation of cyclobutane by imagining that it is planar. If it were, there would be eight pairs of eclipsed hydrogen atoms, which would account for $8 \times 4.2 = 33.6$ kJ mole^{-1} (8.0 kcal mole^{-1}) of the total strain energy of cyclobutane. However, in contrast to cyclopropane, cyclobutane is not planar but "puckered" (Figure 4.9a). Puckering, which arises when hydrogen atoms are twisted away from each other, reduces hydrogen–hydrogen eclipsing interactions. This twisting does not produce a fully staggered arrangement of hydrogen atoms because the decrease in torsional strain energy is balanced by some increase in the bond angle strain.

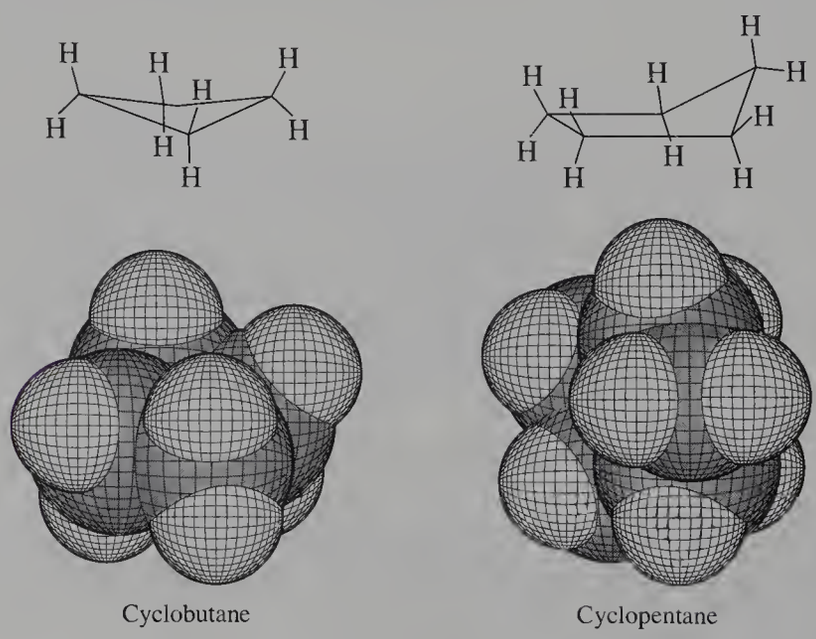


FIGURE 4.9
Conformations of Cyclobutane and Cyclopentane
(a) The conformation of cyclobutane is a slightly bent ring so that the hydrogen atoms on adjacent carbon atoms are not quite eclipsed.
(b) The conformation of cyclopentane is described as an "envelope". One of the carbon atoms is out of the plane. This feature decreases the number of eclipsing interactions of hydrogen atoms on adjacent carbon atoms.

Cyclopentane

A cyclopentane ring can exist in a planar conformation with little angle strain because the internal angle of a pentagon is 108°, quite close to the tetrahedral angle of 109°. However, if cyclopentane were planar, all ten hydrogen atoms would be eclipsed, and the torsional energy would be $10 \times 4.2 = 42$ kJ mole^{-1} (10 kcal mole^{-1}). This undesirable state of affairs can be minimized by twisting of the cyclopentane ring into a lower energy, nonplanar, conformationally mobile conformation called the **envelope** conformation (Figure 4.9b).

Cyclohexane

Cyclohexane exists mainly in a conformation where all C—H bonds on neighboring carbon atoms are staggered, with the dihedral angles equal to 60°. Figure 4.10 shows a bond-line representation of the **chair conformation** of cyclohexane. Four of the carbon atoms form the "seat" of the chair, one carbon atom is the "back" of the chair, and one carbon atom is the "footrest".

Hydrogen atoms in the chair conformation fall into two sets. Six point up or down with respect to the average plane of the ring of carbon atoms. They are **axial**. If a particular axial hydrogen atom points "up", the axial hydrogen atoms on the two adjacent carbon atoms point "down". This up-down relationship alternates all the way around the ring. The remaining six hydrogen atoms lie approximately in the average

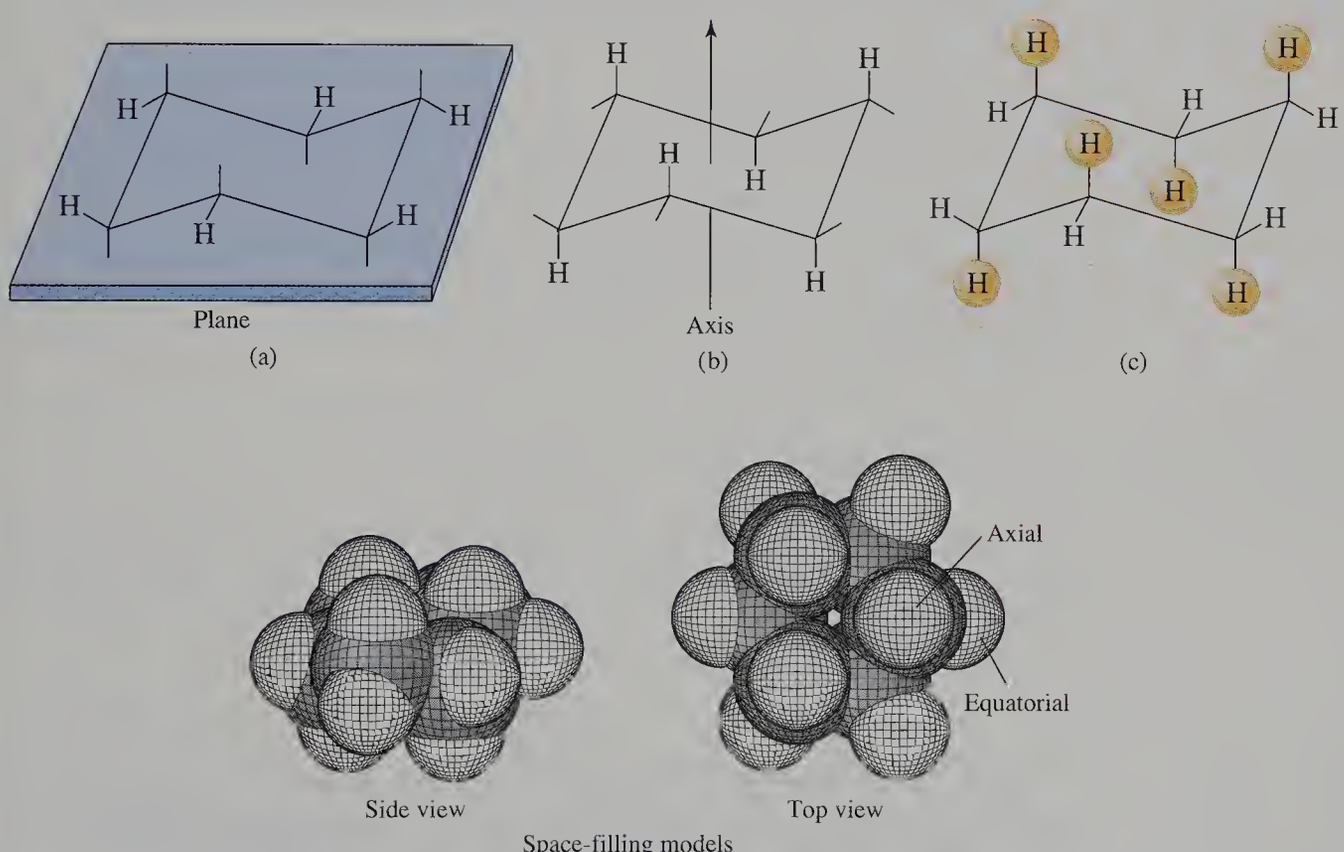


FIGURE 4.10 Axial and Equatorial Hydrogen Atoms in Cyclohexane
The equatorial C—H bonds shown in (a) are located in a band around the "equator" of the ring. Each carbon atom has one equatorial hydrogen atom. The six axial C—H bonds are parallel to the axis shown perpendicular to the plane in (b). Three hydrogen atoms are pointed up from the average plane of the ring; three hydrogen atoms are pointed down. The axial hydrogen atoms are located in an alternating up/down relationship. All hydrogen atoms are shown in (c). The axial hydrogen atoms are circled.

plane of the ring. They extend away from the ring and are called **equatorial** atoms. Each carbon atom has one equatorial and one axial C—H bond.

The chair conformation of cyclohexane has no torsional strain; all C—H bonds of adjacent carbon atoms are staggered, with a dihedral angle equal to 60°. Cyclohexane is best studied by building a molecular model. When we make a model of the chair conformation of cyclohexane, we can easily see the torsional relationships and the orientation of the equatorial and axial hydrogen atoms. We can also analyze the arrangement of equatorial and axial hydrogen atoms in a Newman projection formula by sighting along both the C-2 to C-3 and the C-5 to C-6 bonds (Figure 4.11). (The same perspective would result by sighting along any pair of parallel carbon–carbon bonds.) We note that the C-1 and C-4 atoms are in a gauche relationship similar to the gauche relationship between the C-1 and C-4 atoms of butane. The same relationship occurs between any two atoms separated by a CH_2—CH_2 unit throughout the ring.

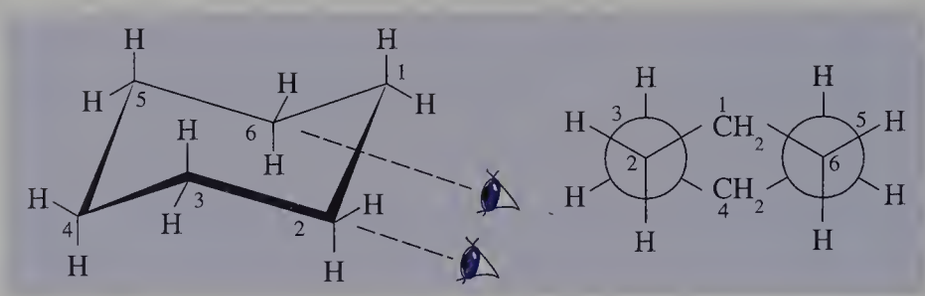
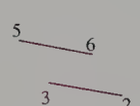


FIGURE 4.11 Newman Projection Formula of Cyclohexane
The C-2 to C-3 and C-5 to C-6 bonds of cyclohexane are both viewed and the two ethane-like Newman projections are written side by side. The C-1 and C-4 atoms are placed to join the two units.

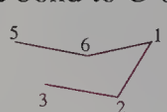
Drawing Cyclohexane Rings

We can draw the carbon skeleton of cyclohexane with three sets of parallel lines having different slopes. To do this, we proceed as follows.

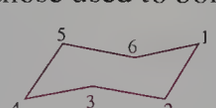
First, draw one set of parallel lines that slant slightly downward. They form the "seat" of the chair. So that the orientation of the ring corresponds to that shown in Figure 4.10, the bonds are the C-2 to C-3 and C-5 to C-6 bonds. These four carbon atoms lie in a plane.



Next, place C-1 above and to the right of C-2. Connect C-1 to C-6 using a slope in the opposite direction from those forming the seat. Connect C-1 to C-2 using a line in the same direction as for the bond to C-6, but at a steeper slope.



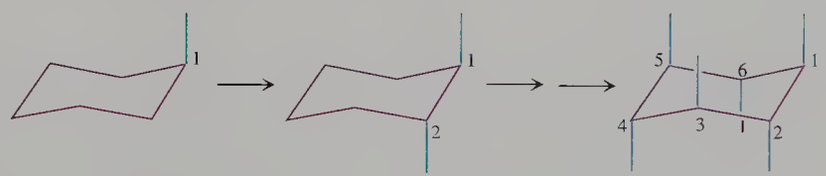
Next, place C-4 below and to the left of C-5. Connect C-4 to C-3 and to C-5 using slopes in the opposite direction from those forming the seat. The two different lines required are parallel to those used to bond C-1 to C-2 and C-6.



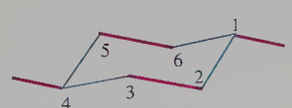
When we look at the six lines that make up the outline of the cyclohexane ring, we see that they are divided into three sets of parallel lines.

1. The line linking C-5 to C-6 is parallel to the line connecting C-3 and C-2.
2. The line linking C-4 to C-5 is parallel to the line connecting C-2 and C-1.
3. The line linking C-6 to C-1 is parallel to the line connecting C-3 and C-4.

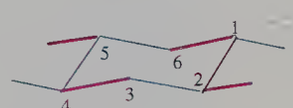
Having drawn the carbon skeleton, we add the axial and equatorial bonds. The axial bonds are easy to place. Start at C-1 and point the bond up. Now proceed around the ring placing axial bonds in an alternating up/down arrangement. The up bonds are at C-1, C-3, and C-5. The down bonds are at C-2, C-4, and C-6).



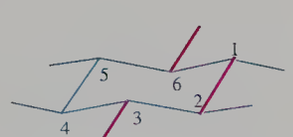
The equatorial bonds are harder for most people to place. Like the bonds in the ring itself, they can be considered as three sets of parallel lines. Each set is also parallel to two ring bonds. The easiest C—H bonds to draw are at C-1 and C-4. The equatorial bond at C-1 is parallel to the C-2 to C-3 bond (as well as the C-5 to C-6 bond). The equatorial C—H bond parallel to the C—H bond at C-1 is located at C-4. We now have two parallel C—H bonds that also parallel two C—C bonds.



The equatorial bond at C-2 is parallel to the C-3 to C-4 bond (as well as the C-6 to C-1 bond). The equatorial C—H bond that is parallel to the C—H bond at C-2 is located at C-5. Thus, we now have a second set of four parallel lines.



Finally, the equatorial bond at C-3 is parallel to the C-1 to C-2 bond (as well as the C-4 to C-5 bond). The equatorial C—H bond that is parallel to the C—H bond at C-3 is located at C-6. These lines constitute the third set of four parallel lines.



4.16 Conformational Mobility of Cyclohexane

The most stable conformation of cyclohexane is a chair, but different chair conformations rapidly interconvert at room temperature. This process—known as a **ring inversion**, a **chair–chair interconversion**, or simply a **ring flip**—is shown in Figure 4.12. When the cyclohexane ring flips, every equatorial bond becomes axial and every axial bond becomes equatorial. This process can be clearly seen by practicing with molecular models. To flip a cyclohexane ring, hold the four atoms of the "seat" in place while pushing one "end" carbon downward and the other "end" carbon upward. At each of these two "end" atoms, an equatorial position becomes an axial position and vice versa. The hydrogen atoms on every other carbon atom also

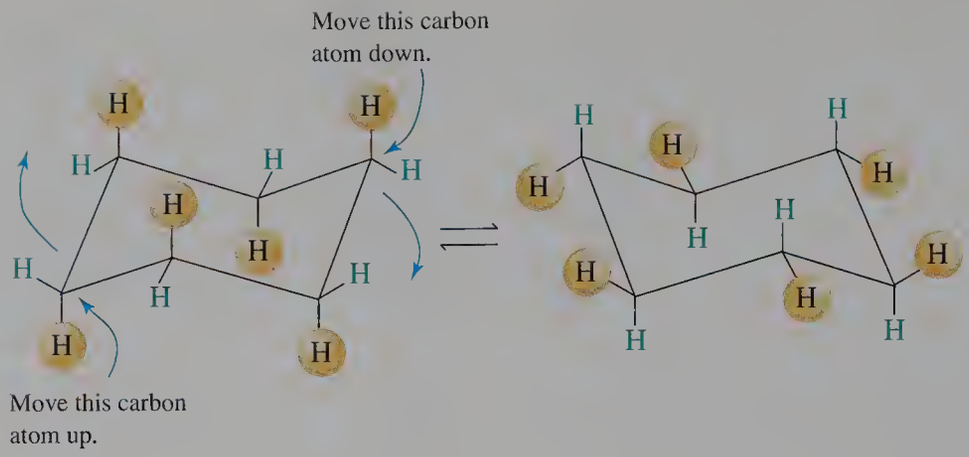


FIGURE 4.12 Conformational Mobility of the Cyclohexane Ring
The interconversion of chair conformations of cyclohexane is called a ring flip. When the atoms are moved in the indicated direction, one conformation is converted into another conformation. An axial position in one chair conformation becomes an equatorial position in the other conformation and vice versa. The interconversion is rapid.

undergo the same transformation. You should confirm this fact using your own set of models.

Boat Conformation of Cyclohexane

In the process of flipping, the chair conformation of cyclohexane can pass through another conformation known as the **boat conformation** (Figure 4.13). The boat conformation of cyclohexane is approximately 29 kJ mole^{-1} (7.0 kcal mole^{-1}) less stable than the chair conformation. This strain is due to several factors, all of which are structurally related to the methyl–methyl eclipsed conformation of butane. We can view the steric interactions in boat cyclohexane by drawing a Newman projection. When we sight along the C-2 to C-3 and the C-5 to C-6 bonds, we see that there are four pairs of eclipsed hydrogen atoms. Also, the C-1 and C-4 atoms are eclipsed, and hydrogen atoms on each carbon atom are sufficiently close to cause additional strain.

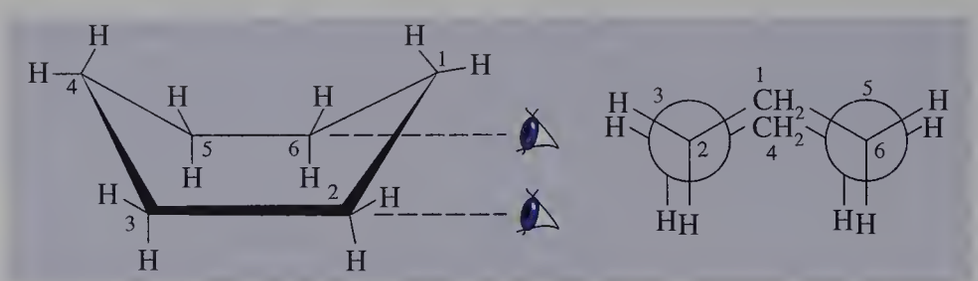
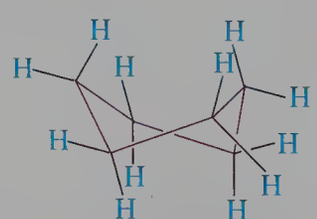


FIGURE 4.13 Newman Projection Formula of Boat Conformation
Both the C-2 to C-3 and C-5 to C-6 bonds of the boat conformation are viewed and the two ethane-like Newman projection formulas are written side by side. The C-1 and C-4 atoms are placed to join the two units. These two atoms are eclipsed.

Because the boat conformation of cyclohexane is 29 kJ mole^{-1} less stable than the chair conformation, only a tiny fraction of cyclohexane molecules exist in a boat conformation. The steric energy of the boat conformation can be lowered by rotation of the bonds, which decreases the hydrogen–hydrogen eclipsing interactions. The result is a **twist boat** conformation. It is about 22 kJ mole^{-1} (5.5 kcal mole^{-1}) less stable than the chair conformation. This energy difference means that only about 0.01% of the cyclohexane molecules are in the twist boat conformation.



twist boat conformation

The potential energies of the chair, boat, and twist boat conformations of cyclohexane can be related to one another as shown in an energy diagram (Figure 4.14). The point of maximum energy corresponds to a conformation in which a fifth carbon atom is brought into the plane of the four carbon atoms that form the "seat" of the chair. This conformation is a transition state called the **half chair,** with a potential energy of about 42 kJ mole^{-1} (10 kcal mole^{-1}) higher than the chair conformation. This transition state is strained because there are increased torsional interactions as well as bond angle strain.

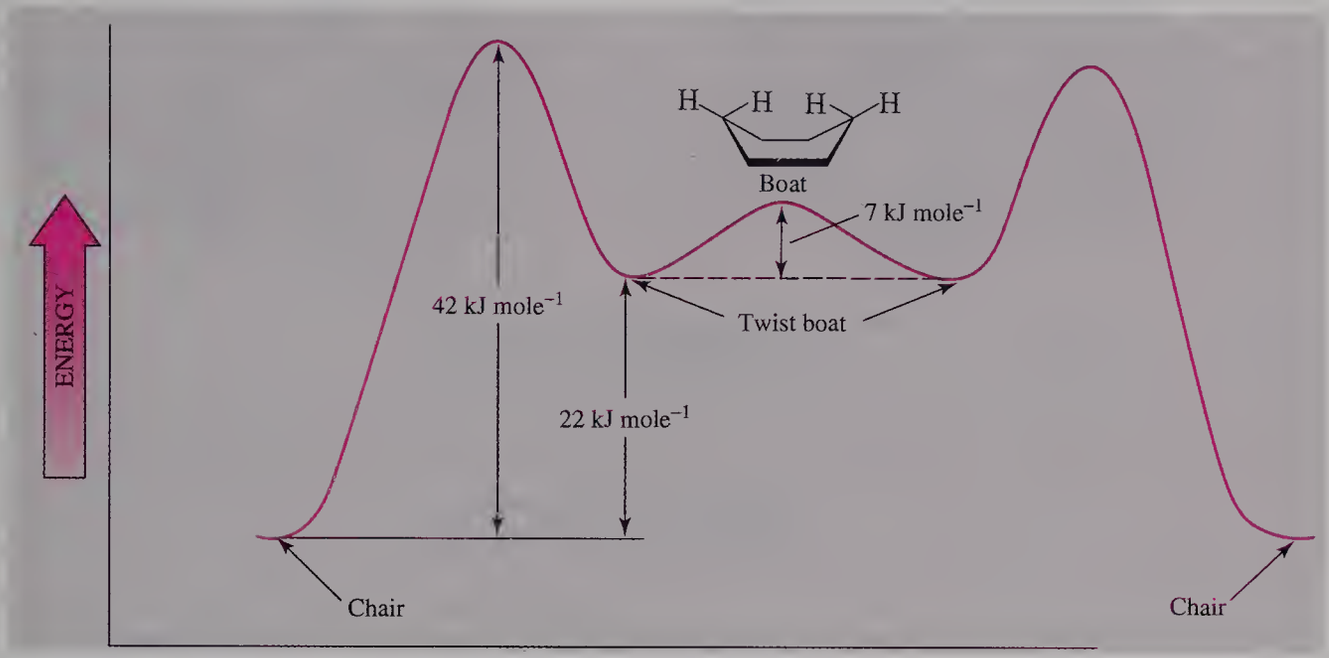


FIGURE 4.14 Conformational Energy of Cyclohexane
The interconversion of two chair conformations proceeds via a pathway that produces twist boat conformations that are in equilibrium with a boat conformation.

As the half chair converts to the twist boat, its potential energy decreases. Twist boat conformations rather easily interconvert. A twist boat converts to a chair conformation by passing through a half chair conformation. These processes take place continuously as chair conformations interconvert.

4.17 Monosubstituted Cyclohexanes

We have seen that when a cyclohexane ring flips, all equatorial bonds become axial and all axial bonds become equatorial. Now let's consider the consequences of flipping a substituted cyclohexane ring. The chair–chair interconversion of monosubstituted cyclohexanes occurs very rapidly. However, unlike those of cyclohexane, the two conformations are not equally stable.

Let's consider methylcyclohexane in a chair conformation with an equatorial methyl group. When the ring flips, the equatorial methyl group moves into an axial position (Figure 4.15). These two structures are different conformations, not structural isomers. A methyl group in an axial position is 8.1 kJ mole^{-1} (1.7 kcal mole^{-1}) less stable than a methyl group in an equatorial position. At equilibrium, about 95% of the mixture has an equatorial methyl group.

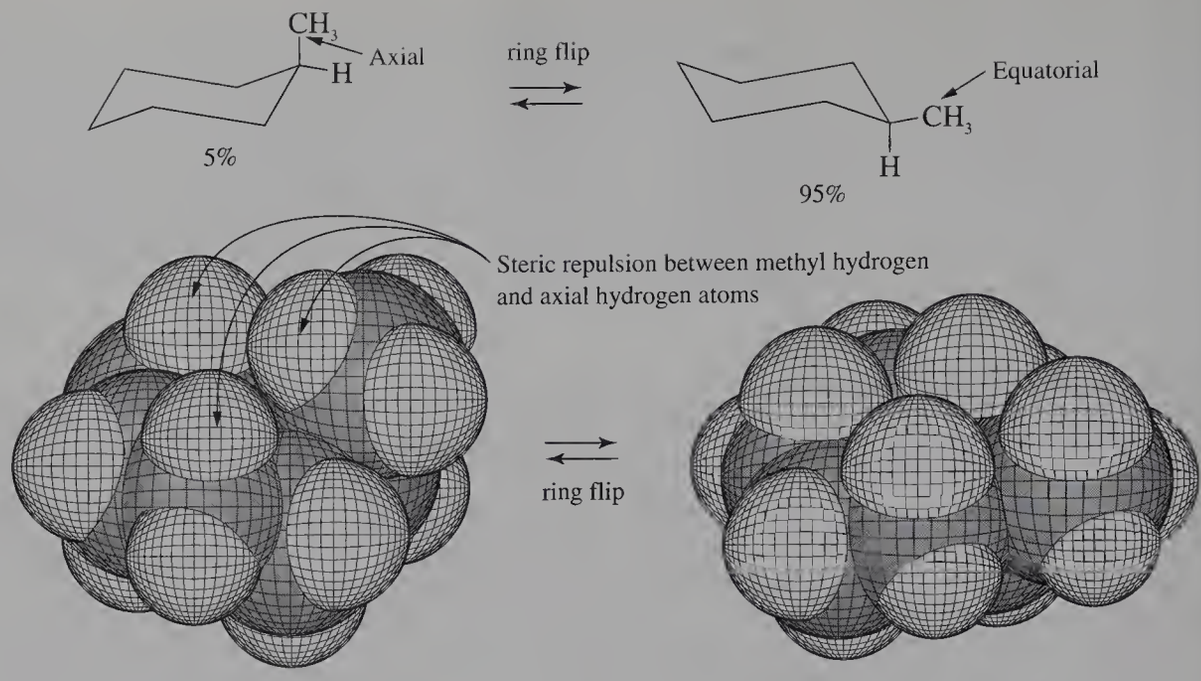


FIGURE 4.15 Conformations of Methylcyclohexane
Methylcyclohexane interconverts rapidly between two conformation of unequal energy. At any time there is 95% of the equatorial conformation and 5% of the axial conformation. The axial conformation has unfavorable interactions between the methyl group hydrogen atoms and the axial hydrogen atoms on the C-3 and C-5 carbon atoms.

The conformation with an axial methyl group is less stable than the conformation with an equatorial methyl group because an axial methyl group experiences steric strain from axial hydrogen atoms at the C-3 and C-5 atoms. This **1,3-diaxial strain** is not really a new phenomenon. We are already familiar with the steric repulsion between two methyl groups in the gauche conformation of butane. The same relationship occurs twice in the axial conformation of methylcyclohexane (Figure 4.16). When we examine the C-1 to C-2 bond, we see that the methyl group is at a 60° dihedral angle to the C-3 atom. A similar relationship exists between the methyl group and the C-5 atom when the view is along the C-1 to C-6 bond. In the equatorial conformation, the methyl group is anti to both the C-3 and C-5 atoms. There-

FIGURE 4.16 1,3-Diaxial Strain in Methylcyclohexane
An axial methyl group is at a 60° dihedral angle with respect to two ring bonds. The two gauche interactions are shown in two Newman projection formulas. Sighting down the C-1 to C-2 bond shows the eclipsing of the methyl group by the C-3 atom. Sighting down the C-1 to C-6 bond shows the eclipsing of the methyl group by the C-5 atom.

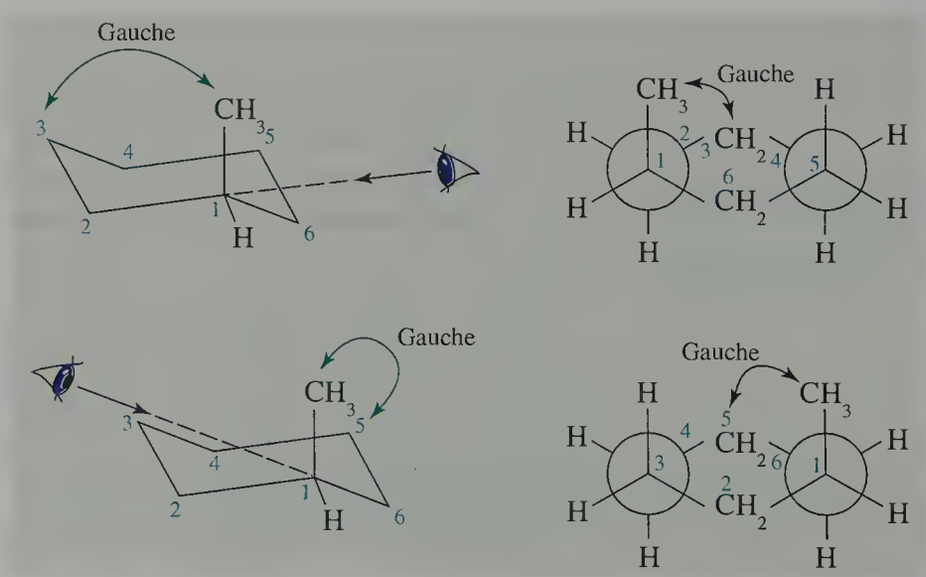


TABLE 4.8
Conformational Preference of Groups

Group	*Strain energy (kJ mole^{-1})*
C≡N	0.8
F	1.0
Cl	2.8
OH	4.2
CH_3	7.6
CH_3CH_2	8.0
$CH(CH_3)_2$	9.2
$C(CH_3)_3$	22
CO_2H	5.8

fore, the steric strain for the axial conformation of methylcyclohexane is twice that of the gauche interaction of butane or $2 \times 3.8 = 7.6$ kJ mole^{-1} (1.8 kcal mole^{-1}).

The conformational properties of other substituted cyclohexanes are similar. That is, the conformation with an equatorial substituent is always more stable than the conformation with an axial one. The conversion of an equatorial to an axial conformation is an endergonic process ($\Delta G° > 0$). The energy difference depends upon the identity of the substituent and is called its **conformational preference**. A list of these energy differences is given in Table 4.8. The conformational preference of a substituent on a cyclohexane ring—that is, the magnitude of the 1,3-diaxial strain—reflects its specific interaction with the cyclohexane ring. The conformational preferences of a methyl group, hydroxyl group, and fluorine atom decrease in the order $CH_3 > OH > F$. This trend reflects in part the decrease in atomic radii from left to right in the periodic table. The conformational preferences of methyl, ethyl, isopropyl, and *tert*-butyl decrease in the order $(CH_3)_3C > (CH_3)_2CH > CH_3CH_2 > CH_3$. The trend reflects the ease with which the alkyl group can be oriented in an equatorial site compared to an axial site. This trend is often said to indicate the "size" of the alkyl group.

Problem 4.23

Predict the steric strain of the axial conformation of a cyclohexane ring substituted with an amino group (NH_2).

Problem 4.24

Calculate the percentage distribution of axial and equatorial conformations of cyclohexanol ($C_6H_{11}OH$).

Problem 4.25

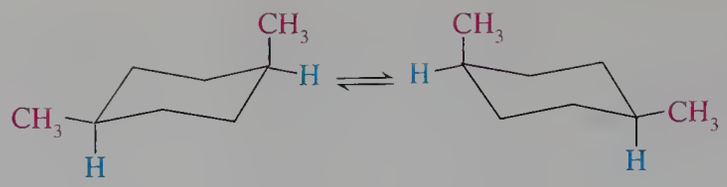
Why is the conformational preference of a cyano (—C≡N) group so small?

4.18 Disubstituted Cyclohexanes

In monosubstituted cyclohexanes, the steric strain and the resulting preference for the equatorial position over the axial position result from the interaction of the substituent with the axial atoms of the ring. In disubstituted cyclohexanes, we have to consider both the inherent steric strain for each individual substituent and any interactions between the substituents. In this section we will examine the isomeric dimethylcyclohexanes and determine the preferred conformation of each molecule. Then we will calculate the difference in energy between isomers.

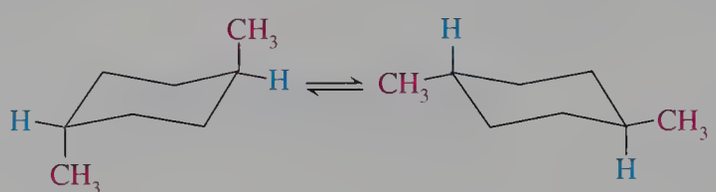
1,4-Dimethylcyclohexanes

Let's start with compounds in which the substituents do not interact with each other. This situation occurs in the isomeric *cis*- and *trans*-1,4-dimethylcyclohexanes. The two methyl groups in the cis isomer are on the same side of the ring. We can place both substituents on the "top" of the ring. In the following chair conformation the "up" position at the C-1 atom is axial; the "up" position at the C-4 atom is equatorial. This conformation can convert to another conformation by a ring flip, which changes the C-1 methyl from axial to equatorial and the C-4 methyl group from equatorial to axial.



This conformational change does not alter the cis relationship of the methyl groups. Moreover, the two conformations are equivalent because each one has an equatorial and an axial methyl group. The steric energy of the cis isomer is 7.6 kJ mole^{-1} (1.8 kcal mole^{-1}), like that of the axial conformation of methylcyclohexane.

Now let's consider *trans*-1,4-dimethylcyclohexane. The trans isomer has the two methyl groups on the opposite sides of the ring. Let's place the methyl group at the C-1 atom on the "top" of the ring, which corresponds to an axial position. The methyl group at the C-4 atom must then be placed on the "bottom" of the ring, also an axial position. Consequently, a diaxial arrangement of methyl groups results, a situation that clearly has considerable steric strain.



The steric strain of the diaxial conformation is twice that of the axial conformation of methylcyclohexane or $2 \times 7.6 = 15.2$ kJ mole^{-1} (3.6 kcal mole^{-1}). However, interconversion of this conformation by a ring flip changes both axial methyl groups into equatorial methyl groups. The steric energy of this conformation is zero, like the equatorial conformation of methylcyclohexane. Thus, the diaxial conformation is 15.2 kJ mole^{-1} less stable than the diequatorial conformation. Because of this energy difference, approximately 99.5% of the compound exists in the diequatorial conformation at 25 °C.

Because *cis*-1,4-dimethylcyclohexane has an axial methyl group in both of its chair conformations, and because *trans*-1,4-dimethylcyclohexane can exist in a conformation in which both methyl groups are equatorial, the trans isomer is more stable than the cis isomer. The two geometric isomers differ in energy by 7.6 kJ mole^{-1} (1.8 kcal mole^{-1}). This energy difference is due solely to the axial methyl group of the cis isomer. The heats of formation given in Table 4.9 confirm this analysis.

TABLE 4.9
Heats of Formation of Isomeric Cycloalkanes

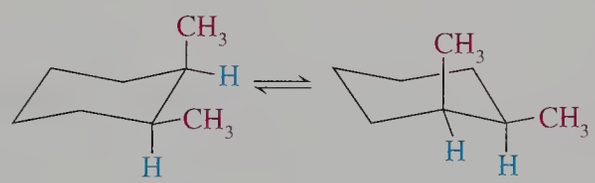
Substituted cycloalkane	ΔH_f° *(kJ mole^{-1})*
trans-1,2-dimethylcyclohexane	−179.9
cis-1,2-dimethylcyclohexane	−172.1
trans-1,3-dimethylcyclohexane	−176.5
cis-1,3-dimethylcyclohexane	−184.6
trans-1,4-dimethylcyclohexane	−184.5
cis-1,4-dimethylcyclohexane	−176.6
trans-1,2-dimethylcyclopentane	−136.1
cis-1,2-dimethylcyclopentane	−129.5
trans-1,3-dimethylcyclopentane	−133.5
cis-1,3-dimethylcyclopentane	−135.9
trans-1,2-dimethylcyclopropane	−3.2
cis-1,2-dimethylcyclopropane	+0.7

	Steric energy
cis-1,4-dimethylcyclohexane	7.6 kJ mole^{-1}
trans-1,4-dimethylcyclohexane (diequatorial)	0.0 kJ mole^{-1}
estimated difference in heat of formation	7.6 kJ mole^{-1}

1,2-Dimethylcyclohexanes

Now let's consider the steric strain of the isomeric 1,2-dimethylcyclohexanes. To do this we will have to consider both the inherent steric strain for each individual substituent and an interaction between the substituents because they are close to each other.

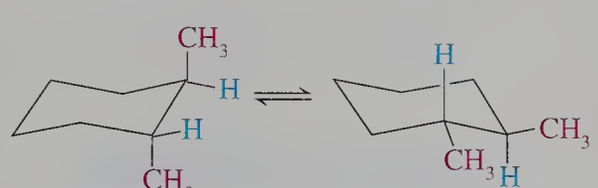
The two methyl groups in *cis*-1,2-dimethylcyclohexane are on the same side of the ring. We can place both substituents on the "top" of the ring. In the following chair conformation, the "up" position at the C-1 atom is axial and the "up" position at the C-2 atom is equatorial. These conformations interconvert by a ring flip that changes the axial methyl at C-1 to an equatorial methyl and the equatorial methyl at C-2 to an axial methyl.



Flipping a cyclohexane ring does not alter the cis relationship of the methyl groups. The two conformations are equivalent because each one has an equatorial and an axial methyl group. The one axial methyl group contributes 7.6 kJ mole^{-1} (1.8 kcal mole^{-1}) to the steric energy of the cis isomer, the same as for the axial conformation of methylcyclohexane. However, both conformations also have a gauche butane interaction between the two methyl groups. Thus the total steric energy is 11.4 kJ mole^{-1} (2.7 kcal mole^{-1}).

1,3-diaxial strain	7.6 kJ mole^{-1}
gauche butane interaction	3.8 kJ mole^{-1}
total strain energy	11.4 kJ mole^{-1}

The two methyl groups in *trans*-1,2-dimethylcyclohexane are on the opposite sides of the ring. As we did for the cis isomer, let's place the methyl group at the C-1 atom on the "top" of the ring, which corresponds to an axial position. Then, the methyl group at the C-2 atom must be placed on the "bottom" of the ring, which is also an axial position. The steric strain of two axial methyl groups is 2(7.6 kJ mole^{-1}) = 15.2 kJ mole^{-1}.



However, interconversion of this conformation by a ring flip changes both axial methyl groups into equatorial methyl groups. Although the 1,3-diaxial interactions are eliminated, a gauche butane interaction between the two methyl groups results.

The steric strain of the diequatorial conformation is 3.8 kJ mole^{-1}. Thus, the diequatorial conformation is more stable than the diaxial conformation by 11.4 kJ mole^{-1}.

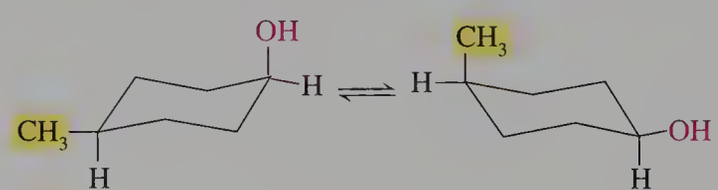
	Steric energy
trans-1,2-dimethylcyclohexane (diaxial)	15.2 kJ mole^{-1}
trans-1,2-dimethylcyclohexane (diequatorial)	3.8 kJ mole^{-1}
difference in steric energy	11.4 kJ mole^{-1}

Because *cis*-1,2-dimethylcyclohexane has an axial methyl group in both of its chair conformations, and because *trans*-1,2-dimethylcyclohexane can exist in a diequatorial conformation, the trans isomer is more stable than the cis isomer. Once again, the heats of formation given in Table 4.9 confirm this analysis.

	Steric energy
cis-1,2-dimethylcyclohexane	11.4 kJ mole^{-1}
trans-1,2-dimethylcyclohexane (diequatorial)	3.8 kJ mole^{-1}
difference in steric energy	7.6 kJ mole^{-1}

Compounds with Two Different Substituents

We can calculate the steric energy of the conformations of cyclohexanes substituted with two different substituents using the same techniques described above. For example, consider the two conformations of *cis*-4-methylcyclohexanol.



steric strain = 4.2 kJ mole^{-1} steric strain = 7.6 kJ mole^{-1}

In the conformation on the left, the methyl group is equatorial and has no steric strain, but the steric strain of the axial hydroxyl group is 4.2 kJ mole^{-1}. In the conformation on the right, the strain energy of the methyl group is 7.6 kJ mole^{-1} (1.8 kcal mole^{-1}) and the equatorial hydroxyl group has no steric strain. The $\Delta G°$ for the interconversion of the two conformations equals the difference between their steric strain energies. The conformation on the left is more stable by 3.4 kJ mole^{-1}. At 298 K, 80% of the conformational mixture exists in the conformation on the left.

Problem 4.26

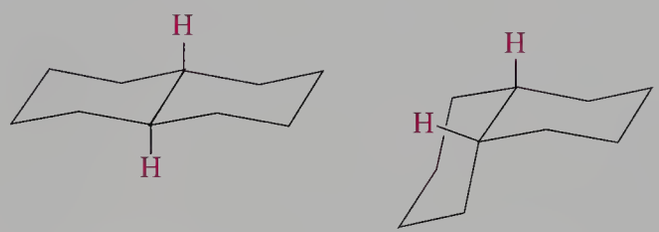
Draw the chair conformations of *cis*- and *trans*-1,3-dimethylcyclohexanes and determine the most stable conformation of each compound. Based on these conformations, calculate the difference in the heats of formations of the two isomers.

Problem 4.27

Draw the chair conformations of *cis*-1-chloro-4-methylcyclohexane and determine the most stable conformation. Based on the conformation preference of each substituent, calculate the percent composition of the conformational mixture.

4.19 Polycyclic Molecules

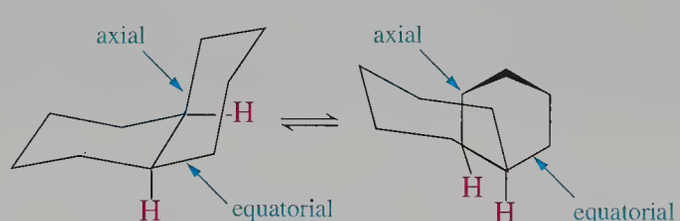
We can extend the analysis of monocyclic ring compounds to polycyclic compounds—compounds with more than one ring. Let's look at the two isomeric bicyclo[4.4.0]decanes commonly called decalins. These structural units are incorporated in steroids, an important class of biomolecules. We recall that there are two geometric isomers, called *trans*-decalin and *cis*-decalin. In *trans*-decalin, the hydrogen atoms bonded to the carbon atoms at the ring junction lie on opposite sides of the rings. In *cis*-decalin, the hydrogen atoms bonded to the carbon atoms at the ring junction lie on the same side of the rings. The two compounds are not different conformations. They cannot interconvert unless a carbon–carbon bond or a carbon–hydrogen bond is broken at the points of fusion.



trans-decalin *cis*-decalin

trans-Decalin is relatively rigid. Neither of its rings can flip. If one did, the CH_2 units bonded to the fusion site would be transformed from a diequatorial into a diaxial arrangement. Of course, the diaxial arrangement is less stable but also, unlike the methyl groups in 1,2-dimethylcyclohexane, the two CH_2 units must remain linked in a ring. The remaining CH_2—CH_2 unit of the ring cannot "reach" and cover the distance from one axial CH_2 unit to the other axial CH_2 unit. Therefore, this conformation is impossible.

cis-Decalin is relatively flexible. A flip of one ring causes a change in the location of the two CH_2 units bonded to it. As in the case of *cis*-1,2-dimethylcyclohexane, the axial CH_2 unit is changed into an equatorial CH_2 and vice versa. Hence, the two conformations have the same energy.

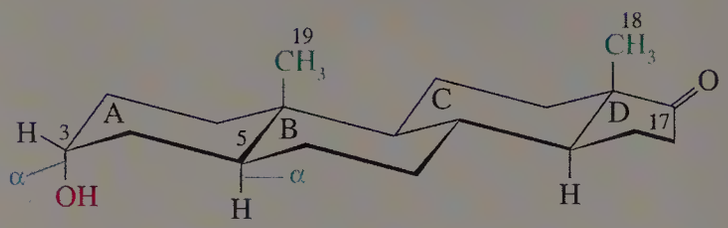


When a decalin ring is linked to substituents, they may be either axial or equatorial. The spatial location of the substituent cannot be changed in *trans*-decalin because the ring system does not flip. However, a substituted *cis*-decalin can exist in two conformations whose energies are not equal.

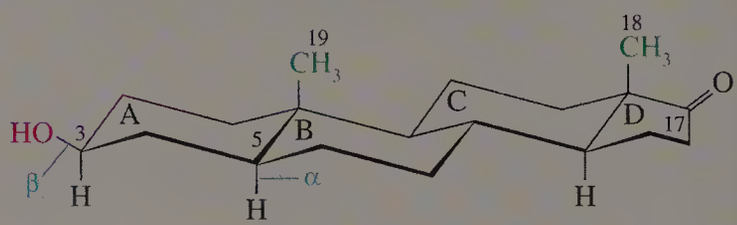
Steroids, many of which are hormones, are fused tetracyclic compounds with three six-membered rings and a five-membered ring. The six-membered rings of the carbon skeleton are designated as A, B, C. The five-membered ring is designated as D (Section 4.8). In most steroids, the ring junctions are all trans, so ring flipping does not occur. *cis*-Decalin is conformationally mobile and undergoes a ring flip. However, a comparable process is not possible in steroids where the A/B junction is cis. The B/C ring junction provides a rigid trans junction that immobilizes the B ring.

Biological Activity of Steroids

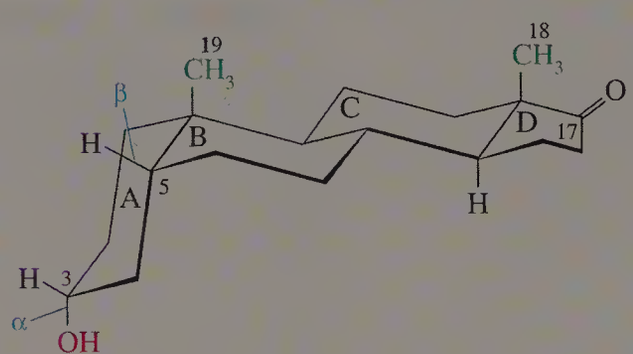
The equatorial and axial locations of functional groups in steroids control the reactivity of these compounds. Androsterone provides an example. It is one of the male sex hormones known as androgens (see the figure). Androsterone has high physiological activity. Both the position of the hydroxyl group and the configuration of the A/B ring junction are important for this activity. The hydroxyl group at C-3 in androsterone is α; it is axial. Epiandrosterone is an isomer with a β hydroxyl group (equatorial). This isomer has much less physiological activity. In the 5β-androsterone, the A/B ring junction is cis and the hydroxyl group is equatorial. This compound has no physiological activity. The activity of these three compounds is related to the spatial arrangement of the hydroxyl group and the ketone located on the D ring, which determines whether or not a given steroid binds to a specific receptor.



androsterone
(high activity)

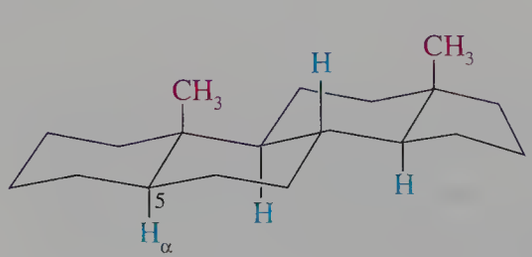


epiandrosterone
(reduced activity)

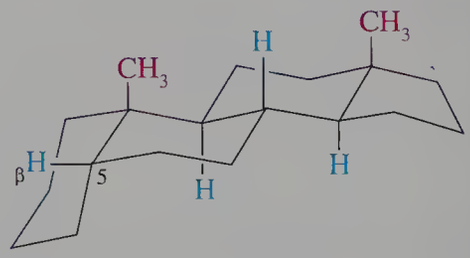


5β-androsterone
(no activity)

Structure and Androgenic Activity



A/B (cis) steroid skeleton

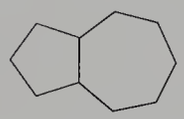


A/B (trans) steroid skeleton

Because the steroid ring system is rigid, functional groups bonded to ring atoms have well-defined positions. Substituents below the plane of the ring are designated as α; those above the plane of the ring are β. We recall that "down" and "up" in substituted cyclohexane compounds are not synonymous with equatorial and axial. For the same reasons, this method of nomenclature for steroids does not indicate whether the substituent is equatorial or axial.

Problem 4.28

When bicyclo[5.3.0]decane is treated with $AlCl_3$/HCl, an isomerization reaction occurs to give *trans*-decalin as the major isomer. What is the driving force for the reaction?



bicyclo[5.3.0]decane

Problem 4.29

A hydroxyl group at the 3β position of a steroid reacts with a carboxylic acid to form an ester faster than a hydroxyl group at the 3α position. Suggest a reason for this fact. Based on your argument, predict the relative rates of esterification of hydroxyl groups at the 4α and 4β positions.

4.20 Medium and Large Cycloalkanes

We can divide cycloalkanes into several broad classes based upon their size. Rings containing three or four atoms are "small" and highly strained. Rings with five or six atoms are only slightly strained or unstrained. Rings with more than six atoms are divided into two categories. Medium-sized rings have 8 to 11 members; large rings have 12 or more members.

Cyclohexane is said to be "strain free" because its heat of formation is six times the average heat of formation of a CH_2 unit. This ring size allows all carbon atoms to maintain tetrahedral angles and form σ bonds by overlap of sp^3 hybrid orbitals along the internuclear axis. Also, when cyclohexane is in a chair conformation, all dihedral angles are 60°.

We might expect rings larger than cyclohexane to be strain free also. However, as shown in Table 4.4, rings containing more than six carbon atoms are somewhat strained. The analysis of the conformations of cycloalkanes containing more than six carbon atoms is more complicated than that of cyclohexane because there are more atoms and bonds to consider. In each individual ring system, there is a compromise between several structural features that cause strain, and each of the cycloalkanes adopts a conformation having the lowest total strain energy. Although these compounds have little bond strain, there is torsional strain between bonds on adjacent carbon atoms as well as some van der Waals repulsion between hydrogen atoms located on carbon atoms not directly bonded to each other.

We will begin our discussion of medium ring compounds by considering cycloheptane. Cycloheptane can be drawn in a "chair" conformation resembling cyclohexane in part, but in which a CH_2—CH_2 unit replaces one CH_2 unit, adding one more carbon atom to the ring (Figure 4.17a). This conformation has no angle strain or torsional strain in five of the carbon atoms, but the CH_2—CH_2 unit has two pairs of eclipsed hydrogen atoms. This torsional strain is decreased by rotation around the carbon–carbon bond of this unit and the other bonds in the molecule to generate a twist chair.

Now let's consider cyclooctane. It can exist in two idealized conformations. The major conformation is a boat-chair. The minor conformation is called a crown (Figure 4.17b). In both conformations, some torsional interactions exist because the dihedral angles are not all 60°.

When we increase the ring size to 10 carbon atoms, we find sufficient flexibility to allow two anti conformations of some of the carbon atoms (Figure 4.17c).

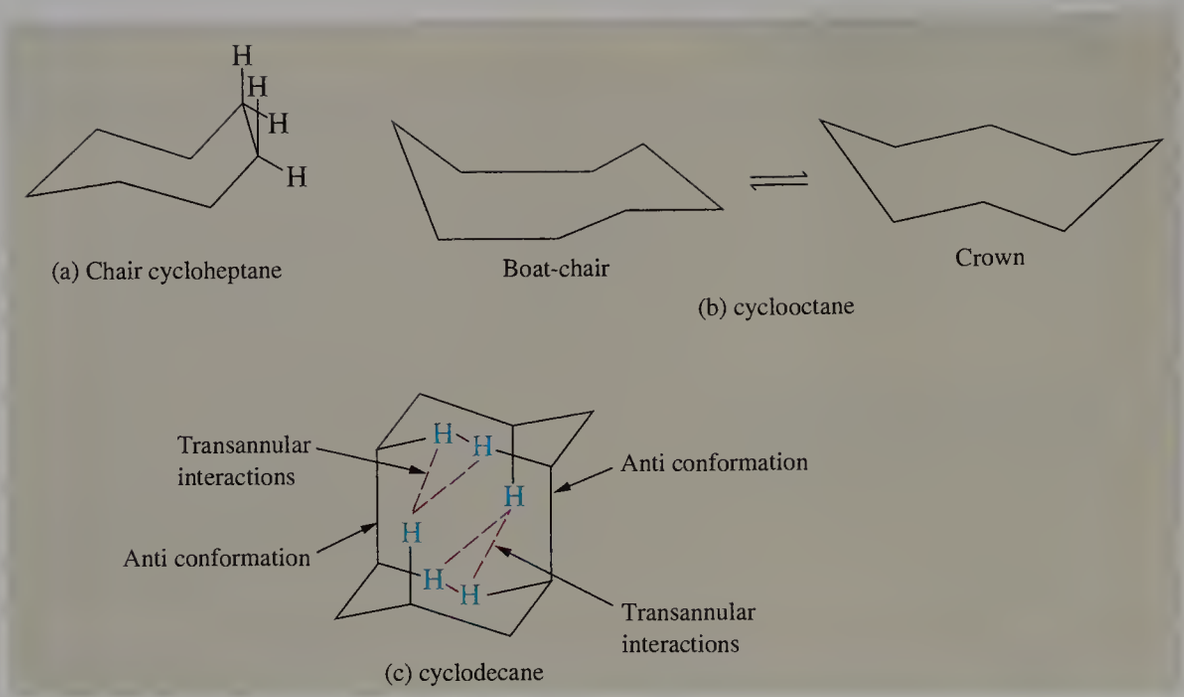


FIGURE 4.17 Conformations of Medium-Sized Cycloalkanes

Therefore, we might expect cyclodecane to have less strain energy than cyclohexane, in which all carbon atoms are in gauche conformations. However, as shown in the figure, two sets of three hydrogen atoms are within their van der Waals radii, so they repel each other. The steric interaction of atoms not bonded to adjacent carbon atoms and located across a ring is called a **transannular interaction**. The transannular interactions decrease when cyclodecane twists. But this twisting introduces some torsional strain. Consequently, the most stable conformation represents a balance between transannular interactions and torsional strain.

As cycloalkane ring size increases beyond 10 carbon atoms, many more conformations are possible, and the energy differences among them are small. Furthermore, the larger number of ring atoms allows some staggered anti arrangements that avoid transannular interactions. Although there is still some strain energy, the strain energy per CH_2 unit becomes progressively smaller as ring size increases.

EXERCISES

Molecular Formulas

4.1 Does each of the following molecular formulas for an acyclic hydrocarbon represent a saturated compound?
(a) C_6H_{12} **(b)** C_5H_{12} **(c)** C_8H_{16} **(d)** $C_{10}H_{22}$

4.2 Can each of the following formulas correspond to an actual acyclic or cyclic molecule?
(a) C_6H_{14} **(b)** $C_{10}H_{23}$ **(c)** C_7H_{14} **(d)** C_5H_{14}

4.3 Beeswax contains approximately 10% hentriacontane, a normal alkane with 31 carbon atoms. What is the molecular formula of hentriacontane? Write a completely condensed formula of hentriacontane.

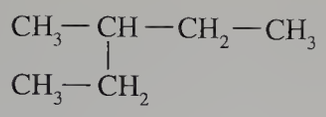
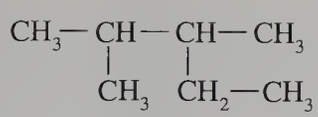
4.4 Hectane is a normal alkane with 100 carbon atoms. What is the molecular formula of hectane? Write a completely condensed formula of hectane.

Structural Formulas

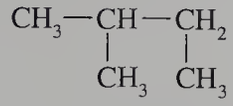
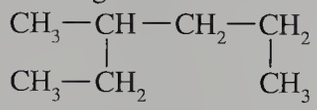
4.5 Redraw each of the following so that the longest continuous chain is written horizontally.

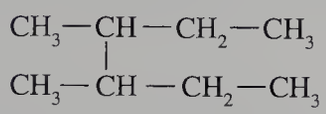
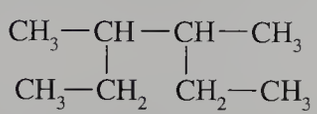
(a)
$$\begin{array}{l} CH_3{-}CH_2 \\ \qquad\quad | \\ \qquad CH_2{-}CH_3 \end{array}$$

(b)
$$\begin{array}{l} CH_2{-}CH_2{-}CH{-}CH_2{-}CH_3 \\ \quad | \qquad\qquad\quad | \\ \quad CH_3 \qquad\quad CH_2{-}CH_3 \end{array}$$

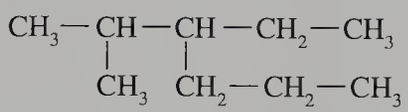
(c)  (d) 

4.6 Redraw each of the following so that the longest continuous chain is written horizontally.

(a)  (b) 

(c)  (d) 

4.7 Which of the following represent the same compound?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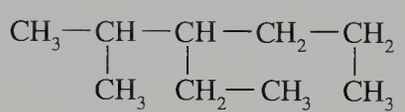
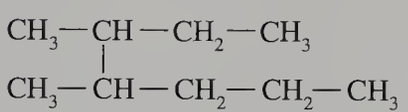

II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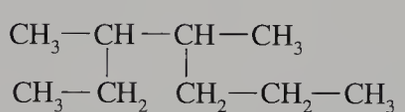
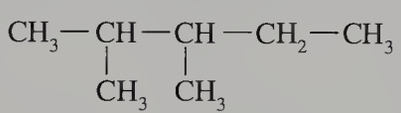

IV

4.8 Which of the following represent the same compound?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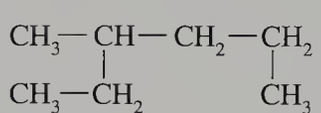
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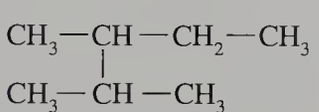
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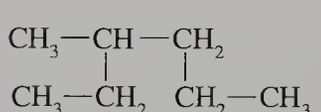
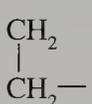
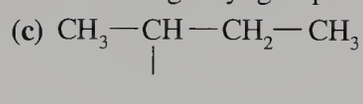
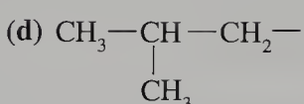
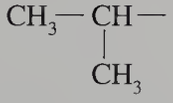
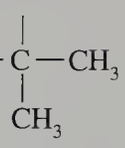

IV

Alkyl Groups

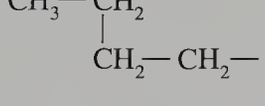
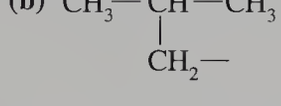
4.9 What is the common name for each of the following alkyl groups?

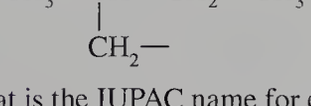
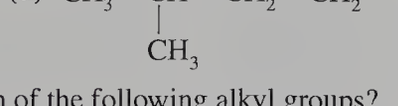
(a) CH_3- (b)  (c)  (d) 

4.10 What is the common name for each of the following alkyl groups?

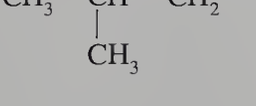
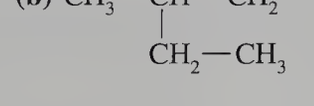
(a) CH_3-CH_2- (b)  (c) $CH_3-CH_2-CH_2-CH_2-$ (d) 

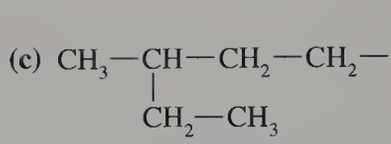
4.11 What is the IUPAC name for each of the following alkyl groups?

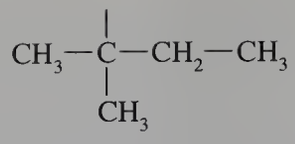
(a)  (b) 

(c)  (d) 

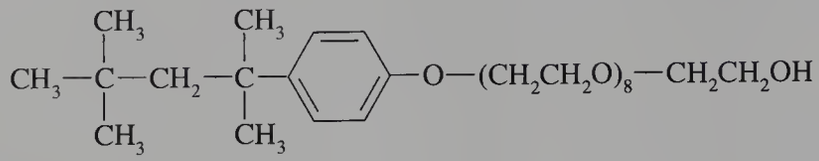
4.12 What is the IUPAC name for each of the following alkyl groups?

(a)  (b) 

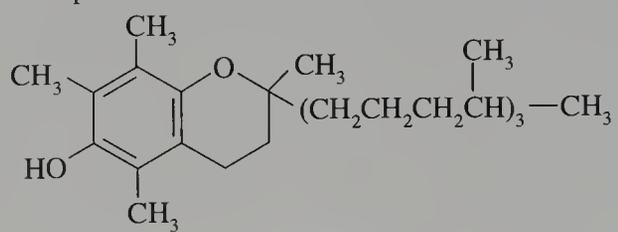
(c) 

(d) 

4.13 The spermicide octoxynol-9 is used in diverse contraceptive products. Name the alkyl group to the left of the benzene ring.

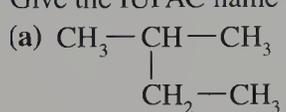


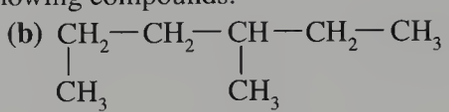
4.14 The name vitamin E actually refers to a series of closely related compounds called tocopherols. Name the complex alkyl group present in α-tocopherol.

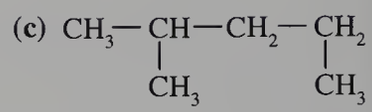


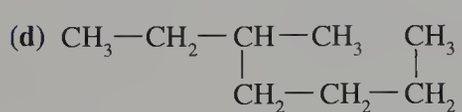
Nomenclature of Alkanes

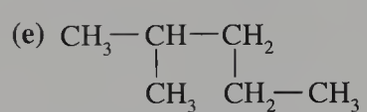
4.15 Give the IUPAC name for each of the following compounds.

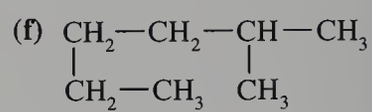
(a) 

(b) 

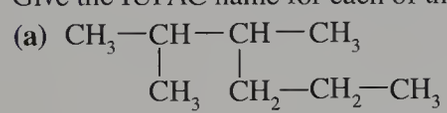
(c) 

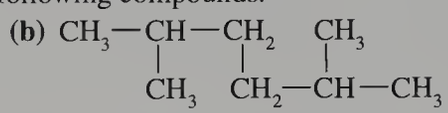
(d) 

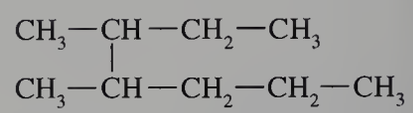
(e) 

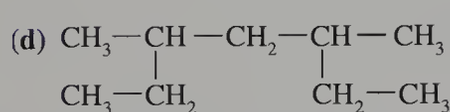
(f) 

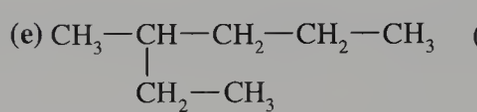
4.16 Give the IUPAC name for each of the following compounds.

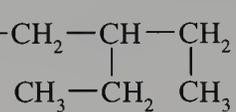
(a) 

(b) 

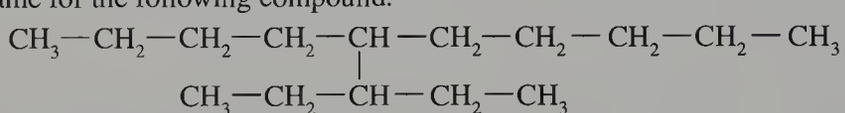
(c) 

(d) 

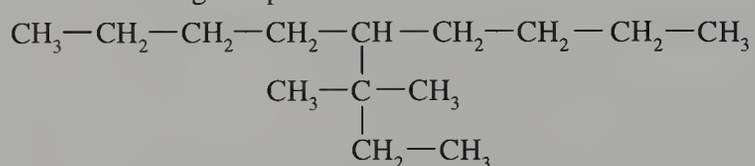
(e) 

(f) 

4.17 Give the IUPAC name for the following compound.



4.18 Give the IUPAC name for the following compound.



4.19 Write the structural formula for each of the following compounds.

(a) 3-methylpentane **(b)** 3,4-dimethylhexane **(c)** 2,2,3-trimethylpentane
(d) 4-ethylheptane **(e)** 2,3,4,5-tetramethylhexane

4.20 Write the structural formula for each of the following compounds.

(a) 2-methylpentane **(b)** 3-ethylhexane **(c)** 2,2,4-trimethylhexane
(d) 2,4-dimethylheptane **(e)** 2,2,3,3-tetramethylpentane

4.21 Write the structural formula for each of the following compounds.
(a) 4-(1-methylethyl)heptane **(b)** 5-(1,1-dimethylethyl)nonane **(c)** 5-(1-methylpropyl)decane

4.22 Write the structural formula for each of the following compounds.
(a) 5-(2-methylpropyl)nonane **(b)** 4-butylnonane **(c)** 5-(2,2-dimethylpropyl)decane

Isomers

4.23 There are nine isomeric C_7H_{16} compounds. Name the isomers that have a single methyl group as a branch.

4.24 There are nine isomeric C_7H_{16} compounds. Name the isomers that have two methyl groups as branches and are named as dimethyl-substituted pentanes.

Classification of Carbon Atoms

4.25 Classify each carbon atom in the following compounds.

(a) $CH_3-CH_2-CH_2-CH_2-CH_3$

(b) $CH_3-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_3$

(c) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2-CH_3$

(d) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

4.26 Classify each carbon atom in the following compounds.

(a) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

(b) $CH_3-CH_2-CH_2-CH_3$

(c) $CH_3-\underset{\displaystyle CH_3-CH-CH_3}{\underset{|}{CH}}-CH_3$

(d) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

4.27 Draw the structure of a compound with molecular formula C_5H_{12} that has one quaternary and four primary carbon atoms.

4.28 Draw the structure of a compound with molecular formula C_6H_{14} that has two tertiary and four primary carbon atoms.

4.29 Determine the number of primary, secondary, tertiary, and quaternary carbon atoms in each of the following compounds.

(a) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

(b) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_3$

(c) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_2-CH_3$

(d) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

4.30 Determine the number of primary, secondary, tertiary, and quaternary carbon atoms in each of the following compounds.

(a) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$

(b) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

(c) $CH_3-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_3$

(d) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

Heats of Formation of Alkanes

4.31 The ΔH_f° values of 2-methylhexane and 3-methylhexane are −174.7 and −172.0 kJ mole^{-1}, respectively. Which compound is the more stable?

4.32 The ΔH_f° values of 3-ethylheptane and 4-ethylheptane are −231.46 and −231.75 kJ mole^{-1}, respectively. Based on these values, can the composition of an equilibrium mixture of these compounds be calculated?

4.33 The ΔH_f° of 2,2-dimethylbutane is −184 kJ mole^{-1}. Estimate the ΔH_f° of 2,2-dimethylhexane.

4.34 The ΔH_f° of 2,2-dimethyldecane is −308.2 kJ mole^{-1}. Estimate the ΔH_f° of 2,2-dimethyloctadecane.

4.35 Estimate the ΔH_f° of the following compounds.
(a) 2,5-dimethylhexane **(b)** 2,4-dimethyloctane **(c)** 2,4,6-trimethylheptane

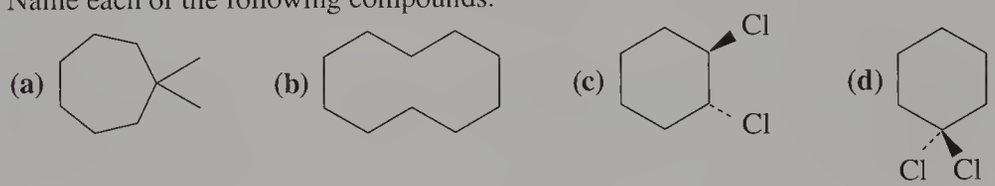
4.36 Which of the isomeric C_6H_{14} compounds has the most negative heat of formation?

Cycloalkanes

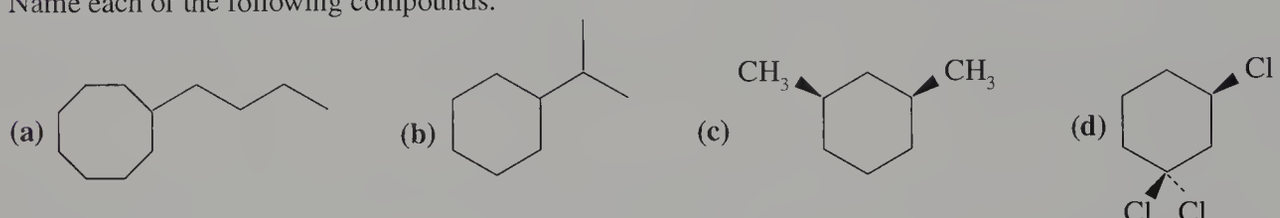
4.37 Write condensed planar formulas for each of the following compounds.
(a) chlorocyclopropane **(b)** 1,1-dimethylcyclobutane **(c)** cyclooctane

4.38 Write condensed planar formulas for each of the following compounds.
(a) bromocyclobutane **(b)** 1,1-dichlorocyclopropane **(c)** cyclopentane

4.39 Name each of the following compounds.



4.40 Name each of the following compounds.

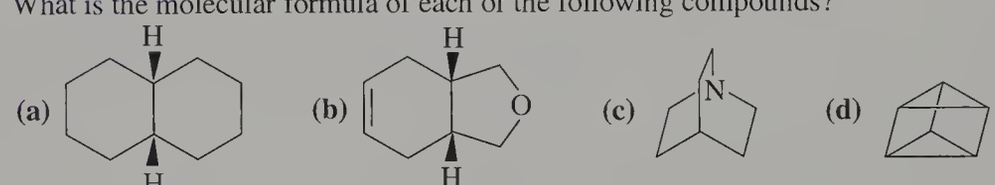


4.41 A saturated refrigerant has the molecular formula C_4F_8. Draw structural formulas for two possible isomers of this compound.

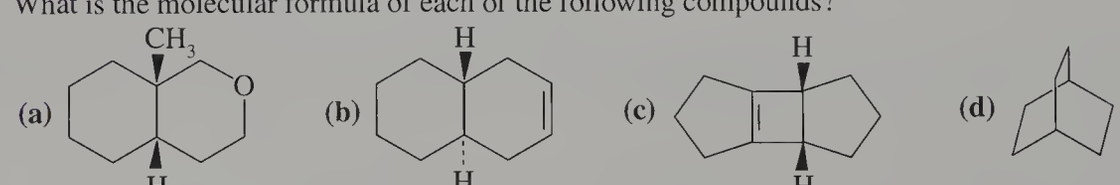
4.42 How many isomeric saturated hydrocarbons have the molecular formula C_5H_{10}?

Bicyclic Compounds

4.43 What is the molecular formula of each of the following compounds?

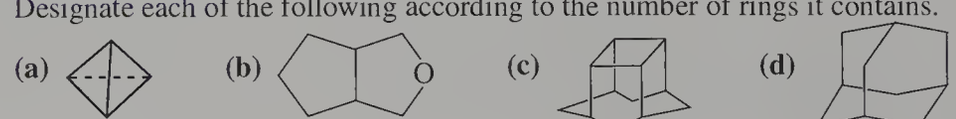


4.44 What is the molecular formula of each of the following compounds?

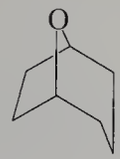


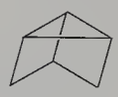
Polycyclic Compounds

4.45 Designate each of the following according to the number of rings it contains.



4.46 Designate each of the following according to the number of rings it contains.

(a)  (b)  (c) 

(d) 

Heats of Formation of Cycloalkanes

4.47 The ΔH_f° of propylcyclohexane is −193.2 kJ mole^{-1}. Estimate the ΔH_f° of butylcyclohexane.

4.48 The ΔH_f° of cyclohexane is −120.1 kJ mole^{-1}. Estimate the ΔH_f° of ethylcyclohexane.

4.49 The ΔH_f° values of *cis*-1,2-dimethylcyclopropane and *trans*-1,2-dimethylcyclopropane are −309.8 and −316.8 kJ mole^{-1}, respectively. Which compound is the more stable?

4.50 The ΔH_f° values of *cis*-1,2-dimethylcyclopentane and *trans*-1,2-dimethylcyclopentane are −87.51 and −87.67 kJ mole^{-1}, respectively. Based on these values, can the composition of an equilibrium mixture of these compounds be calculated?

Properties of Hydrocarbons

4.51 Which of the isomeric C_8H_{18} compounds has the highest boiling point? Which has the lowest boiling point?

4.52 The boiling point of methylcyclopentane is lower than the boiling point of cyclohexane. Suggest a reason why.

Newman Projection Formulas of Alkanes

4.53 Draw the Newman projection of the staggered conformation of 2,2-dimethylpropane around the C-1 to C-2 bond.

4.54 Draw the Newman projections of the two possible staggered conformations of 2,3-dimethylbutane around the C-2 to C-3 bond.

4.55 Draw the Newman projections of the two possible staggered conformations of 2-methylbutane around the C-2 to C-3 bond. Which is the more stable?

4.56 Draw the Newman projections of the two possible staggered conformations of 2,2-dimethylpentane around the C-3 to C-4 bond. Which is the more stable?

Stability of Acyclic Conformations

4.57 The barrier to rotation of chloroethane is 14.9 kJ mole^{-1} (3.56 kcal mole^{-1}). Predict the energy of the rotational barrier for 1,1,1-trichloroethane.

4.58 The barrier to rotation of bromoethane is 15 kJ mole^{-1} (3.6 kcal mole^{-1}). What is the energy of the hydrogen–bromine eclipsing interaction?

4.59 The barrier to rotation around the C-1 to C-2 bond of 2-methylpropane is 16.2 kJ mole^{-1} (3.87 kcal mole^{-1}). How does this value compare to the predicted value?

4.60 Do you expect the barrier to rotation around the central bond for $CH_3—CH_2—SiH_2—CH_3$ to be smaller or larger than the barrier to rotation for butane? Why?

4.61 Draw a potential energy diagram for rotation around the C-2 to C-3 bond of 2,2-dimethylbutane.

4.62 Draw a potential energy diagram for rotation around the C-2 to C-3 bond of 2-methylbutane.

4.63 2-Chloroethanol ($ClCH_2CH_2OH$) is most stable in the gauche conformation. Suggest a reason for this fact.

4.64 1-Chloropropane is most stable in the gauche conformation. What does this fact indicate about the interaction of chlorine and a methyl group in this compound?

4.65 Draw the two staggered conformations of 1,2-dichloroethane. Which of the conformations has a dipole moment? The dipole moment of 1,2-dichloroethane is 1.1 D. Does this fact provide any information about the composition of the mixture of conformations?

4.66 Ethylene glycol ($HOCH_2CH_2OH$) forms intramolecular hydrogen bonds. Does this fact provide any information about the composition of the mixture of conformations?

Conformations of Cyclohexanes

4.67 Draw the most stable conformation of the equatorial form of methylcyclohexane showing the relationship of the methyl hydrogen atoms to the hydrogen atom at C-1.

4.68 Draw the most stable conformation of the axial form of methylcyclohexane showing the relationship of the methyl hydrogen atoms to C-2 and C-6.

4.69 Draw the most stable chair conformation of each of the following compounds.
(a) *trans*-1-fluoro-3-methylcyclohexane **(b)** *trans*-1-*tert*-butyl-3-methylcyclohexane
(c) *trans*-1,2-dimethylcyclohexane

4.70 Draw the most stable chair conformation of each of the following compounds.
(a) *cis*-1,1,4-trimethylcyclohexane **(b)** *trans*-1,1,3-trimethylcyclohexane
(c) *cis*-1-fluoro-4-ethylcyclohexane

4.71 Predict the $\Delta H°$ between the equatorial and axial conformations of ethynylcyclohexane. (The ethynyl group is —C≡C—H.)

4.72 Predict the steric strain caused by a methoxy group (—OCH_3) in the axial position of methoxycyclohexane.

4.73 Why is the steric strain caused by the *tert*-butyl group so different from those of methyl, ethyl, and isopropyl groups?

4.74 Within experimental error, the steric strain caused by a bromine atom is the same as that of a chlorine atom. Taking into account the "size" of the atoms and the length of the carbon–halogen bond, explain this data.

4.75 *cis*-1,3-Cyclohexanediol is most stable in a diaxial conformation. Suggest a reason for this "unusual" stability.

4.76 *trans*-1,3-Di-*tert*-butylcyclohexane exists in a twist boat conformation, rather than a chair conformation. Why?

4.77 The diaxial conformation of *cis*-1,3-dimethylcyclohexane is 23 kJ $mole^{-1}$ (5.4 kcal $mole^{-1}$) less stable than the diequatorial conformation. Why is this value larger than twice the steric strain of a methyl group?

4.78 The diaxial conformation of *cis*-1-chloro-3-methylcyclohexane is 16 kJ $mole^{-1}$ (3.7 kcal $mole^{-1}$) less stable than the diequatorial conformation. Why is this value larger than the sum of the steric strains of a chlorine atom and a methyl group?

Stability of Cycloalkanes

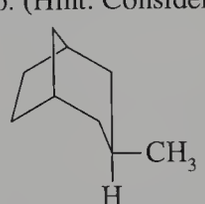
4.79 Which isomer should have the higher heat of formation, *cis*- or *trans*-1,2-dimethylcyclopentane?

4.80 The heats of formation of the cis and trans isomers of 1,2-dimethylcyclopropane are +0.7 and −3.2 kJ $mole^{-1}$, respectively. Explain why.

Bicyclic Compounds

4.81 An isomerization equilibrium between *cis*-decalin and *trans*-decalin can be established by heating the mixture to about 300 °C in the presence of a palladium catalyst. The trans isomer predominates. The $\Delta H°$ of the conversion of the cis to the trans isomer is −10.4 kJ $mole^{-1}$. Show why this value is "expected".

4.82 Which of the following isomers is the more stable? Discuss the steric features to consider when calculating the energy difference between the two. (Hint: Consider the data given in Exercise 4.77.)



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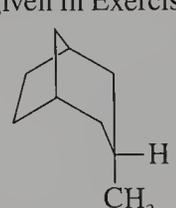


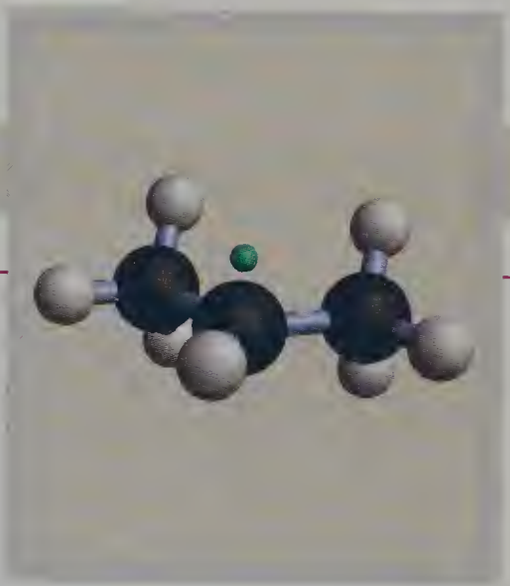
II

Steroids

4.83 Examine the structure of an A/B (trans) steroid skeleton and determine whether each of the following is in an equatorial or axial location.
(a) a 2α hydroxyl group **(b)** a 3α chlorine atom **(c)** a 6α amino (—NH_2) group
(d) an 11β bromine atom **(e)** a 12β cyano group

4.84 Examine the structure of an A/B (cis) steroid skeleton and determine whether each of the following is in an equatorial or axial location.
(a) a 1β hydroxyl group **(b)** a 4β chlorine atom **(c)** a 6β amino (—NH_2) group
(d) an 11α bromine atom **(e)** a 12α cyano group

5



Reactions of Alkanes and Cycloalkanes

5.1 Reactivity of Saturated Hydrocarbons

When we introduced functional groups in Chapter 2, we noted that each functional group undergoes a characteristic set of reactions. In this chapter we will consider reactions of the carbon skeleton in alkanes and cycloalkanes. These molecules are not very reactive. In fact, alkanes are also called **paraffins**, a name derived from the Latin *parum affinis*, meaning little activity. Alkanes contain only nonpolar carbon–carbon and carbon–hydrogen σ bonds. The bonding electrons are tightly held in a small region of space between the atoms. Thus, electrons in carbon–carbon bonds are not easily accessible to reagents. Although the electrons in carbon–hydrogen bonds are more susceptible to attack by reagents, such bonds usually react only under extreme conditions. Hydrocarbons react explosively with oxygen, although a spark is required to trigger the reaction. The reaction of alkanes with oxygen is known as combustion. In this chapter we will pay particular attention to the heat energy released when alkanes burn. A second major topic is the reaction of hydrocarbons with halogens. Both processes occur by free radical mechanisms.

5.2 Bond Dissociation Energies

Much of the chemical reactivity of hydrocarbons is associated with the carbon–hydrogen bond. Therefore, we will begin by considering the strength of carbon–hydrogen bonds. The **bond dissociation energy**, $DH°$, of the C—H bond of methane is 439 kJ mole^{-1} (105 kcal mole^{-1}). This bond dissociation energy is given by the $\Delta H°$ for the following reaction.

$$CH_3—H \longrightarrow CH_3\cdot + \cdot H \qquad \Delta H° = 438 \text{ kJ mole}^{-1}$$

Table 5.1 shows the variation of C—H bond strengths with structure. The decrease in the energy required to cleave the R—H bond homolytically to give R· is given by the order methane > primary C—H > secondary C—H > tertiary C—H. This order reflects the stability of the radical products.

TABLE 5.1
Bond Dissociation Energies of Representative Compounds

Bond	$DH°$ (kJ mole^{-1})	Bond	$DH°$ (kJ mole^{-1})
H—H	435	HO—H	497
F—F	159	CH_3O—H	426
Cl—Cl	242	CH_3—OH	383
Br—Br	192	CH_3CH_2—OH	380
I—I	150	HOO—H	377
		HO—OH	213
H—F	568		
H—Cl	431	CH_3—Cl	349
H—Br	366	CH_3CH_2—Cl	341
H—I	297	$CH_3CH_2CH_2$—Cl	341
		$(CH_3)_2CH$—Cl	339
CH_3—H	438	$(CH_3)_3C$—Cl	330
CH_3CH_2—H	422		
$CH_3CH_2CH_2$—H	422	CH_3—Br	293
$(CH_3)_2CH$—H	410	CH_3CH_2—Br	289
$(CH_3)_3C$—H	401	$(CH_3)_2CH$—Br	284
		$(CH_3)_3C$—Br	264
CH_2=CH—H	452		
C_6H_5—H	460	CH_3—CH_3	368
CH_2=$CHCH_2$—H	356	CH_3CH_2—CH_3	356
$C_6H_5CH_2$—H	356	$(CH_3)_2CH$—CH_3	351
HC≡C—H	523	$(CH_3)_3C$—CH_3	335

The methyl radical produced from methane is less substituted than the simplest primary radical generated from ethane. The C—H bond dissociation energy of ethane is 422 kJ mole^{-1} (101 kcal mole^{-1}).

$$CH_3CH_2—H \longrightarrow \underset{\text{ethyl radical}}{CH_3CH_2\cdot} + \cdot H \qquad \Delta H° = 422 \text{ kJ mole}^{-1}$$

The methyl and ethyl radicals are electron-deficient species that have a carbon atom with only seven electrons in its valence shell. The $DH°$ for the C—H bond of ethane (422 kJ mole^{-1}) is smaller than that for the C—H bond of methane (438 kJ mole^{-1}) because it is stabilized by the inductive effect of the CH_3 group bonded to the radical center.

If alkyl groups stabilize a free radical by an electron-donating inductive effect, then we should see a difference in the $DH°$ values for the two different C—H bonds in propane.

$$CH_3CH_2CH_2—H \longrightarrow \underset{\text{propyl radical}}{CH_3CH_2CH_2\cdot} + \cdot H \qquad \Delta H° = 422 \text{ kJ mole}^{-1}$$

$$\begin{array}{l} \quad\ CH_3 \\ CH_3CH—H \end{array} \longrightarrow \underset{\text{isopropyl radical}}{\begin{array}{l} \quad\ CH_3 \\ CH_3CH\cdot \end{array}} + \cdot H \qquad \Delta H° = 410 \text{ kJ mole}^{-1}$$

The $DH°$ values for the primary C—H bonds of propane and ethane are the same, which means that the stabilities of the primary propyl radical and the ethyl radical are the same. This shows that a methyl group and an ethyl group have the same ef-

fect on the stability of the radical. Either group counts as an alkyl group. In contrast, the $DH°$ for the secondary C—H bond of propane is smaller, reflecting the greater stability of the secondary radical, which has two electron-releasing alkyl groups bonded to the electron-deficient center. The isomeric propyl and isopropyl radicals differ in energy by 12 kJ mole^{-1} (3 kcal mole^{-1}) (Figure 5.1a).

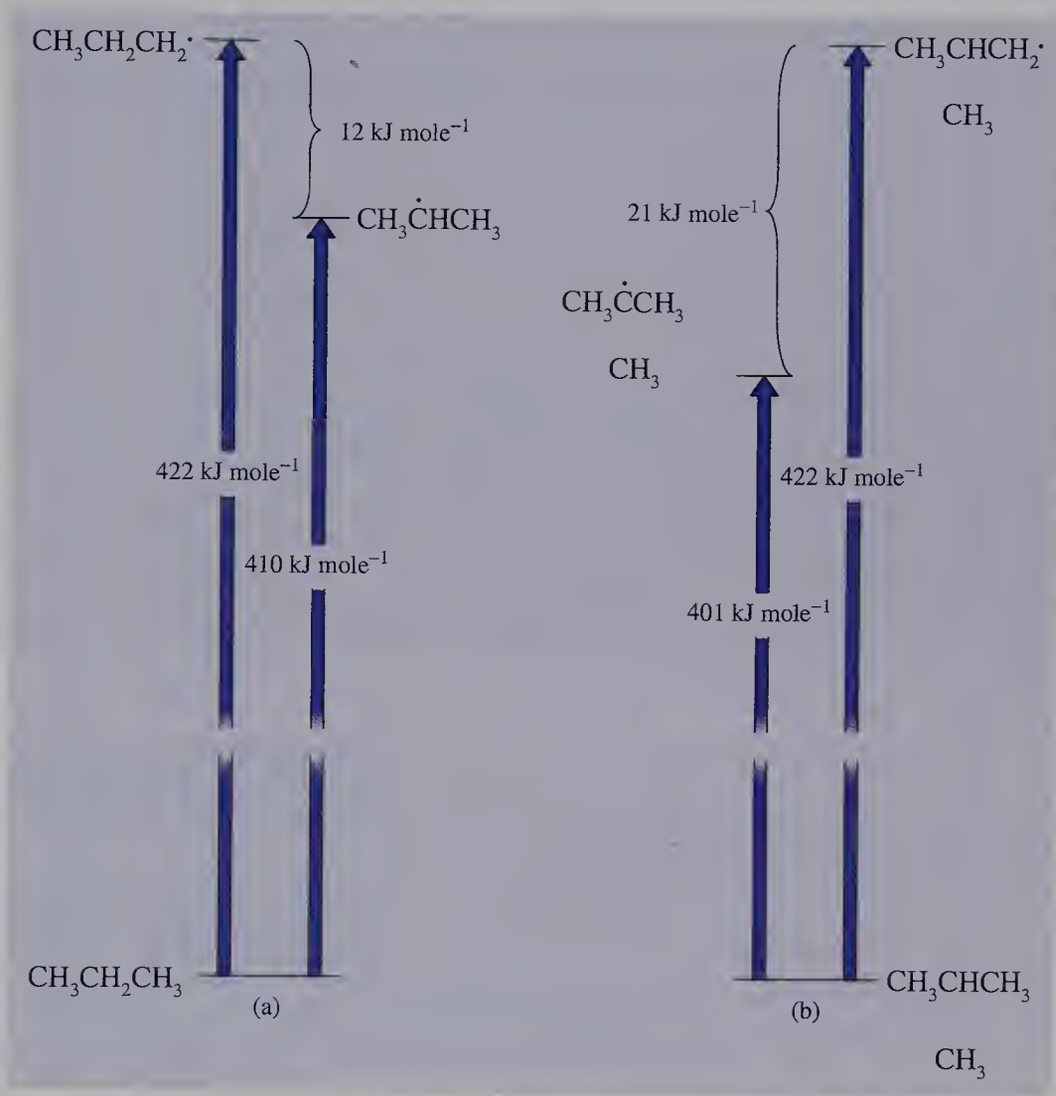


FIGURE 5.1 Relative Energies of Radicals from Alkanes
(a) A comparison of the relative energies of the propyl and isopropyl radicals derived from propane.
(b) A comparison of the relative energies of the isobutyl and *tert*-butyl radicals derived from 2-methylpropane

Now let's compare the $DH°$ values for the two nonequivalent C—H bonds in 2-methylpropane. Cleavage of the C-1 to H bond yields the isobutyl radical, a primary radical. Cleavage of the C-2 to H bond yields the *tert*-butyl radical, a tertiary radical.

$$\mathrm{CH_3CH(CH_3)CH_2{-}H} \longrightarrow \underset{\text{isobutyl radical}}{\mathrm{CH_3CH(CH_3)CH_2\cdot}} + \cdot\mathrm{H} \qquad \Delta H° = 422 \text{ kJ mole}^{-1}$$

$$\mathrm{(CH_3)_3C{-}H} \longrightarrow \underset{\textit{tert}\text{-butyl radical}}{\mathrm{(CH_3)_3C\cdot}} + \cdot\mathrm{H} \qquad \Delta H° = 401 \text{ kJ mole}^{-1}$$

Free Radicals in Petroleum Refining

The low-boiling components of petroleum, which consists of a mixture of hydrocarbons, are separated by distillation to give gasoline and kerosene. Higher boiling fractions are used as fuel oil and diesel fuel. Ultimately the nonvolatile residue is used as asphalt. Because the need for various fuels varies with the season and economic conditions, the petroleum industry uses chemical reactions that change the composition of the petroleum and increase the percent of desired fractions. One such process is **cracking**, which converts high molecular weight components into additional lower molecular weight components.

The cracking process initially used involved high temperature that caused homolysis of carbon–carbon bonds to give free radicals. These radicals react to form lower molecular weight alkanes and alkenes. Consider the cleavage of two possible carbon–carbon bonds in the area represented by the following generalized hydrocarbon.

$$R{-}CH_2{-}CH_2{-}CH_2{-}R' \longrightarrow R\cdot + \cdot CH_2{-}CH_2{-}CH_2{-}R'$$

$$R{-}CH_2{-}CH_2{-}CH_2{-}R' \longrightarrow R{-}CH_2\cdot + \cdot CH_2{-}CH_2{-}R'$$

$$R{-}CH_2{-}CH_2{-}CH_2{-}R' \longrightarrow R{-}CH_2{-}CH_2\cdot + \cdot CH_2{-}R'$$

The radicals can recombine in a variety of ways and some lead to lower molecular weight materials. Examples of free radical recombination reactions are given by the following equations.

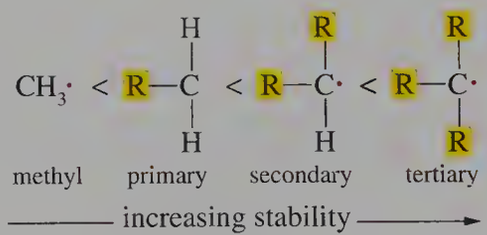
$$R\cdot + \cdot R \longrightarrow R{-}R$$

$$R\cdot + \cdot CH_2{-}R' \longrightarrow R{-}CH_2{-}R'$$

$$R\cdot + \cdot CH_2{-}R \longrightarrow R{-}CH_2{-}R$$

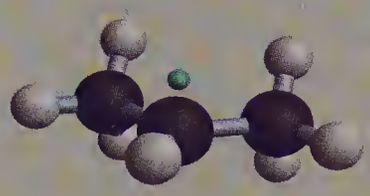
The $DH°$ is the same for primary C—H bonds of 2-methylpropane, propane, and ethane. The $DH°$ for the tertiary C—H bond of 2-methylpropane is smaller. Therefore, the tertiary radical, which has three alkyl groups bonded to the electron-deficient center, is more stable (Figure 5.1b). The isomeric isobutyl and *tert*-butyl radicals differ in energy by 21 kJ mole^{-1} (5 kcal mole^{-1}).

Based on the bond dissociation energy data for the simple alkanes, we conclude that the C—H bond energy depends on whether the carbon atom is primary, secondary, or tertiary and not on the particular alkane in which it is found. The bond dissociation energy reflects the stabilities of the radical products, which increase in this order.



The stabilities of cycloalkyl radicals containing five or more atoms follow the same trends for alkyl radicals. However, the stabilities of cyclopropyl and cyclobutyl radicals are affected by the C—C—C bond angle, which is much smaller than the 120° required for an sp^2-hybridized carbon atom. Thus, a radical at these centers is strained, and therefore less stable.

Disproportionation reactions resulting from transfer of a hydrogen atom between two radicals also yield low molecular weight substances. The radical obtaining the hydrogen atom forms an alkane. The radical from which the hydrogen atom is abstracted gives an unsaturated compound. The possible disproportionation reactions include



isopropyl radical

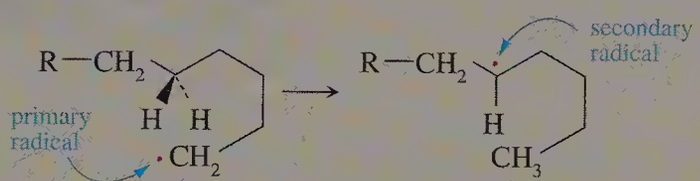
$$R\cdot + \cdot CH_2{-}CH_2{-}CH_2{-}R' \longrightarrow R{-}H + CH_2{=}CH{-}CH_2{-}R'$$

$$R{-}CH_2\cdot + \cdot CH_2{-}CH_2{-}R' \longrightarrow R{-}CH_3 + CH_2{=}CH{-}R'$$

$$R\cdot + \cdot CH_2{-}CH_2{-}R' \longrightarrow R{-}H + CH_2{=}CH{-}R'$$

$$R{-}CH_2{-}CH_2\cdot + \cdot CH_2{-}R' \longrightarrow R{-}CH{=}CH_2 + CH_3{-}R'$$

More complex fragmentation processes as well as hydrogen transfer reactions occur. Intramolecular hydrogen atom transfer occurs to convert primary radicals into secondary radicals. Such transfers may occur via a cyclic mechanism of six atoms: five carbon atoms and a hydrogen atom.



Problem 5.1

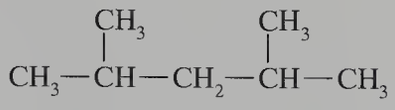
Write the structures of all the possible radicals originating from dissociation of C—H bonds of 2-methylbutane. Estimate the dissociation energy for the formation of each radical.

Problem 5.2

How many radicals can result by cleavage of the C—H bonds of 2,4-dimethylpentane? Which has the smallest bond dissociation energy?

Sample Solution

There are four CH_3 groups, two CH units, and one CH_2 unit in the molecule.



The four methyl groups are located in structurally equivalent positions and give only one primary free radical by cleavage of a carbon–hydrogen bond. Cleavage of a carbon–hydrogen bond of the single CH_2 unit gives a secondary free radical. The two CH units are structurally equivalent and cleavage of either carbon–hydrogen bond gives a single tertiary free radical. This bond has the lowest bond dissociation energy because a tertiary radical results.

Problem 5.3

Write the structures of all possible radicals formed by removal of a hydrogen atom from pentane. Estimate the C—H bond dissociation energy for the formation of each radical.

Problem 5.4

Explain why four isomeric radicals result from removal of a hydrogen atom from methylcyclopentane but only one from cyclohexane.

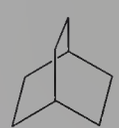
Sample Solution

Abstraction of any of the three hydrogen atoms of the methyl group of methylcyclopentane gives a primary radical. A tertiary radical results from abstraction of the C-1 hydrogen atom. Removal of either of the two hydrogen atoms at C-2 gives the same secondary radical. The fourth radical, which is also secondary, results from removal of either of the two hydrogen atoms at C-3.

Cyclohexane is a symmetrical compound. All six carbon atoms are equivalent. Removal of either of the two hydrogen atoms of any CH_2 units yields the cyclohexyl radical, a secondary radical.

Problem 5.5

Explain why only two isomeric radicals result from removal of a hydrogen atom from bicyclo[2.2.2]octane.



bicyclo[2.2.2]octane

5.3 Combustion of Alkanes and Cycloalkanes

The complete combustion of a hydrocarbon with oxygen gives carbon dioxide and water. The combustion of hydrocarbons occurs by an extraordinarily complex free radical mechanism, which includes the following steps.

$$R{-}H + O_2 \longrightarrow R\cdot + H{-}O{-}O\cdot$$

$$R\cdot + O_2 \longrightarrow R{-}O{-}O\cdot$$

$$R{-}O{-}O\cdot + R{-}H \longrightarrow R{-}O{-}O{-}H + R\cdot$$

$$R{-}O{-}O{-}H \longrightarrow R{-}O\cdot + \cdot O{-}H$$

The combustion of hydrocarbons is not an important chemical reaction in the laboratory, but it is one of the two most prevalent reactions on Earth. (The other is the photosynthetic reaction, an endothermic process using the energy of the sun.) The burning of natural gas, gasoline, and fuel oil to generate energy is essential in industrialized societies. When an alkane burns completely, the combustion products are water and carbon dioxide. Incomplete combustion produces carbon monoxide and other compounds that contribute to smog. Even carbon dioxide is not a harmless product of a combustion reaction because it is a "greenhouse gas" that traps the sun's heat in the atmosphere. This greenhouse effect may make a major contribution to global warming.

The combustion of methane, the major component of natural gas, releases 888 kJ mole^{-1} (212 kcal mole^{-1}). Although the reaction is spontaneous, a small spark or flame is required to initiate the reaction.

$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O \qquad \Delta H^\circ_{rxn} = -888 \text{ kJ mole}^{-1}$$

All combustion reactions of hydrocarbons are exothermic—that is, $\Delta H^\circ_{rxn} < 0$. However, the **heat of combustion**, ΔH°_c, which is defined as $-\Delta H^\circ_{rxn}$, is commonly used to tabulate this information. This allows the use of only positively signed numbers. Thus the heat of combustion of methane is 888 kJ mole^{-1}.

The general equations for the combustion of any hydrocarbon, C_xH_y, and for the combustion of an alkane, C_nH_{2n+2}, are

$$C_xH_y + (x + y/4)\,O_2 \longrightarrow x\,CO_2 + y/2\,H_2O$$

$$C_nH_{2n+2} + \{(3n + 1)/2\}O_2 \longrightarrow n\,CO_2 + (n + 1)\,H_2O$$

Accordingly, the molecular formula of a compound and its structure determine how much heat energy is released in the combustion process. Because the heat of combustion can be measured with high precision (within about 0.02%), we can use heats of combustion to discuss the stabilities of hydrocarbons. In fact, heats of combustion are used to calculate heats of formation of hydrocarbons using Hess's law. The relationship between the ΔH°_f and ΔH°_c is shown in Figure 5.2.

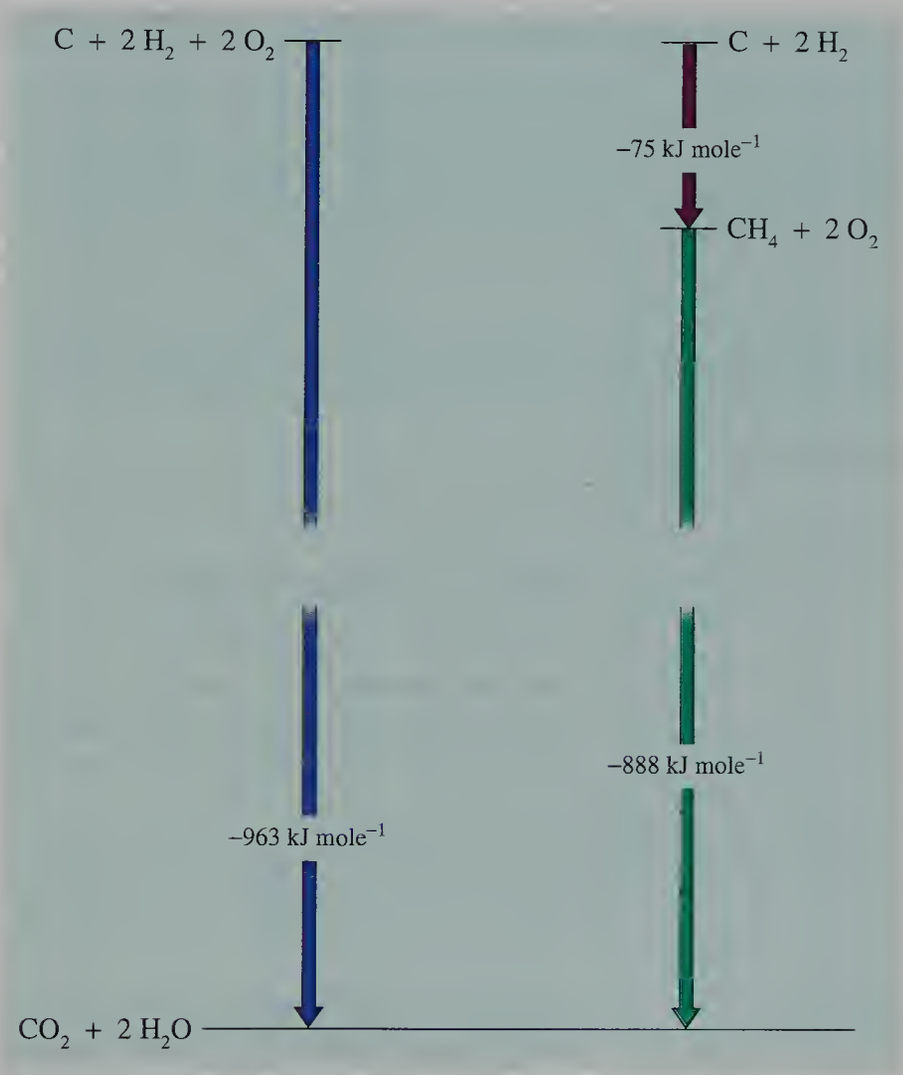


FIGURE 5.2 Heat of Formation and Heat of Combustion of Methane
The heat of formation of methane plus the heat of combustion of methane must equal the heat of combustion of one mole of carbon atoms and two moles of hydrogen molecules. Thus, the heat of formation can be calculated from the two heats of combustion terms.

Heat of Combustion of Alkanes

We recall that the heats of formation of most organic compounds are negative. However, the heats of formation for some low molecular weight, strained, cyclic compounds are positive. For that reason, we must retain the proper sign for heats of formation. In contrast, the heat of reaction, ΔH°_{rxn}, for the combustion of any hydro-

carbon is negative because the products of the reaction, carbon dioxide and water, have stronger bonds than the carbon–carbon and carbon–hydrogen bonds of hydrocarbons.

The heats of combustion of a homologous series of alkanes increase with increasing molecular weight (Table 5.2). However, the difference between the energy required to break bonds in the reactants and that to form bonds in the products depends on the stoichiometry of the reaction, so we cannot use heats of combustion to compare the stabilities of compounds that have different molecular weights. However, we can remove the contribution of molecular weight and determine the effect of structure on the heat of combustion by calculating the heat of combustion per $—CH_2—$ unit. We find that the heats of combustion for successive members of a series of homologous alkanes differ by about 658.8 kJ mole^{-1} (157.4 kcal mole^{-1}). This difference equals the contribution of one $—CH_2—$ unit to the heat of combustion. The contribution corresponds to the following reaction.

$$—CH_2— + \tfrac{3}{2}O_2(g) \longrightarrow CO_2(g) + H_2O(l) \qquad \Delta H^\circ_{rxn} = -658.8 \text{ kJ mole}^{-1}$$

TABLE 5.2
Heats of Combustion of Alkanes

Formula	*Alkane*	ΔH_c *(kJ mole^{-1})*	*Methylalkane*	ΔH_c *(kJ mole^{-1})*
C_5H_{12}	pentane	3535	2-methylbutane	3528
C_6H_{14}	hexane	4163	2-methylpentane	4157
			3-methylpentane	4159
C_7H_{16}	heptane	4817	2-methylhexane	4812
			3-methylhexane	4815
C_8H_{18}	octane	5471	2-methylheptane	5466
			3-methylheptane	5468
C_9H_{20}	nonane	6125	2-methyloctane	6118
			3-methyloctane	6120
$C_{10}H_{22}$	decane	6778	2-methylnonane	6771
			3-methylnonane	6773

Stability of Isomeric Alkanes

We can use the heats of combustion of isomeric alkanes to compare their relative stabilities because the same number of moles of combustion products is formed. For example, the ΔH°_c values of pentane and 2-methylbutane are 3534.6 and 3527.5 kJ mole^{-1} (844.8 and 843.1 kcal mole^{-1}), respectively.

$$CH_3CH_2CH_2CH_2CH_3(l) + 8\,O_2(g) \longrightarrow 5\,CO_2(g) + 6\,H_2O(l) \qquad \Delta H^\circ_{rxn} = -3534.6 \text{ kJ mole}^{-1}$$

$$(CH_3)_2CHCH_2CH_3(l) + 8\,O_2(g) \longrightarrow 5\,CO_2(g) + 6\,H_2O(l) \qquad \Delta H^\circ_{rxn} = -3527.5 \text{ kJ mole}^{-1}$$

Because the combustion reaction of pentane is more exothermic than that of 2-methylbutane, pentane has a higher energy content than does 2-methylbutane. Because the S°_f values of the compounds are similar, we conclude that 2-methylbutane is thermodynamically more stable than pentane.

The relationship between energies of the two isomers is shown graphically in Figure 5.3. We can compare their energies directly because the compounds are converted to the same number of moles of CO_2 and H_2O. Also, we recall that the same relative energies were established using heat of formation data (Section 4.4). We can now make several generalizations about the stability of isomeric alkanes.

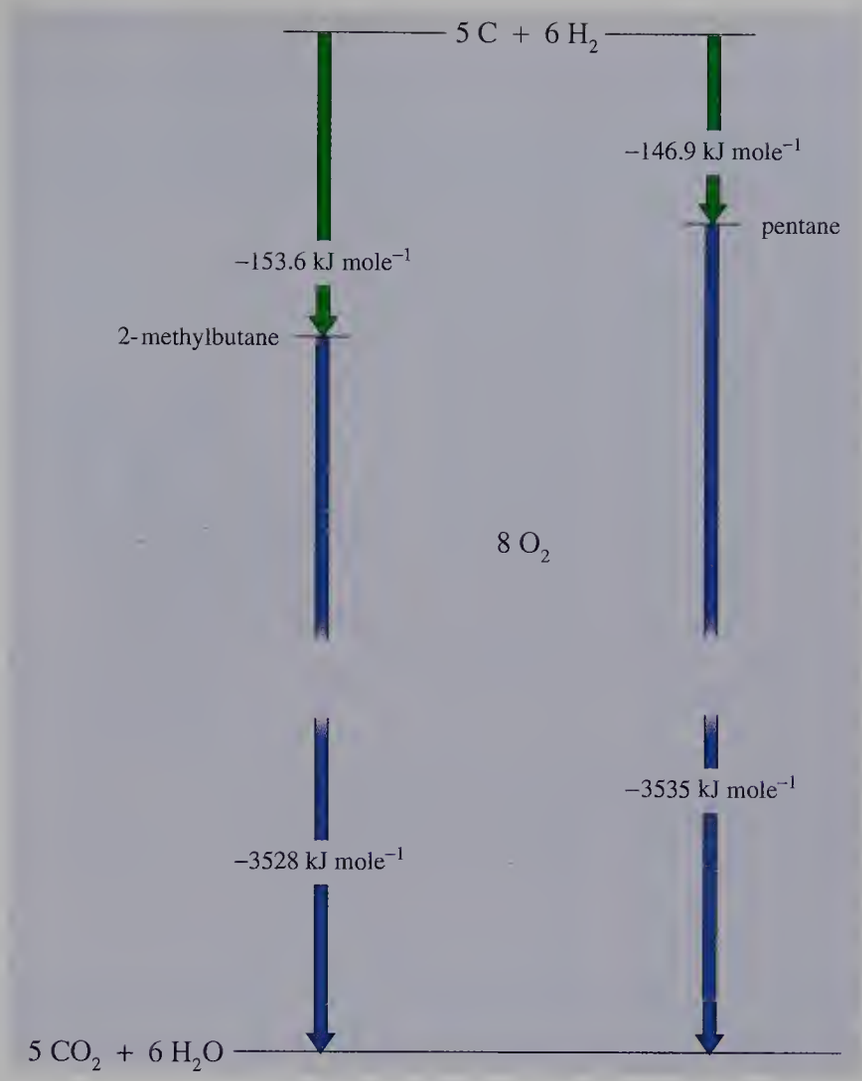


FIGURE 5.3 Heat of Combustion of Isomeric Pentanes
The heat of combustion of pentane is greater than the heat of combustion of 2-methylbutane. Thus, pentane has a higher energy content. The heat of formation of 2-methylpentane is larger than the heat of formation of pentane.

1. Thermodynamic stability and enthalpy content are inversely related, provided that the $S°$ values do not differ substantially.
2. Thermodynamically more stable compounds release less heat energy in the combustion reaction.
3. Branched alkanes are more stable than normal alkanes.

Heat of combustion data can be used to calculate $\Delta H°_{rxn}$ for the isomerization reaction of pentane to form 2-methylbutane using Hess's law. We write the equation for the combustion of pentane and the reverse of the equation for the combustion of 2-methylbutane. (Remember that when a chemical equation is reversed, the sign of $\Delta H°_{rxn}$ changes.) We add the two chemical equations to give the equation for the isomerization of pentane to 2-methylbutane. The $\Delta H°_{rxn}$ for the reaction is obtained by summing the appropriate $\Delta H°_{rxn}$ values.

$$CH_3CH_2CH_2CH_2CH_3(l) + 8\,O_2(g) \longrightarrow 5\,CO_2(g) + 6\,H_2O(l) \qquad \Delta H°_{rxn} = -3534.6 \text{ kJ mole}^{-1}$$

$$5\,CO_2(g) + 6\,H_2O(l) \longrightarrow (CH_3)_2CHCH_2CH_3(l) + 8\,O_2(g) \qquad \Delta H°_{rxn} = +3527.5 \text{ kJ mole}^{-1}$$

$$CH_3CH_2CH_2CH_2CH_3(l) \longrightarrow (CH_3)_2CHCH_2CH_3(l) \qquad \Delta H°_{rxn} = -7.1 \text{ kJ mole}^{-1}$$

Stability of Cycloalkanes

Ring strain, which affects the stability of cycloalkanes, was discussed in Section 4.7 using heats of formation data. We can arrive at the same conclusions about ring strain

Octane Numbers

In an automobile engine, the fuel and air are drawn into the cylinder on its downward intake stroke. The piston compresses the mixture on the upward stroke. The firing of a spark plug ignites the mixture at the top of the stroke, producing an explosion that drives the piston downward again. As the piston compresses the gas on the next upward stroke, normal alkanes tend to ignite prematurely when the cylinder is hot. The result is a pinging sound, which indicates that a force is resisting the upward motion of the piston. Hence, normal alkanes are not suitable as fuel in an automobile engine.

2,2,4-trimethylpentane

The resistance of gasoline to pinging is rated by an octane number scale (see the table). An octane number of 100 is assigned to 2,2,4-trimethylpentane, an excellent fuel. Heptane, a poor fuel, is assigned an octane number of zero. Gasoline with the same burning characteristics as a 90% mixture of 2,2,4-trimethylpentane and 10% heptane is rated at 90 octane. Hydrocarbons that burn more efficiently than 2,2,4-trimethylpentane have octane numbers greater than 100. Hydrocarbons that burn less efficiently than heptane have negative octane numbers. Octane numbers decrease with increasing molecular weight. For isomeric compounds, increased branching increases the octane number.

The rate of the combustion process depends on the ease of formation of radicals and the efficiency of their reaction in chain processes. Branched hydrocarbons, which more easily form radicals, burn more smoothly and are the more efficient fuels. Thus, the octane number does not reflect the amount of energy that a compound can release. Normal alkanes have higher heats of combustion, but cause more "knocking".

Octane Numbers of Hydrocarbons

Formula	*Compound*	*Octane number*
C_4H_{10}	butane	94
C_5H_{12}	pentane	62
	2-methylbutane	94
C_6H_{14}	hexane	25
	2-methylpentane	73
	2,2-dimethylbutane	92
C_7H_{16}	heptane	0
	2-methylhexane	42
	2,3-dimethylpentane	90
C_8H_{18}	octane	−19
	2-methylheptane	22
	2,3-dimethylhexane	71
	2,2,4-trimethylpentane	100

by using heats of combustion data (Table 5.3). Provided that the same numbers of atoms are compared, thermodynamically more stable compounds release less heat energy in the combustion reaction. We recall that the stability (and strain energy) of cycloalkanes based on their heats of formation was discussed using the heat of formation per $—CH_2—$ unit (Section 4.7). Now we consider the heat of combustion per $—CH_2—$ unit to compare the stability of cycloalkanes (Table 5.3). These quantities are obtained by dividing the heat of combustion by the number of carbon atoms in the compound. We have just learned that an average difference of 658.8 kJ $mole^{-1}$ (157.4 kcal $mole^{-1}$) is seen for the heats of combustion of the series of alkanes that differ from one another by a $—CH_2—$ unit. The difference between the experimental heat of combustion and the predicted value obtained by multiplying the average value per $—CH_2—$ and the number of methylene units reflects the strain energy of the compound. Strained compounds release more energy because they are of higher energy.

TABLE 5.3
Heats of Combustion of Cycloalkanes

Cycloalkane	ΔH_c *(kJ mole^{-1})*	*Dimethylcycloalkane*	ΔH_c *(kJ mole^{-1})*
cyclopropane	2091	*cis*-1,2-dimethylcyclopropane	3369
cyclobutane	2721	*trans*-1,2-dimethylcyclopropane	3365
cyclopentane	3291	*cis*-1,2-dimethylcyclopentane	4691
cyclohexane	3920	*trans*-1,2-dimethylcyclopentane	4688
cycloheptane	4599	*cis*-1,3-dimethylcyclopentane	4684
cyclooctane	5267	*trans*-1,3-dimethylcyclopentane	4685
cyclononane	5933	*cis*-1,2-dimethylcyclohexane	5233
cyclodecane	6587	*trans*-1,2-dimethylcyclohexane	5217
cycloundecane	7237	*cis*-1,3-dimethylcyclohexane	5212
cyclododecane	7845	*trans*-1,3-dimethylcyclohexane	5219
		cis-1,4-dimethylcyclohexane	5219
		trans-1,4-dimethylcyclohexane	5212

Problem 5.6

The heat of combustion of 2,2-dimethylpropane is 3514.3 kJ mole^{-1}. Compare the stability of this compound with its two isomers. What is responsible for the difference?

Sample Solution

The heats of combustion of pentane and 2-methylbutane are 3534.6 and 3527.5 kJ mole^{-1}, respectively. Thus less energy is released in the combustion of 2,2-dimethylpropane compared to the other two isomeric hydrocarbons. A lower heat of combustion results from the combustion of the more stable isomer. The greater thermodynamic stability of 2,2-dimethylpropane is the result of a larger number of branches. There are two branches compared to one and none in 2-methylbutane and pentane, respectively.

Problem 5.7

The heats of combustion of 2-methylpentane and 3-methylpentane are 4157 and 4159 kJ mole^{-1}, respectively. Based on these data, calculate the heat of reaction for the isomerization of 2-methylpentane to form 3-methylpentane.

Problem 5.8

Using the heat of combustion of decane, predict the heat of combustion of dodecane ($C_{12}H_{26}$).

Sample Solution

The heat of combustion of decane is 6778 kJ mole^{-1}. The heat of combustion is increased on average by 658.8 kJ mole^{-1} per $-CH_2-$ unit. Because dodecane has two more methylene units than decane, its heat of combustion is approximately 8096 kJ mole^{-1}.

Problem 5.9

The heat of combustion of 3-methylnonane is 6773 kJ mole^{-1}. Predict the heat of combustion of 3-methyltridecane.

5.4 Halogenation of Saturated Hydrocarbons

Alkanes react with halogens at high temperature or in the presence of light. A halogen atom replaces a hydrogen atom in a substitution reaction. A radical chain mechanism for this reaction was given in Section 3.15. The substitution reaction of hydrogen by chlorine (chlorination) is exothermic, but since the carbon–hydrogen bond is strong, the reaction has a large activation energy. Methane reacts with chlorine when heated to a high temperature or when exposed to ultraviolet light.

$$CH_4 + Cl_2 \xrightarrow{400\ ^\circ C} \underset{\substack{\text{chloromethane}\\ \text{bp } -24.2\ ^\circ C}}{CH_3Cl} + HCl$$

The reaction is difficult to control because the product also has carbon–hydrogen bonds that can react with additional chlorine to produce several substitution products. The composition of the reaction mixture depends on the relative concentrations of reactants and reaction time. The products can be separated by distillation.

$$CH_3Cl + Cl_2 \xrightarrow{400\ ^\circ C} \underset{\substack{\text{dichloromethane}\\ \text{(methylene chloride)}\\ \text{bp } 40.2\ ^\circ C}}{CH_2Cl_2} + HCl$$

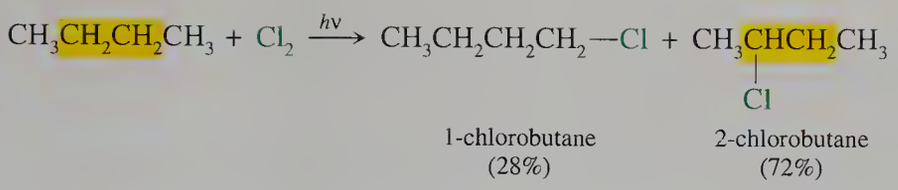
$$CH_2Cl_2 + Cl_2 \xrightarrow{400\ ^\circ C} \underset{\substack{\text{trichloromethane}\\ \text{(chloroform)}\\ \text{bp } 61.2\ ^\circ C}}{CHCl_3} + HCl$$

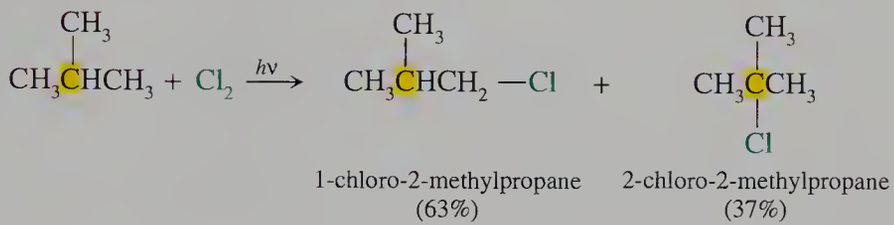
$$CHCl_3 + Cl_2 \xrightarrow{400\ ^\circ C} \underset{\substack{\text{tetrachloromethane}\\ \text{(carbon tetrachloride)}\\ \text{bp } 76.8\ ^\circ C}}{CCl_4} + HCl$$

Chlorinated methane compounds are used as industrial solvents and degreasing agents. Methylene chloride is used in some commercially available paint removers. It has also been used to remove caffeine from coffee beans. However, methylene chloride is toxic and is now being replaced by other substances. In the past, chloroform was used as an anesthetic, and carbon tetrachloride was used as a dry-cleaning solvent. These chlorinated methane compounds are also toxic and are no longer used for these purposes.

Regioselectivity of Halogenation of Alkanes

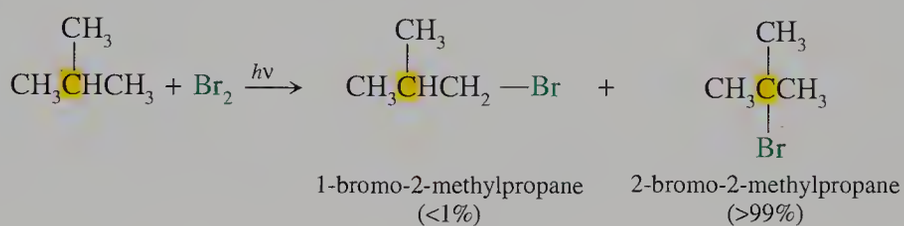
The chlorination of higher molecular weight alkanes yields a mixture of isomeric monochlorinated products. For example, the chlorination of butane or 2-methylpropane, which have nonequivalent hydrogen atoms, yields significant amounts of isomeric monochlorinated derivatives.





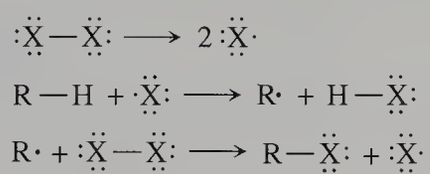
If one of several possible isomers predominates, a reaction is said to be **regioselective**. The data for the chlorination of butane and 2-methylpropane indicate that the chlorination of alkanes is not very regioselective. In fact, there doesn't appear to be a simple explanation for the product distribution in these chlorination reactions. For example, in the chlorination of butane, the major product, 2-chlorobutane, arises when a chlorine atom replaces a secondary hydrogen atom rather than a primary hydrogen atom. However, in the case of 2-methylpropane, the major product, 1-chloro-2-methylpropane, arises when a chlorine atom replaces a primary hydrogen atom rather than a tertiary hydrogen atom. We will return to this in the next section.

In contrast to chlorination, the bromination of alkanes is highly regioselective. For example, in the photochemical bromination of 2-methylpropane, more than 99% of the product results from substitution of bromine for the tertiary hydrogen atom.



Reactivity and Statistical Factors

The halogenation of an alkane occurs by a free radical mechanism. The first step is the formation of a halogen radical, which subsequently abstracts a hydrogen atom from the alkane. These steps yield a carbon radical, which reacts with the halogen molecule to give a halogenated product.



Let's consider the chlorination of butane again. If the propagation step generates a primary radical, the product is a primary halide—the butyl radical gives 1-chlorobutane.

$$CH_3CH_2CH_2CH_2{-}H + \cdot\ddot{Cl}: \longrightarrow \underset{\substack{\text{butyl radical}\\ \text{(a primary radical)}}}{CH_3CH_2CH_2CH_2\cdot} + HCl$$

$$CH_3CH_2CH_2CH_2\cdot + Cl_2 \longrightarrow \underset{\text{1-chlorobutane}}{CH_3CH_2CH_2CH_2{-}Cl} + \cdot\ddot{Cl}:$$

If the propagation step generates a secondary radical, the product is a secondary halide—the *sec*-butyl radical gives 2-chlorobutane.

$$CH_3CH_2CH_2CH_3 + \cdot\ddot{Cl}: \longrightarrow \underset{\substack{\textit{sec}\text{-butyl radical}\\ \text{(a primary radical)}}}{CH_3CH_2\dot{C}HCH_3} + HCl$$

$$CH_3CH_2\dot{C}HCH_3 + Cl_2 \longrightarrow \underset{\text{2-chlorobutane}}{CH_3CH_2\overset{\displaystyle Cl}{\overset{|}{C}}HCH_3} + \cdot\ddot{Cl}:$$

Therefore, the percent of each chlorinated product formed is directly related to the percent of the two possible radicals formed by abstraction of hydrogen from butane.

Now that we understand the origin of the products, we may ask why the reaction of butane with chlorine yields 1-chlorobutane and 2-chlorobutane in the ratio 28:72. Butane has six primary hydrogen atoms and four secondary hydrogen atoms, so there are six ways to form the butyl radical and four ways to form the *sec*-butyl radical. If the primary and secondary hydrogen atoms of butane reacted at the same rate, the ratio of 1-chlorobutane to 2-chlorobutane would be 6:4, but it isn't. To account for the 28:72 ratio, we have to know why more *sec*-butyl radical is formed than butyl radical.

A similar question arises from the product distribution data for the chlorination of 2-methylpropane. If the primary and tertiary hydrogen atoms of 2-methylpropane reacted at the same rate, the ratio of products formed would be 9:1, but it isn't. The larger than expected quantity of 2-chloro-2-methylpropane means that the *tert*-butyl radical is formed more easily than the isobutyl radical.

We recall that the order of radical stability is tertiary > secondary > primary (Section 3.13). There is a correlation between reactivity of a C—H bond and the stability of the resulting radical: the most stable radical is produced by cleavage of the most reactive C—H bond. Let's use the product distribution data for butane to calculate the rate of abstraction per hydrogen atom. The relative amount of a given product formed is equal to the number of ways that it can be formed times the relative rate for each of those equivalent paths. In the case of chlorination of butane, we see that there are four ways to get 2-chlorobutane and six ways to obtain 1-chlorobutane. The ratio of 2-chlorobutane to 1-chlorobutane therefore equals the relative rate of abstraction of a secondary hydrogen atom times 4 divided by the relative rate of abstraction of a primary hydrogen atom times 6.

$$\frac{\%\text{ 2-chlorobutane}}{\%\text{ 1-chlorobutane}} = \frac{(\text{rate of 2° H abstraction}) \times 4\text{ atoms}}{(\text{rate of 1° H abstraction}) \times 6\text{ atoms}}$$

$$\frac{\text{rate of 2° H abstraction}}{\text{rate of 1° H abstraction}} = \frac{\%\text{ 2-chlorobutane} \times 6\text{ atoms}}{\%\text{ 1-chlorobutane} \times 4\text{ atoms}} = \frac{72 \times 6}{28 \times 4} = \frac{3.9}{1}$$

Hence, 2-chlorobutane forms in preference to 1-chlorobutane because a single secondary hydrogen atom is abstracted 3.9 times as rapidly as a single primary hydrogen atom.

A similar analysis for the chlorination of 2-methylpropane illustrates the reactivity per hydrogen atom even more dramatically. Recall that the primary product predominates.

$$\frac{\%\text{ 2-chloro-2-methylpropane}}{\%\text{ 1-chloro-2-methylpropane}} = \frac{(\text{rate of } 3^\circ \text{ H abstraction}) \times 1 \text{ atom}}{(\text{rate of } 1^\circ \text{ H abstraction}) \times 9 \text{ atoms}}$$

$$\frac{\text{rate of } 3^\circ \text{ H abstraction}}{\text{rate of } 1^\circ \text{ H abstraction}} = \frac{\%\text{ 2-chloro-2-methylpropane} \times 9}{\%\text{ 1-chloro-2-methylpropane} \times 1} = \frac{37 \times 9}{63 \times 1} = \frac{5.3}{1}$$

In this case, the major product does not result from abstraction of the more reactive hydrogen atom. A tertiary hydrogen atom is abstracted at a faster rate than a single primary hydrogen atom, but more primary product forms because there are enough primary hydrogen atoms to offset the difference in relative reactivities.

The order of reactivity per hydrogen atom in the chlorination of alkanes illustrates the low regioselectivity of the reaction.

——— relative rate of chlorination ⟶		
primary H <	secondary H <	tertiary H
(1)	(3.9)	(5.3)

In contrast to chlorination, which is not very regioselective, the bromination of alkanes is highly regioselective. We saw that the bromination of 2-methylpropane yields 2-bromo-2-methylpropane as the major product, even though there are nine primary hydrogen atoms and only one tertiary hydrogen atom. Based on data for a variety of structures, the range of reactivities of tertiary, secondary, and primary hydrogen atoms with bromine is found to be much greater than for reaction with chlorine.

——— relative rate of bromination ⟶		
primary H <	secondary H <	tertiary H
(1)	(80)	(1650)

Problem 5.10

How many mono-, di-, and trichlorinated compounds result from the chlorination of ethane?

Problem 5.11

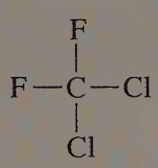
How many dichlorinated compounds can result from the chlorination of butane? How many dichlorinated compounds can result from the chlorination of 2-methylpropane?

Problem 5.12

Explain why the free radical chlorination of methylcyclopentane yields six isomeric $C_6H_{11}Cl$ compounds.

Freon, Radicals, and the Ozone Layer

Halogenated alkanes are less flammable than alkanes. Some haloalkanes, such as carbon tetrachloride, will not burn at all. At one time carbon tetrachloride was used in fire extinguishers to provide an inert atmosphere to prevent oxygen from reaching the flames. Reduced combustibility makes haloalkanes useful for many purposes. For example, dichlorodifluoromethane, known by its commercial name Freon 12, is produced in large quantities for use in air conditioners. It was also used until recently as an aerosol propellant.



Freon 12

Although Freon 12 is inert at the Earth's surface, in the presence of ultraviolet radiation in the stratosphere, it decomposes. Ultraviolet radiation breaks the carbon–chlorine bond to produce the $\cdot CF_2Cl$ radical and a chlorine radical.

$$CF_2Cl_2 \longrightarrow Cl\cdot + \cdot CF_2Cl$$

This process is partially responsible for destruction of the ozone layer in the stratosphere. Ozone in the stratosphere protects us from solar ultraviolet radiation by absorbing ultraviolet radiation, which splits the ozone molecules into molecular oxygen and atomic oxygen. These products then recombine and release heat energy. These two reactions protect organisms on Earth from extensive doses of ultraviolet radiation.

$$O_3 \xrightarrow{\text{UV light}} O_2 + O$$

$$O_2 + O \longrightarrow O_3 + \text{heat energy}$$

The chlorine radical from Freon 12 reacts with ozone in the stratosphere. Then the $\cdot ClO$ formed reacts with atomic oxygen.

$$Cl\cdot + O_3 \longrightarrow ClO\cdot + O_2$$

$$ClO\cdot + O \longrightarrow Cl\cdot + O_2$$

Note that a chlorine radical reacts in the first equation and is a product in the second equation. Thus, the chlorine is a catalyst for the destruction of ozone. The net reaction of these two steps is the destruction of an ozone molecule for each cycle initiated by the chlorine atom.

$$O_3 + O \longrightarrow 2O_2$$

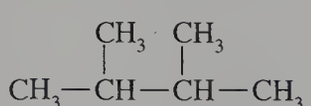
These reactions effectively remove ozone and atomic oxygen from the atmosphere, diminishing the protection provided by the ozone layer. The destruction of the ozone layer is most pronounced at the South Pole, but recently a similar effect has been detected at the North Pole. Continued destruction of the ozone layer now appears to be happening at mid-latitudes as well, where more of the Earth's inhabitants live. Ultraviolet radiation disrupts the structure of DNA, causing genetic damage. As the amount of UV radiation reaching the Earth's surface increases, the incidence of skin cancer may also increase.

Problem 5.13

Calculate the percentages of monochlorinated products formed in the reaction of chlorine with 2,3-dimethylbutane.

Sample Solution

First determine the number of sets of equivalent hydrogen atoms in this hydrocarbon and the number of hydrogen atoms in each set.



There are two equivalent tertiary carbon atoms and four equivalent primary carbon atoms. Thus the ratio of tertiary to primary hydrogen atoms is 2:12. Using the relative reactivities of primary and tertiary hydrogen atoms we determine the ratio of the two products.

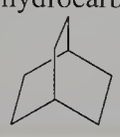
$$\frac{\%\text{ tertiary product}}{\%\text{ primary product}} = \frac{(\text{rate of } 3^\circ \text{ H abstraction}) \times 2 \text{ atoms}}{(\text{rate of } 1^\circ \text{ H abstraction}) \times 12 \text{ atoms}} = \frac{5.3 \times 2}{1 \times 12} = 0.88$$

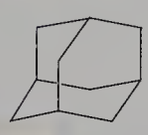
The percent of either product can be solved algebraically knowing the ratio of the two products and the sum of the two products which is 100%.

$$\%\text{ tertiary product} + \%\text{ primary product} = 100\%$$
$$(0.88)(\%\text{ primary product}) + \%\text{ primary product} = 100\%$$
$$\%\text{ primary product} = 53\%$$
$$\%\text{ tertiary product} = 100\% - 53\% = 47\%$$

Problem 5.14

Calculate the percentage of the monochlorinated products formed from each of the following hydrocarbons.

(a) 

(b) 

Problem 5.15

What is the major product of the free radical bromination of ethylcyclohexane?

5.5 Enthalpy of Reaction for Halogenation

In Section 3.15, we discussed the mechanism for the free radical chlorination of methane. Now we return to this reaction in a more general way and consider the enthalpy changes that accompany the various propagation steps in the reaction. We will examine the enthalpy change for each step and see how it contributes to the overall enthalpy change.

$$\begin{array}{lll} CH_3{-}H + \cdot\ddot{X}: \longrightarrow CH_3\cdot + H{-}\ddot{X}: & & \Delta H_1^\circ \\ CH_3\cdot + :\ddot{X}{-}\ddot{X}: \longrightarrow CH_3{-}\ddot{X}: + :\ddot{X}\cdot & & \Delta H_2^\circ \\ \hline CH_4 + :\ddot{X}{-}\ddot{X}: \longrightarrow CH_3{-}\ddot{X}: + H{-}\ddot{X}: & & \Delta H_{rxn}^\circ = \Delta H_1^\circ + \Delta H_2^\circ \end{array}$$

First, let's examine the fluorination of methane and the enthalpy changes associated with the two propagation steps.

$$\begin{array}{lll} CH_3{-}H + \cdot\ddot{F}: \longrightarrow CH_3\cdot + H{-}\ddot{F}: & & \Delta H_1^\circ = -134 \text{ kJ mole}^{-1} \\ CH_3\cdot + :\ddot{F}{-}\ddot{F}: \longrightarrow CH_3{-}\ddot{F}: + :\ddot{F}\cdot & & \Delta H_2^\circ = -305 \text{ kJ mole}^{-1} \\ \hline CH_4 + :\ddot{F}{-}\ddot{F}: \longrightarrow CH_3{-}\ddot{F}: + H{-}\ddot{F}: & & \Delta H_{rxn}^\circ = -439 \text{ kJ mole}^{-1} \end{array}$$

The propagation steps for fluorination are highly exothermic, and the reaction is difficult to control. The large quantity of heat released during the reaction causes the reaction temperature to rise, which in turn increases the rate of the reaction. As a consequence, the reaction may lead to an explosion.

When we turn to chlorination, we find that the first propagation step is very slightly endothermic. The second step is exothermic, but less so than the second step in fluorination.

$$CH_3—H + \cdot\ddot{Cl}: \longrightarrow CH_3\cdot + H—\ddot{Cl}: \qquad \Delta H_1^\circ = +4 \text{ kJ mole}^{-1}$$

$$CH_3\cdot + :\ddot{Cl}—\ddot{Cl}: \longrightarrow CH_3—\ddot{Cl}: + :\ddot{Cl}\cdot \qquad \Delta H_2^\circ = -112 \text{ kJ mole}^{-1}$$

$$CH_4 + :\ddot{Cl}—\ddot{Cl}: \longrightarrow CH_3—\ddot{Cl}: + H—\ddot{Cl}: \qquad \Delta H_{rxn}^\circ = -108 \text{ kJ mole}^{-1}$$

The net reaction is exothermic, but the enthalpy change is less than for fluorination. Chlorination reactions can be more easily controlled than fluorination, so free radical chlorination is an important industrial process.

When we examine the enthalpy changes for the propagation steps in the bromination of methane, we find that the first step is now even more endothermic than the comparable step for chlorination. The overall process is exothermic only because the second step is exothermic.

$$CH_3—H + \cdot\ddot{Br}: \longrightarrow CH_3\cdot + H—\ddot{Br}: \qquad \Delta H_1^\circ = +67 \text{ kJ mole}^{-1}$$

$$CH_3\cdot + :\ddot{Br}—\ddot{Br}: \longrightarrow CH_3—\ddot{Br}: + :\ddot{Br}\cdot \qquad \Delta H_2^\circ = -104 \text{ kJ mole}^{-1}$$

$$CH_4 + :\ddot{Br}—\ddot{Br}: \longrightarrow CH_3—\ddot{Br}: + H—\ddot{Br}: \qquad \Delta H_{rxn}^\circ = -37 \text{ kJ mole}^{-1}$$

For iodination, we find that the first step is so endothermic that the overall reaction is endothermic even though the second step is exothermic.

$$CH_3—H + \cdot\ddot{I}: \longrightarrow CH_3\cdot + H—\ddot{I}: \qquad \Delta H_1^\circ = +146 \text{ kJ mole}^{-1}$$

$$CH_3\cdot + :\ddot{I}—\ddot{I}: \longrightarrow CH_3—\ddot{I}: + :\ddot{I}\cdot \qquad \Delta H_2^\circ = -87 \text{ kJ mole}^{-1}$$

$$CH_4 + :\ddot{I}—\ddot{I}: \longrightarrow CH_3—\ddot{I}: + H—\ddot{I}: \qquad \Delta H_{rxn}^\circ = +59 \text{ kJ mole}^{-1}$$

The data tell us that the total energy released in halogenation of methane decreases in the order $F_2 > Cl_2 > Br_2 > I_2$. This order of halogen reactivity with methane is primarily controlled by the ΔH_{rxn}° for the propagation step, in which the halogen atom abstracts the hydrogen atom. Furthermore, the enthalpy change for this step parallels the strength of the hydrogen–halogen bond. When the H—X bond is strong, as in H—F, this step is highly exothermic. When the H—X is weak, as in H—I, this step is highly endothermic.

5.6 Activation Energy for Halogenation

In the preceding section, we considered the enthalpy changes for the propagation steps of free radical halogenation. We did not consider the activation energies for these steps, although we implicitly assumed that the rates of reaction are related to the enthalpy change for the reaction. Free radical halogenation is a multistep reaction. Each step has a characteristic activation energy that controls the rate of reaction for that step. The overall rate of the reaction is controlled by the step with the higher activation energy. This is the rate-determining step for the reaction. In the preceding section, we learned that the enthalpy change for the first propagation step in halogenation is always less exothermic than the enthalpy change for the second step. This step is

rate-determining. The second step, which is quite exothermic, has a very low activation energy (less than 1 kJ mole^{-1}).

Let's compare the activation energies for the first step for halogenation by each halogen.

	E_a (*kJ mole*$^{-1}$)	$\Delta H°_{rxn}$ (*kJ mole*$^{-1}$)
$CH_3—H + \cdot\ddot{F}: \longrightarrow CH_3\cdot + H—\ddot{F}:$	+5	−134
$CH_3—H + \cdot\ddot{Cl}: \longrightarrow CH_3\cdot + H—\ddot{Cl}:$	+16	+4
$CH_3—H + \cdot\ddot{Br}: \longrightarrow CH_3\cdot + H—\ddot{Br}:$	+78	+67
$CH_3—H + \cdot\ddot{I}: \longrightarrow CH_3\cdot + H—\ddot{I}:$	+138	+146

These activation energies parallel the reactivity of the halogens, $F_2 > Cl_2 > Br_2 > I_2$. The activation energies also parallel the $\Delta H°$ for the first propagation step. As the reaction becomes more endothermic, the activation energy increases. This relationship is illustrated in Figure 5.4 for chlorination and bromination.

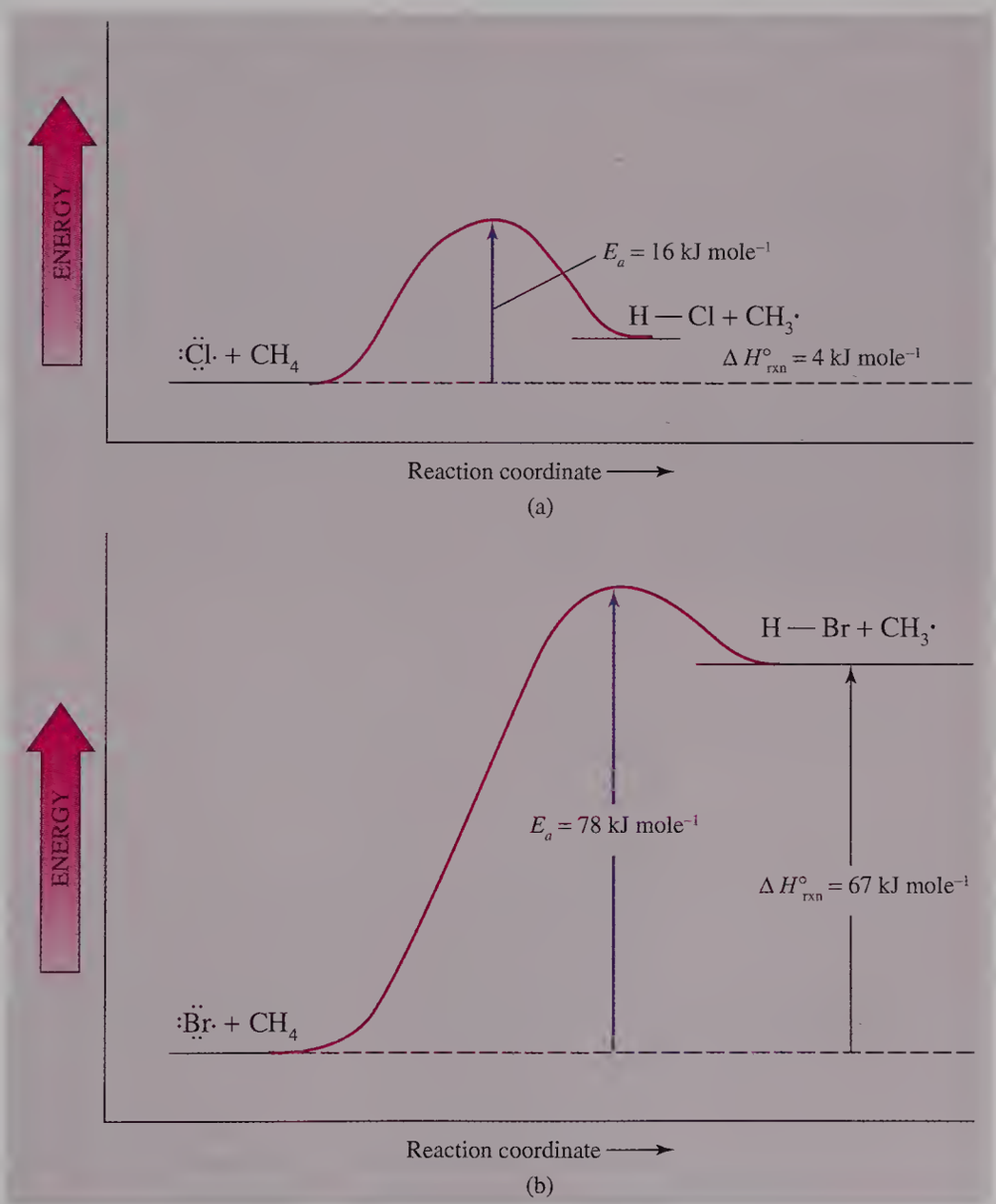


FIGURE 5.4 Potential Energy Diagrams for Halogenation Reactions
The energy of activation for the abstraction of a hydrogen atom by a chlorine atom (a) is smaller than the energy of activation for the abstraction of a hydrogen atom by a bromine atom (b).

Reactivity and Selectivity

We now know that bromine is less reactive than chlorine in the rate-determining step of halogenation of methane. We also recall that bromine is more selective than chlorine. Both the rate of reaction and the selectivity of free radical halogenation are related to the first propagation step, so let's look at the relationship between reactivity and selectivity in terms of the structure of the transition states for chlorination and bromination.

Because the first propagation step of the chlorination reaction is very slightly endothermic, the transition state is only moderately past the "center" of the reaction coordinate axis. In contrast, the transition state for the more endothermic bromination reaction is farther along the reaction coordinate axis (Figure 5.4). What does this information tell us about the structure of the transition states for the two reactions? We recall that the Hammond postulate states that the structures of transition states most closely resemble those species that are most similar in energy (Section 3.17). Thus, the structure of the transition state for an exothermic process is more reactant-like, and the structure of the transition state for an endothermic process is more product-like. These two transition states are sometimes called "early" and "late", respectively.

The first propagation step for the chlorination reaction is very slightly endothermic. Thus, the position of the transition state along the reaction coordinate is a bit past the midpoint (Figure 5.4). The extent to which the C—H bond is broken and the extent to which the H—Cl bond is formed are comparable because the C—H and H—Cl bond dissociation energies are similar.

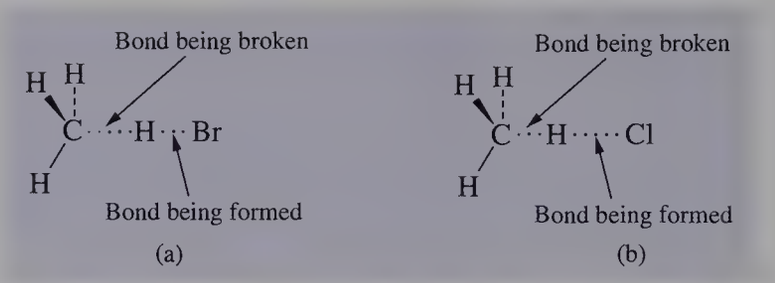


FIGURE 5.5 Transition State Structures for Halogenation
(a) The transition state for abstraction of hydrogen by a bromine atom has the C—H bond largely broken and the H—Br bond largely formed. (b) The transition state for abstraction of hydrogen by a chlorine atom has the C—H bond broken to a lesser degree and the H—Cl bond only partially formed.

The first propagation step for the bromination of methane is strongly endothermic, so the transition state is more product-like (Figure 5.5). The C—H bond is broken to a significant extent, and the H—Br bond is more strongly formed.

What are the consequences of the degree of bond homolysis in the transition state on the selectivity of the reagent? In the less reactive bromination reaction, the transition state for the first propagation step is more product-like and resembles the radical product. Thus the ease with which the C—H bond is broken, which reflects the effect of alkyl groups on the stability of the radical, is quite important. The reaction then shows a selectivity that reflects the stability of the radical product. In the chlorination reaction, the transition state is more reactant-like, and the alkyl group has not developed much radical character. Hence, the type of C—H bond—primary, secondary, or tertiary—has little effect on the reaction, and low selectivity is the result.

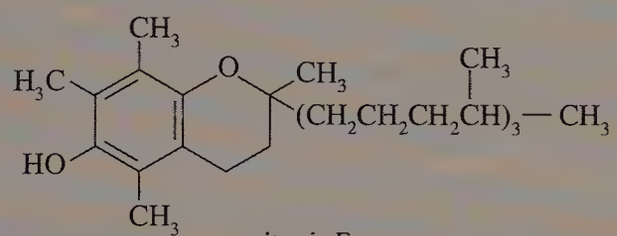
Throughout our study of organic reactions, we will find that, for structurally similar reactions, the more reactive reagent shows lower selectivity. Many factors account for this selectivity, including inductive, resonance, and steric effects. Regardless of the factors, the less reactive reagent has a more fully developed transition state (less reactant-like) and the role of structural features in stabilizing the transition state becomes more important.

Free Radicals in Aging

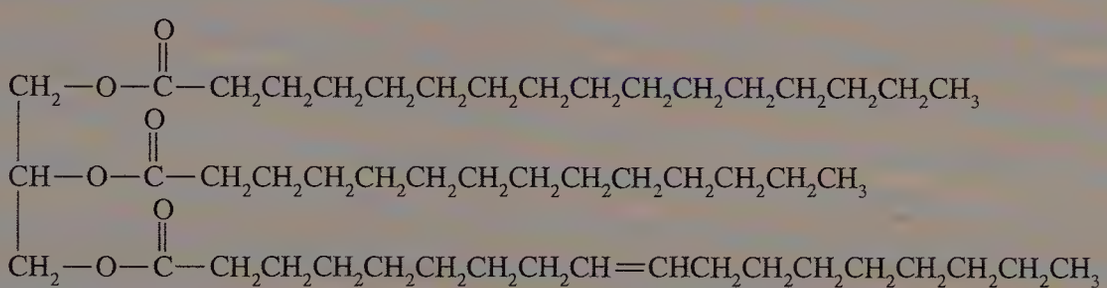
Recent research indicates that free radicals are produced by natural processes within the human body. Particularly important are the hydroxyl radical, HO·, and various alkoxyl radicals, RO·. Because oxygen is more electronegative than carbon, these oxygen radicals are very reactive. As these radicals are produced by natural processes, we have to live with the consequences.

The long hydrocarbon chains of various types of lipid molecules that make up cell membranes are susceptible to attack by oxygen free radicals. Cell membranes are held together, in part, by London forces between lipid molecules. In addition, the functioning of a cell membrane is a direct consequence of its structure. Thus any free radical reactions that alter the composition of lipids in the cell membrane can have serious effects. Our bodies have mechanisms to repair damage. However, with increasing age these mechanisms become less efficient, and in a cascading effect the cell damage accelerates.

There is evidence that antioxidants prevent the aging process by reacting with hydroxyl radical. The hydroxyl radical abstracts a hydrogen atom from the OH group bonded to the benzene ring of Vitamin E. The resulting resonance-stabilized radical is more stable and therefore less reactive. The role of diet is considered important in providing antioxidants that can retard the aging process.



vitamin E
(α-tocopherol)



(a representative lipid)

EXERCISES

Bond Dissociation Energies

5.1 Estimate the bond dissociation energy of the indicated C—H bond in each of the following compounds.
(a) C-3 to H in 3-ethylpentane **(b)** C-3 to H in 3-methylpentane
(c) C-2 to H in 3-methylhexane **(d)** C-6 to H in 2,2-dimethylhexane

5.2 Estimate the bond dissociation energy of the indicated C—H bond in each of the following compounds.
(a) C-3 to H in *trans*-1,3-dimethylcyclopentane **(b)** C-4 to H in 1,1-dimethylcyclodecane
(c) C-4 to H in 3-methylhexane **(d)** C-1 to H in 2,2-dimethylhexane

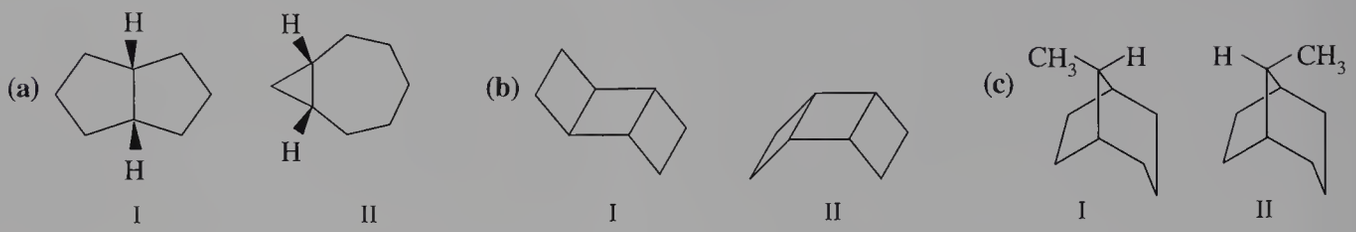
Combustion of Hydrocarbons

5.3 Write a balanced equation for the combustion of each of the following compounds.
(a) octane **(b)** cyclooctane **(c)** ethylcyclohexane **(d)** 2,2-dimethylhexane

5.4 Write a balanced equation for the combustion of each of the following compounds.
(a) *cis*-1,4-dimethylcyclohexane **(b)** *trans*-1,4-dimethylcyclohexane
(c) 1,1-dimethylcyclohexane **(d)** 1,1,3,3-tetramethylcyclobutane

5.5 Identify the hydrocarbon in each of the following groups with the lowest heat of combustion.
(a) 2-methylhexane, 3-ethylpentane, 2,4-dimethylpentane
(b) 2-methylbutane, 2-methylpentane, heptane
(c) methylcyclopentane, 1,1-dimethylcyclobutane, propylcyclopropane

5.6 Identify the hydrocarbon in each of the following pairs with the larger heat of combustion.



5.7 How many products can result from the substitution of one chlorine atom for one hydrogen atom in each of the following compounds?
(a) pentane **(b)** hexane **(c)** 2-methylbutane
(d) 3-methylpentane **(e)** cyclohexane **(f)** 1,1-dimethylcyclohexane

5.8 How many products can result from the substitution of a fluorine atom for one hydrogen atom in each of the following compounds?
(a) 2,2-dimethylbutane **(b)** 2,2-dimethylpentane **(c)** 2,3-dimethylbutane
(d) 2,4-dimethylpentane **(e)** cyclopentane **(f)** 1-methylcyclopentane

5.9 Halothane, an anesthetic, has the formula C_2HF_3ClBr. Draw structural formulas for the four possible isomers of this molecular formula.

5.10 Chlorination of 1,2-dichloro-1,1-difluoropropane gives two isomeric products with the molecular formula $C_3H_3Cl_3F_2$. Name the products.

5.11 A saturated refrigerant has the molecular formula C_4F_8. Draw structural formulas for two possible isomers of this compound.

5.12 Bromination of one of the isomeric C_3H_7Cl compounds gives two products with the molecular formula C_3H_6BrCl. Bromination of the other compound gives three products with the molecular formula C_3H_6BrCl. What are the structures of each C_3H_7Cl compound? Write the products obtained from each.

Mechanism of Free Radical Reactions

5.13 Write the initiation step and the propagation steps for the following generalized reaction of an alkane with CCl_3Br.

$$R{-}H + CCl_3Br \longrightarrow R{-}Br + CHCl_3$$

5.14 Write the initiation step and the propagation steps for the following generalized reaction of an alkane with *tert*-butyl hypochlorite.

$$R{-}H + (CH_3)_3CO{-}Cl \longrightarrow R{-}Cl + (CH_3)_3CO{-}H$$

5.15 The O—O bond dissociation energy of peroxides, R—O—O—R, is about 154 kJ mole^{-1}. Write the most likely initiation step accounting for the fact that di-*tert*-butyl peroxide, $(CH_3)_3C{-}O{-}O{-}C(CH_3)_3$, is a useful initiator in the bromination of alkanes.

5.16 Tetraethyllead, $Pb(CH_2CH_3)_4$ can be used to initiate the reaction of chlorine with hydrocarbons. The C—Pb bond dissociation energy is about 200 kJ mole^{-1}. Write the most likely initiation steps for the chlorination reaction. The temperature required for the initiation is about 150 °C, rather than the 400 °C required for direct thermal chlorination of hydrocarbon. Explain why a lower temperature suffices.

Selectivity of Radical Reactions

5.17 The bond strength of a carbon–deuterium bond is different from that of a carbon–hydrogen bond. Monochlorination of CH_3CH_2D gives 7% CH_3CH_2Cl and 93% of a mixture of CH_3CHDCl and $ClCH_2CH_2D$. Assuming that the deuterium atom has no effect on the rate of abstraction of the hydrogen from the CH_2D group, calculate the reactivity of a C—D bond relative to a C—H bond.

5.18 The bond strength of the O—H bond of water is 497 kJ mole^{-1}. Calculate the ΔH°_{rxn} for the reaction of the hydroxyl radical with methane. Estimate the selectivity of ·OH compared to the halogen atoms.

$$CH_4 + \cdot OH \longrightarrow CH_3\cdot + H_2O$$

5.19 The fluorination of 2-methylpropane gives a mixture containing 1-fluoro-2-methylpropane and 2-fluoro-2-methylpropane in a 6:1 ratio. Calculate the relative reactivity of a tertiary to a primary C—H bond in fluorination.

5.20 The fluorination of butane gives a mixture of 1-fluorobutane and 2-fluorobutane in a 1.25:1 ratio. Calculate the relative reactivity of a secondary to a primary C—H bond in fluorination.

Calculation of Product Ratios

5.21 Chlorination of 2-methylpentane gives the following four isomers in the indicated percentages. Using statistical factors and selectivity factors, confirm that the observed composition of the reaction mixture is reasonable.

2-chloro-3-methylbutane	36%
1-chloro-2-methylbutane	27%
2-chloro-2-methylbutane	23%
1-chloro-3-methylbutane	14%

5.22 The selectivity of the halogens depends on temperature. At 300 °C the reactivities of primary, secondary, and tertiary C—H bonds toward chlorine atoms stand in the order 1:2.5:4. Calculate the composition of the reaction mixture obtained by chlorinating butane and 2-methylpropane.

5.23 The reactivity of the C—H bond in methane in fluorination is 0.5 relative to the C—H bond in ethane. Explain why. Based on this data, predict the relative rates of fluorination of methane and ethane in a mixture containing equimolar amounts of the two hydrocarbons.

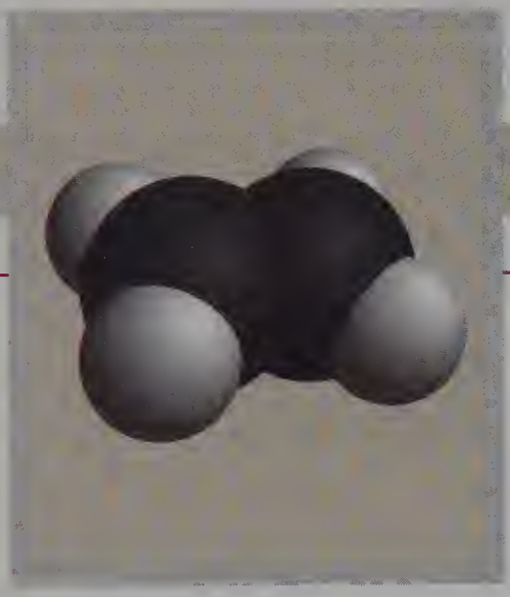
5.24 Using the data for the selectivity of bromine, predict the relative rates of bromination of propane and 2-methylpropane in a mixture containing equimolar amounts of the two hydrocarbons.

5.25 Chlorination of pentane gives a mixture containing 53% of a chloropentane. The remaining fraction of the mixture consists of two isomers in roughly equal amounts. Without detailed calculations using selectivity factors, predict the structure of the major isomer formed.

5.26 Chlorination of heptane gives a mixture of chloroheptanes containing 14% 1-chloroheptane. Without using selectivity factors, estimate the percents of the other three isomers formed in the reaction.

5.27 Chlorination of 2,2,4-trimethylpentane gives a mixture of four isomeric monochlorinated products. Approximately 55% of the mixture consists of two primary alkyl chlorides. Without detailed calculations using selectivity factors, predict the percent of each of the primary alkyl chlorides formed.

5.28 Bromination of 2,2,3-trimethylbutane gives essentially a single monobrominated product. Estimate the approximate percents of the other two possible isomers.



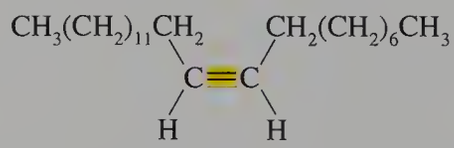
6

Alkenes—Structure and Properties

6.1 Unsaturated Hydrocarbons

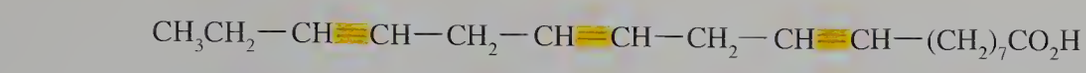
Organic compounds containing one or more carbon–carbon multiple bonds have fewer hydrogen atoms than structurally related alkanes or cycloalkanes. For this reason, these compounds are said to be **unsaturated**. In this chapter we will focus on one group of unsaturated compounds, the alkenes. An alkene must contain at least one carbon–carbon double bond. We recall that in addition to the σ bond there is a π bond that forms from 2*p* orbitals on adjacent carbon atoms overlapping "side by side". We also recall that the carbon atoms in a π bond of an alkene are sp^2 hybridized (Section 1.17).

Alkenes and their chemical cousins, the cycloalkenes, are very common in nature. They occur in fats and oils, some vitamins, and even in some pheromones. For example, an alkene called muscalure is important to the common housefly (*Musca domestica*). Muscalure, an unbranched alkene containing 23 carbon atoms, is released by the female to attract males. Muscalure has been synthesized in the laboratory and can be used to lure male flies to traps.

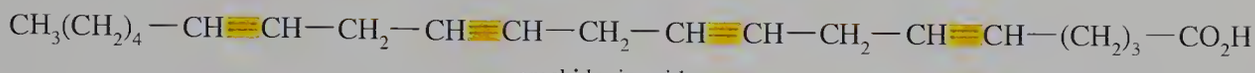


muscalure

Some alkenes, called **polyenes**, contain two or more carbon–carbon double bonds. Alkenes with two, three, and four double bonds are called dienes, trienes, and tetraenes, respectively. Multiple double bonds are present in polyunsaturated compounds called oils. These substances are esters that contain several carbon–carbon double bonds. Polyunsaturated compounds are common in nature. For example, linolenic acid is a triene that is present as an ester in some polyunsaturated oils. Arachidonic acid, a tetraene, is a precursor to physiologically active molecules called prostaglandins.

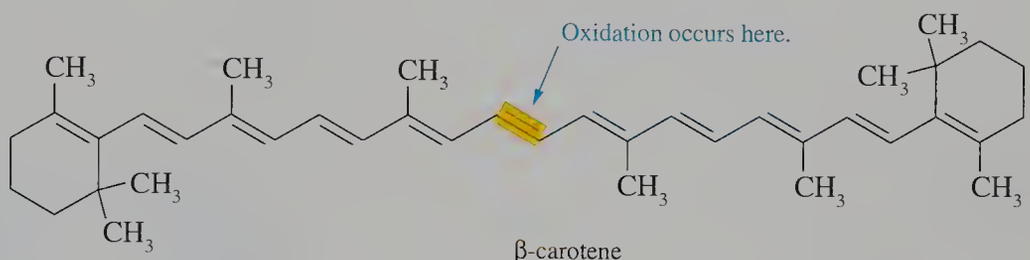


linolenic acid

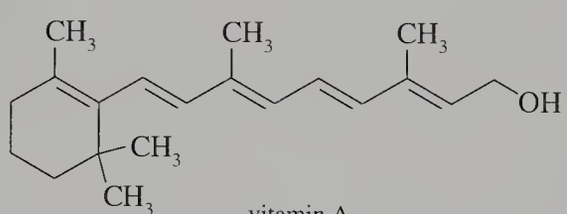


arachidonic acid

β-Carotene, found in carrots, and vitamin A, which is derived from β-carotene, are polyunsaturated alkenes. β-Carotene is converted to vitamin A in mammals by an enzyme-catalyzed reaction that oxidizes β-carotene into two molecules of vitamin A.

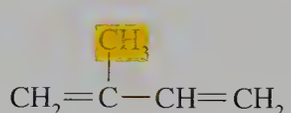


β-carotene

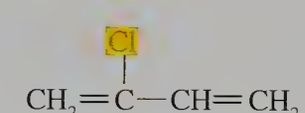


vitamin A

β-Carotene and vitamin A contain double bonds separated from one another by one single bond. We say that the single and double bonds are "alternating". The alternation of single and double bonds is called **conjugation**. Therefore, both β-carotene and vitamin A are **conjugated polyenes**. Some industrial products are derived from conjugated dienes. Natural rubber is a polymer of isoprene. The synthetic rubbers called neoprenes are produced from chloroprene.



isoprene



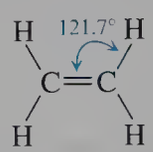
chloroprene

The reactions of conjugated compounds differ from compounds containing double bonds separated by two or more single bonds. The chemistry of conjugated dienes and other more complex conjugated compounds will be discussed in Chapter 12 after we have established a foundation for the typical reactions of alkenes.

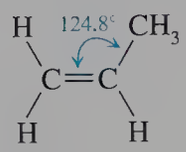
The IUPAC names of alkenes use the suffix *-ene*. Alkynes, which are also unsaturated because they contain one or more carbon–carbon triple bonds, will be discussed in Chapter 11. Unsaturated compounds that contain a benzene ring or structural units that resemble a benzene ring are **aromatic** hydrocarbons. They will be discussed in Chapter 13.

6.2 Structure and Classification of Alkenes

The simplest alkene, C_2H_4, commonly called ethylene, has the IUPAC name ethene. Its structure is shown in Figure 6.1. Alkenes contain trigonal planar sp^2-hybridized carbon atoms. Therefore, the bond angles around the sp^2-hybridized carbon atoms should ideally be 120°. The bond angles of alkenes are typically within a few degrees of this value. For example, the H—C=C bond angle in ethene is 121.7°. The C—C=C bond angle of propene is 124.8°.

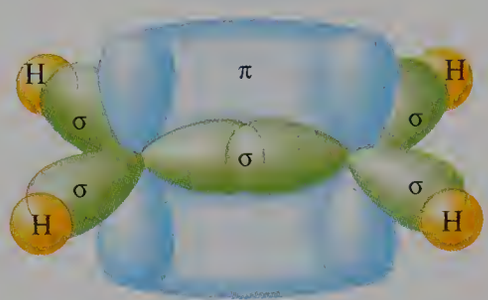


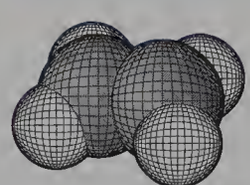
ethene



propene

FIGURE 6.1 Structure of Ethylene
The π bond is formed by sideways overlap of the parallel 2*p* orbitals of adjacent carbon atoms.





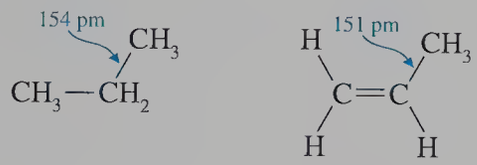
Space-filling model

An sp^2 hybrid orbital has 33% *s* character, whereas an sp^3 hybrid orbital has 25% *s* character. As the percent *s* character of a hybrid orbital increases, the electrons are held closer to the nucleus. The increase in percent *s* character of the σ bonds of ethylene has an important effect on its physical properties.

Bond Length and Bond Energy

The length of a bond between carbon and another atom is shorter for a carbon atom with sp^2 hybrid orbitals than for a carbon atom with sp^3 hybrid orbitals. For example, the C—H bond lengths in ethylene and ethane are 107 pm and 109 pm, respectively. The C—H bond energies of ethylene and ethane are 451 kJ $mole^{-1}$ (108 kcal $mole^{-1}$) and 22 kJ $mole^{-1}$ (101 kcal $mole^{-1}$), respectively.

The length of the σ carbon–carbon bond depends on the hybridization of both carbon atoms. For example, the C—C bond between an sp^2-hybridized and an sp^3-hybridized carbon atom is shorter than the bond between two sp^3-hybridized carbon atoms. The carbon–carbon single bond of propene is 151 pm (1.51 Å) compared to 154 pm (1.54 Å) for propane.



propane propene

The carbon–carbon bond lengths of ethylene and ethane are 133 pm and 154 pm, respectively. The shorter bond length of ethylene is partly due to the sp^2 hybridization of the orbitals used to form the carbon–carbon σ bond. Based on the decrease in bond length caused by one sp^2-hybridized carbon atom in propene (3 pm), we could predict that the length of a σ bond between two sp^2-hybridized carbon atoms would be about 148 pm. The actual bond length is much shorter, only 133 pm. Thus, the most important contribution to the decrease in the carbon–carbon bond length of ethylene is from the increased number of bonds joining the carbon atoms.

The C=C bond energy of ethylene is 605 kJ $mole^{-1}$ (144 kcal $mole^{-1}$). The C—C bond energy of ethane is 368 kJ $mole^{-1}$ (88 kcal $mole^{-1}$). How can we apportion the contributions of the σ and π bonds to the total bond energy? The σ bond energy in ethylene should be somewhat larger than the σ bond energy of ethane because both carbon atoms are sp^2 hybridized. However, using 368 kJ $mole^{-1}$ as an estimate for the σ bond energy of ethene, the portion of the double bond energy attributed to the π bond would be 237 kJ $mole^{-1}$. We conclude that the π bond is substantially weaker than the σ bond.

Classification of Alkenes

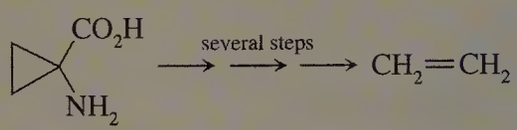
Alkyl groups bonded to the sp^2-hybridized carbon atoms of alkenes affect the stability of a double bond in an alkene. The chemical reactivity of alkenes is also affected by the number of alkyl groups bonded to the sp^2-hybridized carbon atoms. For these reasons it is useful to classify alkenes by the number of alkyl groups attached to the C=C structural unit. This feature is called the **degree of substitution**. An alkene that has a single alkyl group attached to the sp^2-hybridized carbon atom of the double bond is **monosubstituted**. An alkene whose double bond is at the end of a chain of carbon atoms is also sometimes called a terminal alkene. Alkenes that have two, three, and four alkyl groups bonded to the carbon atoms of the double bond are **disubstituted**, **trisubstituted**, and **tetrasubstituted**, respectively.

monosubstituted:	$RCH=CH_2$		
disubstituted:	$RCH=CHR$	or	$R_2C=CH_2$
trisubstituted:	$R_2C=CHR$		
tetrasubstituted:	$R_2C=CR_2$		

Ethylene—The Simplest Hormone?

Hormones are not a single structural class of substances, but rather a large group of compounds with substantial structural diversity. Hormones act as messengers that allow various tissues in multicellular organisms to communicate with one another. Hence, hormones regulate many biological processes.

Although most known hormones are found in animals, hormones are also present in plants. The alkene ethylene is a hormone produced in small amounts in many fruits by a series of steps beginning with an amino acid that contains a cyclopropane ring.



Ethylene stimulates the ripening process. Unripened fruit arrives in the warehouse after being picked green and is exposed to ethylene. To avoid ripening during transport, the fruit is stored in ventilated containers. This decreases the concentration of ethylene and retards the ripening process.

Some fruits can be ripened in the home by placing them in a partially enclosed container that allows some buildup of ethylene in the air around the fruit. Also, fruit that has started to ripen helps to ripen the remaining fruit.

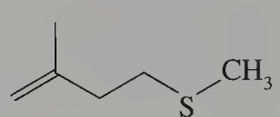

ethylene

Problem 6.1

The C—Cl bond energies in chloroethane and vinyl chloride ($CH_2=CHCl$) are 341 kJ mole^{-1} (83 kcal mole^{-1}) and 368 kJ mole^{-1} (88 kcal mole^{-1}), respectively. Explain this difference. The C—Cl bond length in chloroethane is 178 pm. Predict the C—Cl bond length in vinyl chloride.

Problem 6.2

The urine of the red fox contains a scent marker that is an unsaturated thioether. Classify the degree of substitution of the double bond of the scent marker.

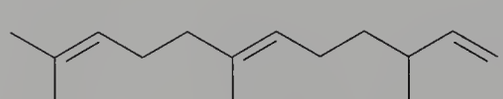


Sample Solution

The compound contains a terminal double bond. The terminal carbon atom has two hydrogen atoms bonded to it. The other carbon atom of the double bond is bonded to a CH_3 group and a CH_2 unit. Thus, the compound contains a disubstituted double bond.

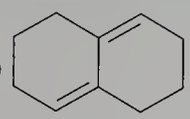
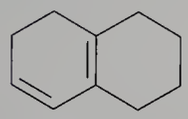
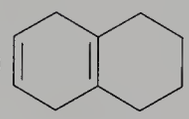
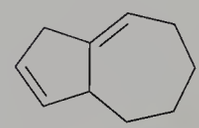
Problem 6.3

Classify each of the three double bonds of farnesene, a compound found in the waxy coating of apples.



Problem 6.4

Classify each double bond in the following isomeric dienes. Which compounds contain conjugated double bonds?

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

6.3 Unsaturation Number

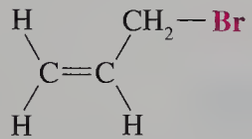
A double bond decreases the number of hydrogen atoms in a molecule by two compared to the corresponding alkane. The general formula of an alkene is C_nH_{2n}, compared to the alkane general formula C_nH_{2n+2}. (Alkynes have *four* fewer hydrogen atoms than alkanes because they have one more π bond than alkenes.) We recall that each ring of a cyclic compound also decreases the number of hydrogen atoms by two. Thus, the molecular formula of an organic compound tells us the combined number of π bonds and rings. We arrive at this information by calculating the **degree of unsaturation**, which equals the number of π bonds and rings. This is done in three steps.

1. Determine the number of hydrogen atoms in an alkane with the same number of carbon atoms.
2. Subtract the actual number of hydrogen atoms in the compound from the number in the alkane.
3. Divide the difference by two to obtain the degree of unsaturation, or unsaturation number.

A formula that gives the numerical result is

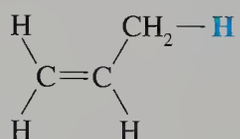
$$\text{unsaturation number} = \frac{[2(\text{no. of C atoms}) + 2] - \text{no. of H atoms}}{2}$$

The unsaturation number can be calculated for molecules containing atoms other than carbon. Because a halogen atom is monovalent, it is regarded as a replacement for hydrogen. Add the number of halogen atoms and hydrogen atoms, then use that quantity in place of the number of hydrogen atoms in the formula. For example, the molecular formula of 3-bromo-1-propene is C_3H_5Br. To calculate the unsaturation number, use a molecular formula with hydrogen replacing bromine, giving C_3H_6.



3-bromo-1-propene

replacing Br by H gives



The unsaturation number of the compound, obtained by substitution into the formula, is 1.

$$\text{unsaturation number} = \frac{[2(3) + 2] - 6}{2} = 1$$

We can also calculate the unsaturation number for compounds that contain divalent oxygen atoms. Oxygen atoms are not involved in calculating the degree of

unsaturation because they can be "removed" from a structure without changing the number of bonds to hydrogen. For example, when we mentally remove the oxygen atom from dimethyl ether and form a carbon–carbon bond to give ethane, there is no change in the number of hydrogen atoms. Similarly, we can mentally remove the oxygen atom from ethanol and form a carbon–hydrogen bond to give ethane. Thus, dimethyl ether and ethanol have the same degree of unsaturation as ethane.

$CH_3—O—CH_3$ removing oxygen gives $CH_3—CH_3$

dimethyl ether

$CH_3—CH_2—OH$ removing oxygen gives $CH_3—CH_2—H$

ethanol

The formula for determining the unsaturation number of nitrogen-containing compounds is modified for the number of bonds that nitrogen forms. Nitrogen compounds have one more hydrogen atom (per nitrogen atom) than a hydrocarbon with an equal number of carbon atoms. Compare the number of hydrogen atoms in ethane and ethanamine.

$CH_3—CH_2—NH_2$ ethanamine (C_2H_7N)

$CH_3—CH_2—H$ ethane (C_2H_6)

The formula to calculate the degree of unsaturation is easily modified to include the effect of the number of nitrogen atoms.

$$\text{unsaturation number} = \frac{[2(\text{no. of C atoms}) + 2] + \text{no. of N atoms} - \text{no. of H atoms}}{2}$$

Problem 6.5

Caryophyllene, which is responsible for the odor of oil of cloves, contains 15 carbon atoms. The compound has two rings and two double bonds. What is the molecular formula for caryophyllene?

Sample Solution

For $n = 15$, the number of hydrogen atoms for a saturated compound without rings is 32. Each ring and each double bond results in a reduction of two hydrogen atoms. Thus the total number of hydrogen atoms is:

$$\text{number of hydrogen atoms} = 32 - 2(\text{no. of rings}) - 2(\text{no. of double bonds})$$

$$= 32 - 2(2) - 2(2) = 24$$

The molecular formula is $C_{15}H_{24}$.

Problem 6.6

Based on its location in the periodic table, how should sulfur be treated in the calculation of the degree of unsaturation of a sulfur-containing organic compound?

Problem 6.7

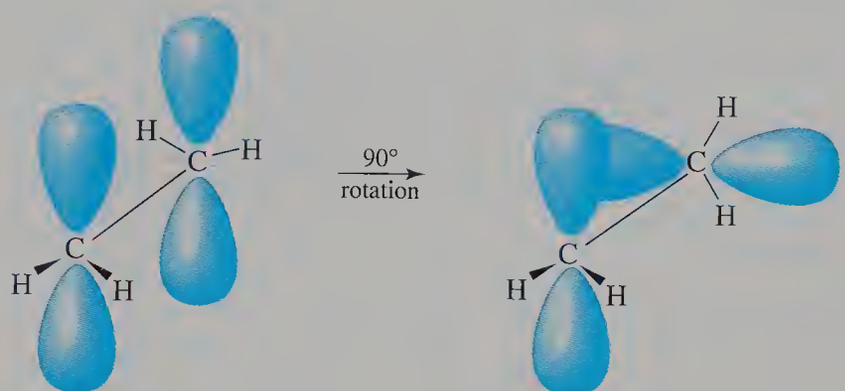
Calculate the unsaturation number for each of the following.

(a) $C_{10}H_{16}$ (b) $C_8H_{10}Br_2$ (c) $C_6H_6O_3$ (d) $C_5H_6N_2$

6.4 Geometric Isomerism

We know that free rotation around carbon–carbon single bonds is fast at room temperature (Section 4.11). Therefore, alkanes can exist in many conformations. Free rotation does not occur around the carbon–carbon double bond of an alkene at room temperature because of its π bond, which forms by side-by-side overlap of two 2*p* orbitals. About 240 kJ mole^{-1} (57 kcal mole^{-1}) is required to break a π bond (Figure 6.2). This quantity is the difference between the bond dissociation energies of a carbon–carbon double bond and a carbon–carbon single bond.

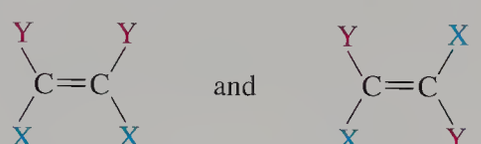
FIGURE 6.2 Rotation About the π Bond
In order for rotation to occur about a carbon–carbon double bond, the π bond must break. Loss of overlap between parallel *p* orbitals requires about 240 kJ mole^{-1} (57 kcal mole^{-1}).



p orbitals are parallel — *p* orbitals are perpendicular

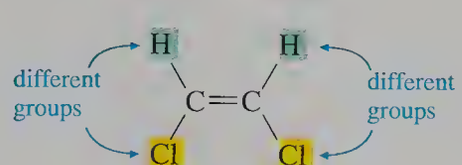
Alkenes with the same molecular formula and the same connectivity of atoms can exist as stereoisomers. These isomers differ because groups bonded to the double bond have different spatial arrangements with respect to each other. These compounds are called **geometric isomers** or cis-trans isomers. Such isomers have different **configurations**.

Consider an alkene whose formula is CXY=CXY. When we draw a more detailed structural formula, we find that two representations are possible.



These two structures represent different molecules (Figure 6.3). In the structure on the left, two X groups are on the same "side" of the molecule. This is the cis isomer. In the structure on the right, the Xs are on opposite "sides" of the molecule. It is called the trans isomer.

Cis and trans isomers are possible only if an alkene has two different atoms or groups of atoms attached to each double-bonded carbon atom. For example, in 1,2-dichloroethene, each unsaturated carbon atom has a chlorine atom and a hydrogen atom attached to it. These groups are different, and both cis and trans isomers are possible.



1,2-dichloroethene

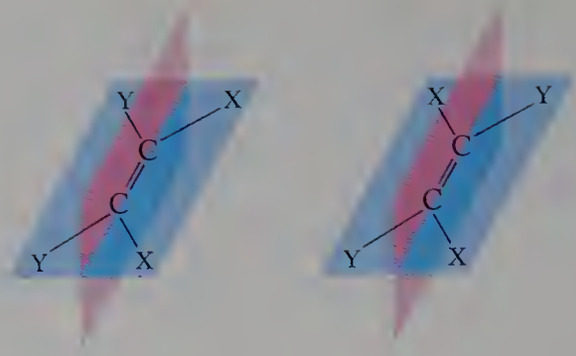
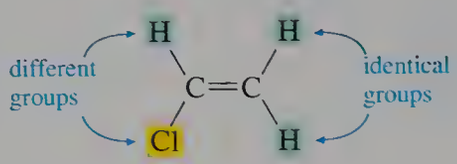
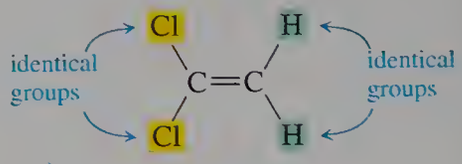


FIGURE 6.3 Geometric Isomerism of Alkenes
(a) The two X groups are on the same side of the plane that is placed perpendicular to the plane containing the molecule. This is the *cis* isomer.
(b) The two X groups are on the opposite sides of the plane that is placed perpendicular to the plane containing the molecule. This is the *trans* isomer.

If one of the unsaturated carbon atoms is attached to two identical groups, cis-trans isomerism is not possible. For example, neither chloroethene nor 1,1-dichloroethene can exist as cis and trans geometric isomers.

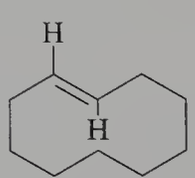


chloroethene

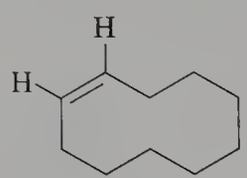


1,1,-dichloroethene

Cycloalkenes most commonly have the cis configuration, especially in small and medium-sized ring compounds. There are not enough carbon atoms within the ring to bridge the two carbon atoms of the double bond in the trans configuration without introducing considerable strain energy. Both *cis*- and *trans*-cyclooctene are stable compounds at room temperature, but the cis isomer is the more stable by approximately 40 kJ mole^{-1}. With an increasing number of methylene units to span the two carbon atoms of the double bond, the strain of the trans isomer becomes less severe. The isomeric cyclododecenes are of comparable stability.



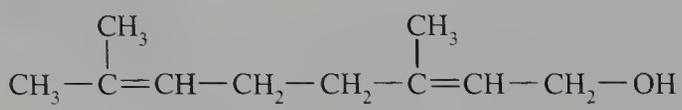
trans-cyclodecene



cis-cyclodecene

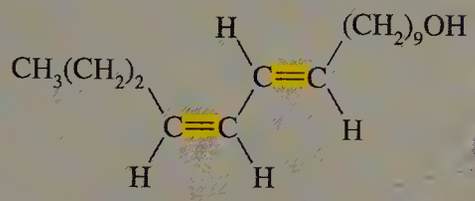
Problem 6.8

Is cis-trans isomerism possible around either of the double bonds of geraniol, a natural oil?



Geometric Isomers and the Sex Life of Moths

We recall that pheromones are released by some animals to transmit information within the species, but not to other species. Some pheromones are sex attractants used to communicate between male and female. The female usually emits the pheromone, and the male responds by seeking the female. Pheromones are effective in amounts as little as 1 picogram (pg; 1 pg = 10^{-12} g).



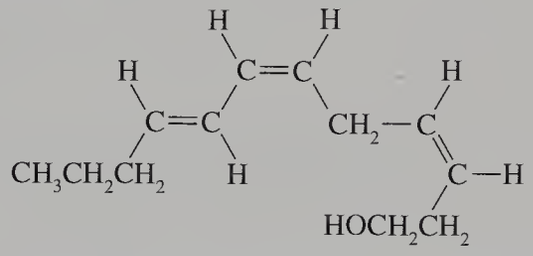
The female silk-worm moth secretes bombykol, a pheromone that attracts male moths. Bombykol is a diene that has both trans and cis arrangements of its double bonds. We see that bombykol contains a trans double bond at C-10 and a cis double bond at C-12, numbered from the carbon atom bearing the hydroxyl group. This is called a trans-cis geometric isomer.

bombykol

Three other geometric isomers (cis-cis, cis-trans, and trans-trans) are possible. They have been synthesized in the laboratory, but do not attract the male silkworm moth. This lack of biological activity suggests that recognition of shape is an important feature of the cell-surface receptor molecules that interact with the pheromone.

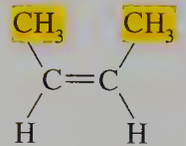
Problem 6.9

Indicate the geometry around the double bonds in the following compound, a trail pheromone of termites. (The chain is numbered starting from the carbon atom with the hydroxyl group.) How many geometric isomers are possible for the structure?

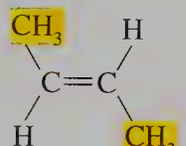


6.5 The *E,Z* Designation of Geometric Isomers

In the previous section, the terms cis and trans were applied to denote the relationship of two substituents in 1,2-dichloroethene, a disubstituted alkene. This type of nomenclature can easily be used for any disubstituted alkenes. Two examples are *cis*-2-butene and *trans*-2-butene.



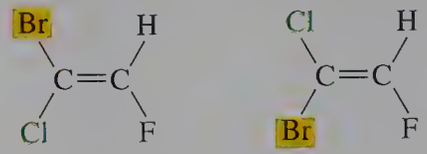
cis-2-butene



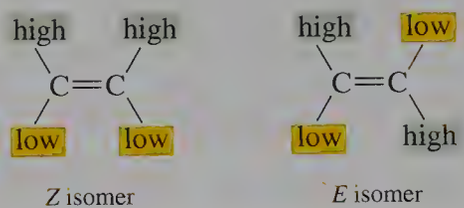
trans-2-butene

However, the cis and trans notation does not describe isomeric trisubstituted and tetrasubstituted alkenes because there is no longer a simple reference giving the

relationship of groups to one another. For example, even the following relatively simple compounds cannot be designated as cis and trans isomers.



We can distinguish the above isomers and all other tri- and tetrasubstituted alkenes by the ***E,Z* system** of nomenclature. The *E,Z* system uses **sequence rules** to assign priorities to the groups bonded to the atoms of the double bond of any alkene. The two groups bonded to each sp^2-hybridized carbon atom are designated low priority and high priority. If the higher priority groups on each carbon atom are on the same side of the double bond, the alkene is the *Z* isomer (German *zusammen*, together). If the higher priority groups on each carbon atom are on opposite sides of the double bond, the alkene is the *E* isomer (German *entgegen*, opposite).



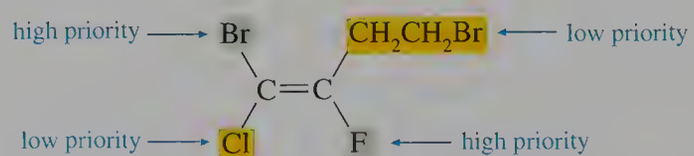
Z isomer *E* isomer

Sequence Rules

The priorities of groups are assigned by a series of rules proposed by Cahn, Ingold, and Prelog in 1964. The first rule is

1. If two atoms with different atomic numbers are directly attached to a double bond, the atom with the higher atomic number receives a higher priority.

The priority order of some common elements is Br > Cl > F > O > N > C> D > H. Applying these priorities to the following alkene, which contains several halogen atoms, allows us to make the *E,Z* assignment.



E isomer

The atomic number of bromine is greater than that of chlorine. Therefore, bromine has a higher priority than chlorine. A fluorine atom has a higher priority than a CH_2CH_2Br group, although the reason for this assignment may not be immediately obvious. The priority of a group depends on the atomic number of the atom directly bonded to the carbon atom of the double bond. In this case, we have to compare carbon to fluorine. Because fluorine has a higher atomic number than carbon, it has the higher priority.

The atoms bonded to a double-bonded carbon atom frequently have the same atomic number, as in the case of various alkyl groups. In such cases, we rely on the second rule, called "the first point of difference."

2. If the atoms directly attached to the carbon atom of the double bond have the same atomic number, the second, third, and farther atoms are considered until a difference is found. Then apply rule 1.

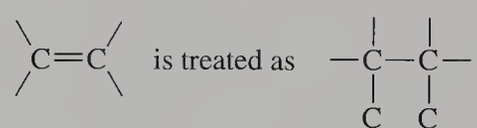
First, let's consider the methyl and ethyl groups. They are equivalent at the first directly bonded atom: a carbon atom in each case. The carbon atom of a methyl group is bonded to three hydrogen atoms. The carbon of the ethyl group is bonded to another carbon atom and two hydrogen atoms. Thus, the ethyl group has a higher priority than a methyl group.

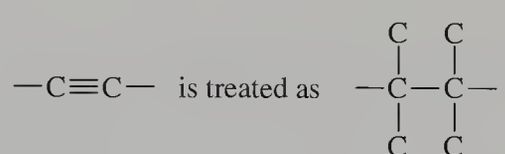
Sometimes the point of first difference is at some distance from the sp^2-hybridized carbon atom. Consider a $-CH_2CH_2OH$ group and a propyl group. Both are equivalent by the first rule of the directly bonded atom. They are also identical at the second atom. A difference is not found until the third atom. Because oxygen has a higher priority than carbon, the $-CH_2CH_2OH$ group has a higher priority than a propyl group.

If the first point of difference is not the type of atom but rather the number of those atoms, then the group with the greater number of high-priority atoms is assigned the higher priority. Based on this consideration, the order of alkyl groups is tert-butyl > isopropyl > ethyl > methyl.

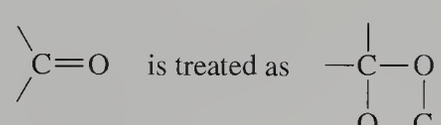
The third rule of assigning priorities of groups deals with multiple-bonded atoms.

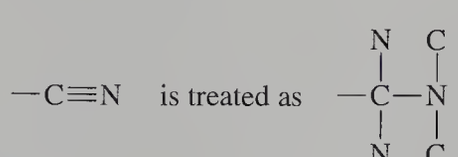
3. A multiple bond is considered equivalent to the same number of single bonds to like atoms. Thus, a double bond is counted as two single bonds for both of the atoms involved. The same principle is used for a triple bond.





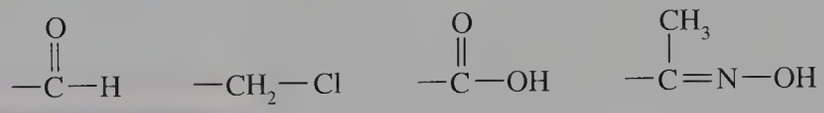
Multiple bonds to atoms other than carbon are also "doubled" or "tripled". For example, a carbonyl group is considered a carbon atom with two single bonds to oxygen atoms, but also an oxygen atom bonded to two carbon atoms. A nitrile group is considered a carbon atom with three single bonds to a nitrogen atom, but also a nitrogen atom bonded to three carbon atoms.





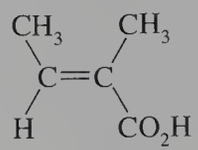
Problem 6.10

Rank the following sets of substituents in order of increasing priority according to the Cahn–Ingold–Prelog rules.



Problem 6.11

Tiglic acid, found in some natural oils, has the following structure. Is it an *E* or a *Z* isomer?

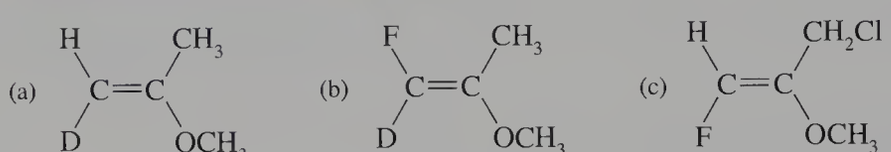


Sample Solution

The methyl group on the carbon atom on the left side of the double bond has a higher priority than the hydrogen atom. However, the methyl group on the right side of the double bond has a lower priority than the CO_2H group. The higher priority groups, CH_3 and CO_2H, are in an *E* arrangement.

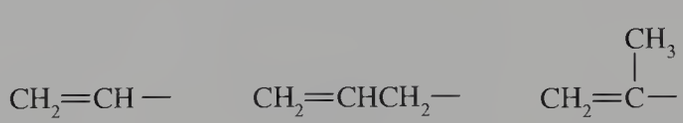
Problem 6.12

Assign *E* or *Z* to each of the following structures.



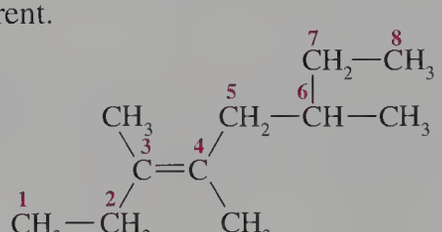
6.6 Nomenclature of Alkenes

The IUPAC rules for naming alkenes are similar to those for alkanes, but the position of the double bond in the chain and the geometric arrangement of substituents around the double bond must be indicated. As in the case of some simple alkyl groups, a few common names are allowed as part of an IUPAC name, including vinyl, allyl, and isopropenyl.



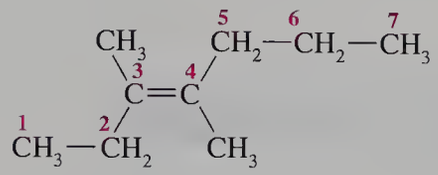
The IUPAC rules are

1. The longest continuous chain that contains the double bond is called the parent.



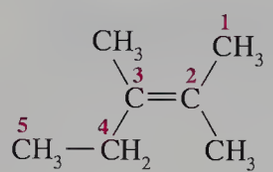
There are eight carbon atoms in this chain, so it is an octene.

2. The parent chain is given the same stem name as if it were an alkane, but the suffix *-ene* replaces *-ane*. The parent name of the structure shown above, for example, is octene.
3. The carbon atoms are numbered consecutively from the end nearer the double bond. The number of the first carbon atom of the double bond is used as a prefix to the parent name, joined by a hyphen.



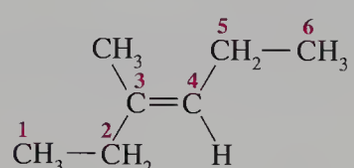
This is a substituted 3-heptene, not a substituted 4-heptene.

4. Alkyl groups and other substituents are named, and their positions on the chain are identified, according to the numbering established by rule 3. Names and numbers are prefixed to the parent name.



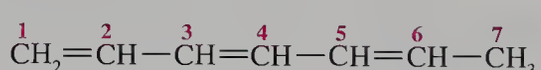
This is 2,3-dimethyl-2-pentene, not 3,4-dimethyl-3-pentene.

5. If the compound can exist as an *E* or *Z* isomer, the appropriate prefix followed by a hyphen is placed within parentheses in front of the name.



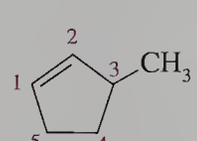
This is (*E*)-3-methyl-3-hexene.

6. If the compound contains more than one double bond, specify the location of each double bond by a number. A prefix to *-ene* indicates the number of double bonds.

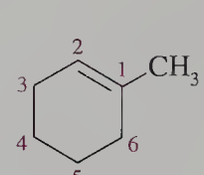


1,3,5-heptatriene

7. Name cycloalkenes by numbering the ring to give the double-bonded carbon atoms the numbers 1 and 2. Choose the direction of numbering so that the first substituent on the ring receives the lower number. The position of the double bond is not given because it is known to be between the C-1 and C-2 atoms.

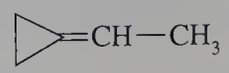


3-methylcyclopentene

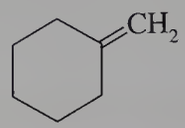


1-methylcyclohexene

8. Compounds with a carbon–carbon double bond positioned between a ring carbon atom and a substituent on the ring are named using **-ylidene** to name the group as a substituent. However, the $=CH_2$ group is named methylene rather than methylidene.



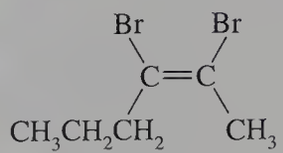
ethylidenecyclopropane



methylenecyclohexane

Problem 6.13

Name the following compound.



Problem 6.14

Draw the structures of the following isomeric compounds.

(a) 1-methyl-1,4-cyclohexadiene
(b) 3-methyl-1,4-cyclohexadiene
(c) 1-methyl-1,3-cyclohexadiene
(d) 2-methyl-1,3-cyclohexadiene
(e) 5-methyl-1,3-cyclohexadiene

Problem 6.15

Draw the structure of each of the following compounds.

(a) (*E*)-1,3-dichloro-2-methyl-3-hexene
(b) 3,3-dimethylcyclohexene
(c) 5-bromo-2,3-dimethyl-2-hexene
(d) (*Z*)-4-bromo-3-methyl-3-heptene

6.7 Physical Properties of Alkenes

The physical properties of the homologous series of alkenes (C_nH_{2n}) are similar to those of the homologous series of alkanes (C_nH_{2n+2}). Alkenes have densities ranging from 0.6 to 0.8 g cm^{-3} (Table 6.1). Alkenes are either nonpolar or very slightly polar. Thus, they are insoluble in water but soluble in nonpolar solvents such as hexane. They are also soluble in diethyl ether and halogenated solvents.

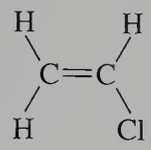
Polarity of Alkenes

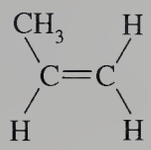
Most alkenes are weakly polar. For example, propene has a dipole moment of 0.3 D. The dipole moments of alkenes containing substituents with bond moments of known direction can be used to establish the bond moment for an sp^3–sp^2 carbon–carbon bond. The dipole moment of chloroethene is 1.4 D. Because chlorine is more electronegative than carbon, the chlorine atom has a partial negative charge. The net dipole moment of *trans*-1-chloropropene is 1.7 D. It results from the cumulative effect of the carbon–carbon single bond and the carbon–chlorine bond. Because the

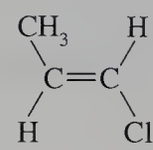
TABLE 6.1
Densities of Alkenes

Alkene	*Density, d^{20} ($g\ cm^{-1}$)*
1-pentene	0.6405
cis-2-pentene	0.6556
trans-2-pentene	0.6482
2-methyl-2-butene	0.662
3-methyl-1-butene	0.648
1-hexene	0.675
2,3-dimethyl-2-butene	0.705
1-heptene	0.698
1-octene	0.716
1-nonene	0.731
1-decene	0.743

dipole moment of *trans*-1-chloropropene is larger than that of 1-chloroethene, the two contributing bond moments in *trans*-1-chloropropene must reinforce each other.


chloroethene
(1.4 D)


propene
(0.3 D)


trans-1-chloropropene
(1.7 D)

Because the bond moments of *trans*-1-chloropropene point in the same direction, the methyl group donates electron density to the sp^2-hybridized carbon atom. We recall that the sp^2-hybridized carbon atom of the double bond has a larger percent s character than the sp^3-hybridized carbon atom of the alkyl group. Thus, the electrons in the σ bond between the methyl group and the double-bonded carbon atom are drawn toward the sp^2-hybridized carbon atom. Other alkyl groups behave similarly.

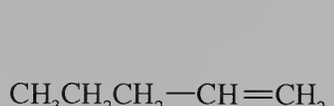
The dipole moments of substituted alkenes depend on the geometric arrangement of the groups. *trans*-2-Butene has no dipole moment because the bond moments of the two bonds to alkyl groups are opposed and cancel. In contrast, the dipole moment of *cis*-2-butene is 0.3 D because the bond moments of the two bonds to alkyl groups do not cancel.

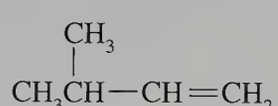
Boiling Points

TABLE 6.2
Boiling Points of Alkenes

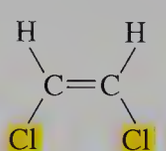
Alkene	*Boiling point (°C)*
ethene	−103.7
propene	−47.4
1-butene	−6.3
2-methylpropene	−6.9
cis-2-butene	+3.7
trans-2-butene	+0.9
1-pentene	30.0
cis-2-pentene	36.9
trans-2-pentene	36.4
1-hexene	63.5
1-heptene	93
1-octene	122.5
1-nonene	146
1-decene	171

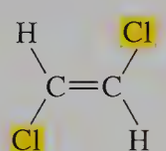
Alkenes that contain fewer than five carbon atoms are gases at room temperature. The boiling points of the alkenes, like those of alkanes, increase with an increasing number of carbon atoms because the London forces increase (Table 6.2). And, like alkanes, alkenes with branched alkyl groups have lower boiling points. Branched alkenes have more compact structures than the unbranched isomers, and thus less intermolecular contact, which diminishes the intermolecular London forces.


bp 30 °C


bp 25 °C

Because geometric isomers have different polarities, their boiling points differ. For example, the boiling points of *cis*- and *trans*-1,2-dichloroethylenes are 60 and 47 °C, respectively. The two C—Cl bond moments of the trans isomer cancel each other, so the compound has no dipole moment. In contrast, the cis isomer has a net dipole moment because the two C—Cl bond moments reinforce each other. Therefore, the cis isomer is polar and has the higher boiling point.


cis-1,2-dichloroethene
bp 60 °C


trans-1,2-dichloroethene
bp 47 °C

6.8 Oxidation of Alkenes

The combustion of alkenes is not a synthetic or commercially useful reaction. (More specific reactions that partially oxidize alkenes and are synthetically useful are considered in Chapter 7.) However, we recall that the heats of combustion can be used to compare the stability of isomeric alkanes as well as isomeric cycloalkanes. The heats of combustion can also be used to compare the thermodynamic stabilities of isomeric alkenes because isomers form the same number of moles of CO_2 and H_2O. We recall that ΔG_c° is the actual criterion of thermodynamic stability, but we can use ΔH_c° values because the S° values for isomers do not normally differ substantially—that is, $\Delta H_c^\circ \approx \Delta G_c^\circ$.

The heats of combustion of alkenes having the formula C_4H_8 are shown in Figure 6.4. We recall that the thermodynamically more stable compound releases less heat energy in the combustion reaction. Therefore, the order of increasing stability of these isomers is

1-butene < *cis*-2-butene < *trans*-2-butene < 2-methylpropene

——— increasing stability (decreasing ΔH_c°) ⟶

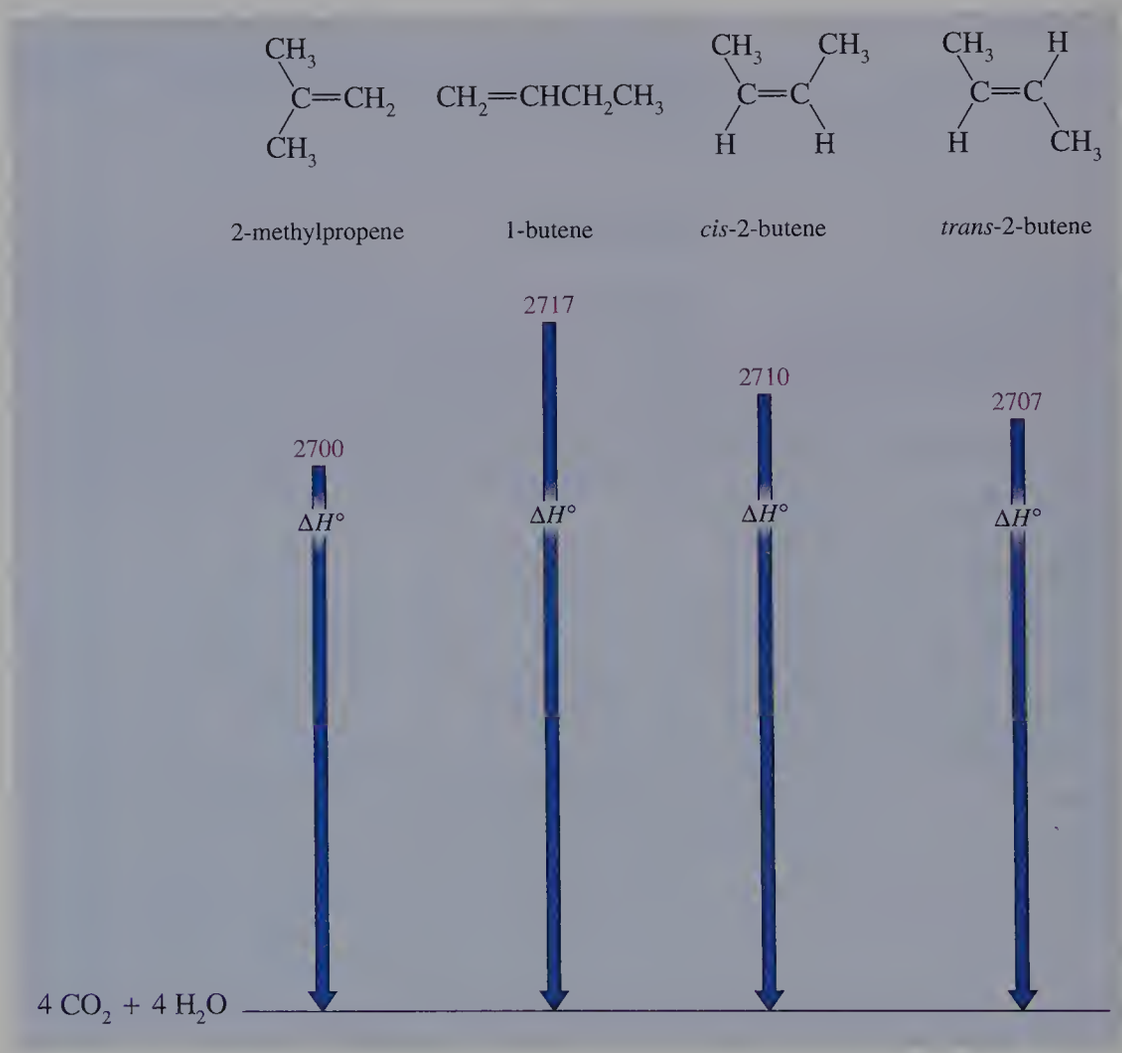
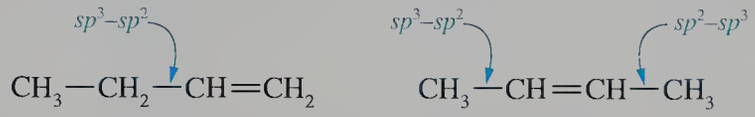


FIGURE 6.4 Heats of Combustion of Isomeric Butenes
The heats of combustion of the isomeric butenes are plotted on the vertical axis in kJ mole^{-1}. All compounds are at higher energy than the common products, which are carbon dioxide and water.

We can explain the relative stabilities of these alkenes using concepts we have already introduced. We recall that a branched alkane is more stable than the isomeric unbranched alkane. For example, 2-methylpropane is more stable than butane. When we examine the relative stabilities of the isomeric C_4H_8 alkenes, we find that the branched isomer is the most stable. However, the principal structural feature that makes one alkene more stable than another isomeric alkene is the degree of substi-

tution. For example, 1-butene, a monosubstituted alkene, is less stable than the disubstituted alkenes *cis*-2-butene and *trans*-2-butene. The sp^3-hybridized carbon atoms of alkyl groups release electron density to the sp^2-hybridized carbon atoms of the alkene. The double bond is stabilized by this effect. The two alkyl groups of *cis*- and *trans*-2-butene release more electron density to the double bond via the two sp^3–sp^2 bonds than the one alkyl group of 1-butene. Of course, 2-methylpropene is also disubstituted, but being branched gives it more stability than *cis*- and *trans*-2-butene.



What is responsible for the difference in the stabilities of *cis*- and *trans*-2-butenes, which have the same carbon skeleton? When we analyze the thermodynamic stabilities of many acyclic alkenes, we find that trans alkenes are more stable than cis alkenes. This energy difference is the result of a steric effect. In a cis alkene, two alkyl groups are close enough to each other to generate van der Waals repulsion (Figure 6.5). This steric effect is related to the intramolecular repulsion found in the eclipsed conformation of butane (Section 4.13). The hydrogen atoms of the two methyl groups in *cis*-2-butene are arranged in a 1,6 relationship, and we expect them to be "touching". The difference in stabilities of cis and trans isomers becomes more pronounced as the size of the alkyl groups increases.

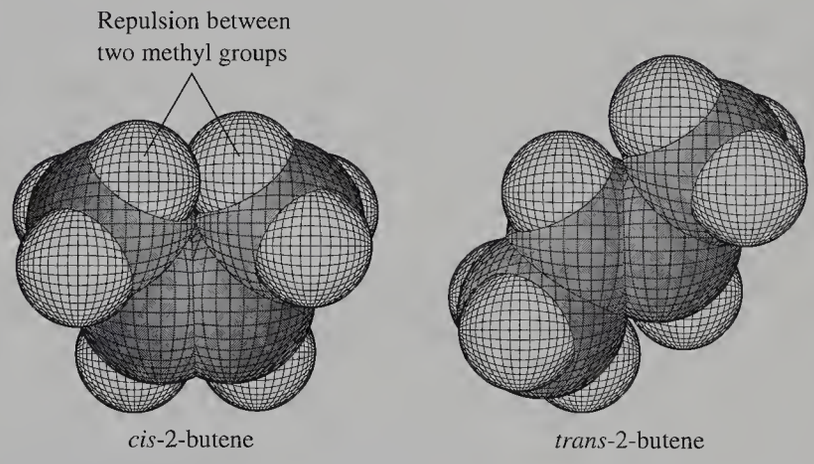
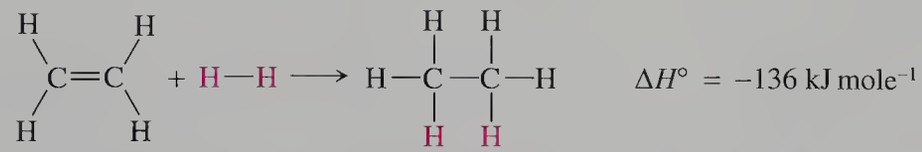


FIGURE 6.5 Steric Effects and Stability of Alkenes
Some of the hydrogen atoms of the two methyl groups in *cis*-2-butene are within their respective van der Waals radii. These atoms are in a 1,6 relationship. Using Newman's rule of 6, the hydrogen atoms are predicted to sterically interfere with each other. There is no steric effect in the trans isomer.

6.9 Reduction of Alkenes

Alkenes and cycloalkenes combine with hydrogen gas in an addition reaction to give saturated compounds. In this process the alkene is reduced. The reaction is also called **hydrogenation**. The hydrogenation of an alkene is an exothermic process, but the reaction has a high activation energy, so it occurs slowly even at high temperatures.

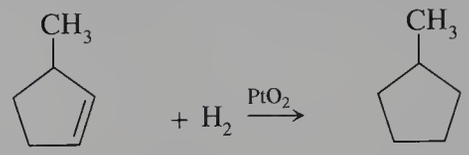


However, the hydrogenation of an alkene, such as 1-octene to octane, occurs rapidly at room temperature in the presence of certain transition metal catalysts. One such catalyst is palladium dispersed on carbon (Pd/C).

The double bond is changed into a single bond.

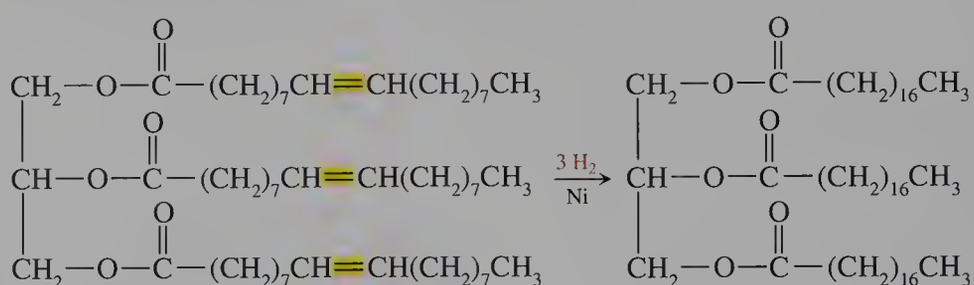
$$CH_3(CH_2)_5CH{=}CH_2 \xrightarrow{Pd/C} CH_3(CH_2)_5CH_2{-}CH_3$$

Adams catalyst, PtO_2, is also an effective catalyst for the hydrogenation of alkenes. Under the reaction conditions, hydrogen gas reduces PtO_2 to a finely divided colloidal suspension of platinum metal, which is the active catalyst.



3-methylcyclopentene methylcyclopentane

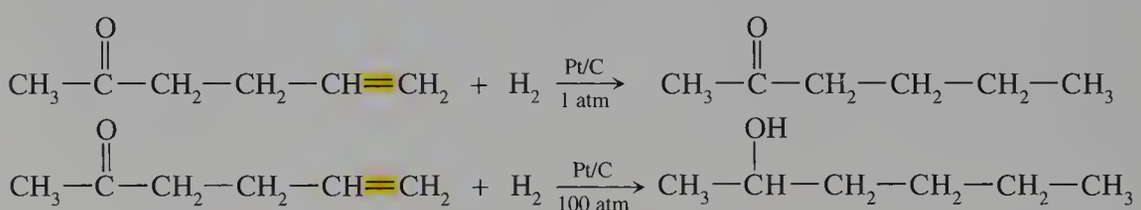
The catalytic hydrogenation of alkenes can also be carried out with a finely dispersed form of nickel known as **Raney nickel**. It is prepared by treating a nickel–aluminum alloy with aqueous base, which reacts with the aluminum, leaving the finely divided nickel. Hydrogenation reactions using Raney nickel usually require higher temperatures or pressures than those required for palladium or platinum catalysts. However, nickel is less expensive than palladium or platinum, so it is used in industrial processes, such as the conversion of triolein, an oil, into tristearin, a fat.



triolein tristearin

None of these metal hydrogenation catalysts dissolves in organic solvents. The catalytic hydrogenation of alkenes is a heterogeneous reaction, and the solution of the alkene must be stirred or shaken vigorously so that the reactants remain in contact with the dispersed solid phase. Solvents commonly used are ethanol (CH_3CH_2OH) and methanol (CH_3OH).

The conditions used for catalytic hydrogenation of an alkene are too mild to reduce the carbon–oxygen double bond of functional groups such as aldehydes, ketones, carboxylic acids, and esters. Catalytic hydrogenation of alkenes requires an H_2 pressure of only 1 atm, whereas hydrogenation of the carbon-oxygen double bonds of aldehydes or ketones requires pressures in the range of 100 atm. Carboxylic acids or esters react only at very high temperatures.



Regioselectivity of Hydrogenation

A reaction that can produce more than one constitutional isomer from a reactant and gives a predominance of one product is said to be **regioselective**. The hydrogenation

reaction, for example, is regioselective. The rate of catalytic hydrogenation of alkenes depends on the degree of substitution of the double bond. Hydrogenation of monosubstituted and disubstituted alkenes at room temperature occurs rapidly under 1 atm pressure of hydrogen. The hydrogenation of trisubstituted alkenes is slower, and usually requires higher temperatures and higher pressures of hydrogen. Tetrasubstituted double bonds are extremely difficult to hydrogenate. The order of reactivity is

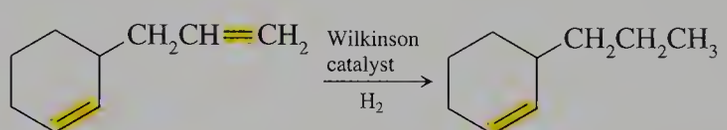
monosubstituted > disubstituted > trisubstituted > tetrasubstituted

These differences in reaction rate make it possible to regioselectively hydrogenate one double bond in a compound with two or more double bonds if their substitution patterns differ substantially. For example, a monosubstituted double bond can be selectively hydrogenated in a compound that also has a trisubstituted or tetrasubstituted double bond.

Although a solution of an alkene must be stirred or shaken so that the alkene will remain in contact with the dispersed solid metal phase in catalytic hydrogenation, the method is widely used because it is easy to isolate the product. The catalyst can be removed by filtration and the solvent evaporated to yield the reduced product.

Homogeneous Catalytic Hydrogenation

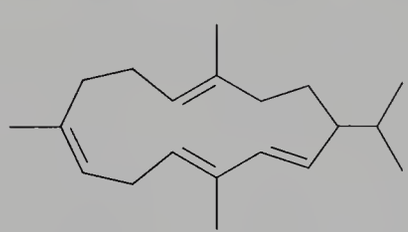
Several homogeneous hydrogenation catalysts have been developed. They cause faster hydrogenation because the reagents remain in continuous contact within the solution. One widely used homogeneous catalyst is $[(C_6H_5)_3P]_3RhClH$, known as the **Wilkinson catalyst**. It does not reduce other functional groups with π bonds such as carbonyl groups, nitro ($—NO_2$), and cyano ($—C{\equiv}N$) under the conditions that reduce alkenes. The most important feature of the Wilkinson catalyst is its regioselectivity. Monosubstituted double bonds can easily be hydrogenated in the presence of disubstituted double bonds.



3-allylcyclohexene 3-propylcyclohexene

Problem 6.16

How many moles of hydrogen gas will react with cembrene, which is present in pine oil? What is the molecular formula of the product?



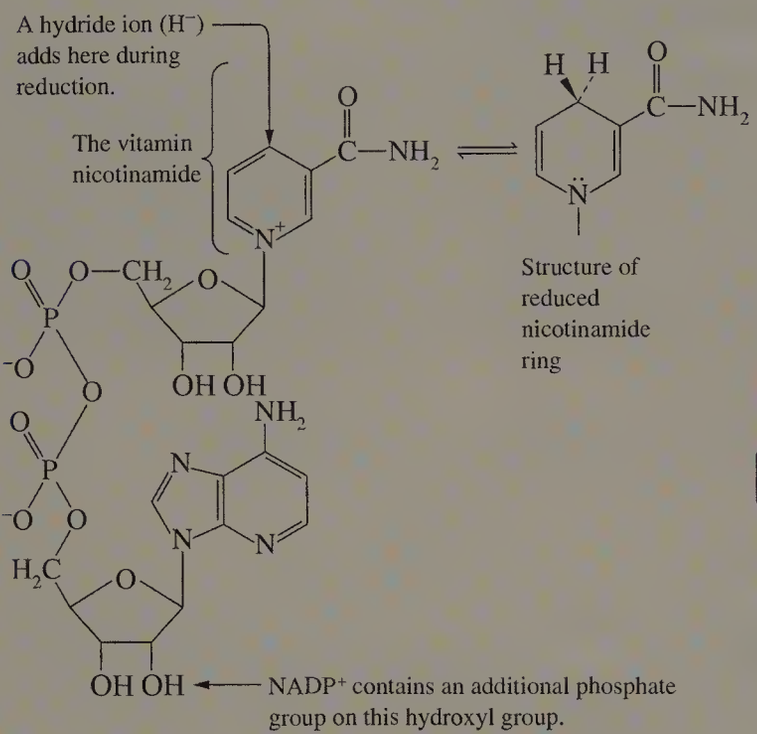
cembrene

Sample Solution

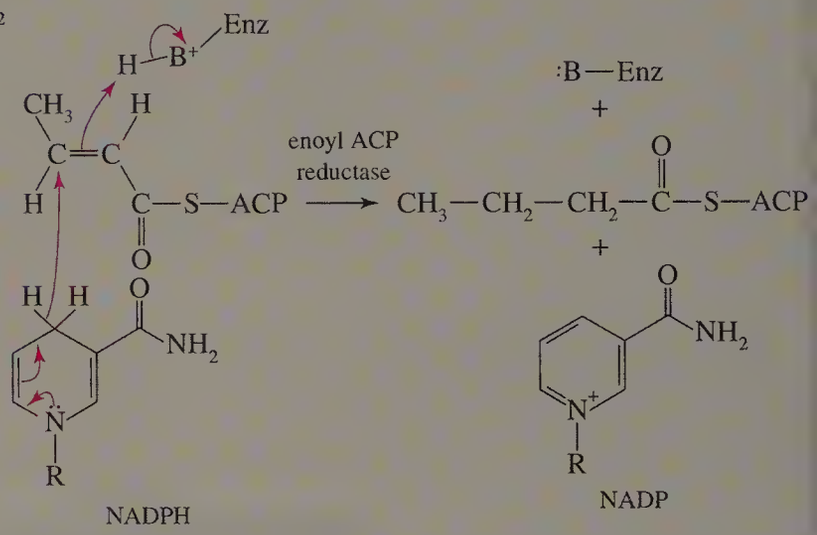
Four moles of hydrogen gas react with the four double bonds. The resulting compound has 14 carbon atoms in the ring, three methyl groups and an isopropyl group for a total of 20 carbon atoms. Because there is a single ring, the unsaturation number is 1 and the number of hydrogen atoms must be two fewer than the number contained in an alkane. For 20 (n) carbon atoms of an alkane there are 42 ($2n + 2$) hydrogen atoms. For the monocyclic compound there are 40 hydrogen atoms. The molecular formula is $C_{20}H_{40}$.

Biological Hydrogenation Reactions

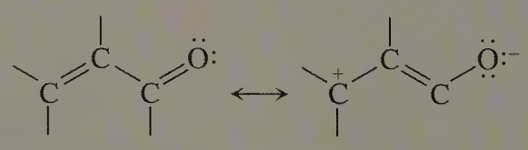
Biological systems reduce carbon–carbon double bonds by homogeneous catalysis, but of course they have neither H_2 nor a Wilkinson catalyst at their disposal. Carbon–carbon double bonds are reduced in cells by the reduced form of either nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH). The structures of these compounds—members of a group called coenzymes—are shown in the figure. Coenzymes act hand in hand with enzymes to carry out specific chemical reactions. NADH and NADPH are sources of hydrogen in the enzymatic reduction of carbon–carbon double bonds. Both coenzymes act by similar mechanisms.



Let's consider the reduction of the double bond in *trans*-Δ^2-butenoic acid. In the bacterium *E. coli*, this molecule is covalently linked as a thioester to a protein called the acyl carrier protein, ACP. So the substrate is really *trans*-Δ^2-butenoyl ACP. The first thing we have to do when we consider any biochemical reactions is solve the "forest and trees problem". That is, we must identify the functional group undergoing change. We are considering hydrogenation, and there is a carbon–carbon double bond in the substrate. It will be reduced, but by what source of hydrogen? NADPH provides one hydrogen as a hydride anion. The reaction occurs by transfer of a hydrogen atom, with its bonding electron pair, from C-4 of the coenzyme to C-3 of the substrate. Because this step adds two electrons to the carbon–carbon bond, the alkene is reduced. The coenzyme, NADPH, loses electrons and is oxidized. When the hydrogen atom and its electron pair add to the double bond, the electron pair of the π bond moves to C-2. This electron pair immediately reacts with an acidic hydrogen atom provided by the enzyme at the active site. This step is an acid–base reaction, not a redox reaction. The overall reaction occurs in one step; that is, it is concerted. The hydrogen atom with its electron pair donated by NADPH and the proton donated by the enzyme provide the equivalent of H_2. Therefore, the enzymatic system is equivalent to the hydrogenation of a carbon–carbon double bond.



We will see in Chapter 7 that a π bond is usually attacked by an electrophile such as a proton. Why then should a hydrogen atom with an electron pair—formally equivalent to a hydride ion—attack a π bond? The carbon–carbon double bond is conjugated with a carbonyl group, which is electron withdrawing. Contributing resonance form 2 indicates how some electron density is withdrawn from the carbon–carbon double bond and makes the C-3 atom susceptible to attack by the hydride ion.



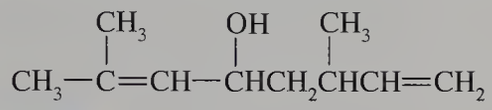
1 2

Problem 6.17

Explain why acetic acid (CH_3CO_2H) and ethyl acetate ($CH_3CO_2CH_2CH_3$) can be used as solvents for catalytic hydrogenation of alkenes.

Problem 6.18

Write the structure obtained by hydrogenation of ipsdienol, a pheromone of the Norwegian spruce beetle, using one equivalent of hydrogen gas and the Wilkinson catalyst.



Problem 6.19

A mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene is obtained in the commercial dimerization of 2-methylpropene. Hydrogenation of the mixture gives a single product. Draw the structures of the alkenes and the product. Explain why a single product forms.

Problem 6.20

Squalene, an intermediate in the biosynthesis of steroids, has the molecular formula $C_{30}H_{50}$. Hydrogenation yields a compound with molecular formula $C_{30}H_{62}$. What is the unsaturation number of squalene? Does the compound contain any rings?

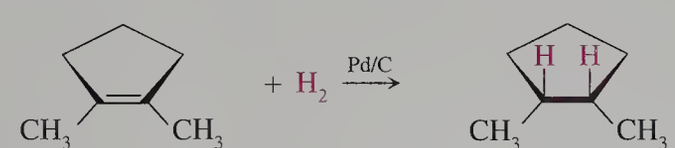
6.10 Mechanism of Catalytic Hydrogenation

The heterogeneous catalytic hydrogenation of alkenes occurs in a series of steps in which hydrogen and the alkene bond to the surface of the metal. In the first step, hydrogen gas is adsorbed onto the surface of the metal catalyst and the H—H bond is broken. Then the alkene forms a complex with the metal in which the π electrons form a coordinate covalent bond with the vacant orbitals of the metal. In subsequent steps, hydrogen atoms add to the carbon atoms of the double bond—probably one atom at a time. The alkene remains attached to the metal surface until both hydrogen atoms are added. Then the reduced product is released.

Stereochemistry of Hydrogenation

The stereochemistry of hydrogenation cannot be determined by studying the reactions of acyclic alkenes such as 1-octene. The product of the hydrogenation of 1-octene is octane, a conformationally flexible molecule. When octene is converted to octane, the hydrogen atoms have added to adjacent carbon atoms, but we cannot tell how the individual atoms approached the plane of the alkene molecule. However, the stereochemistry of hydrogenation *can* be determined with cycloalkenes.

The hydrogenation of 1,2-dimethylcyclopentene produces *cis*-1,2-dimethylcyclopentane. Therefore, hydrogenation of an alkene occurs by the addition of two hydrogen atoms to the same side of the plane of the double bond. The process is called **syn addition**.

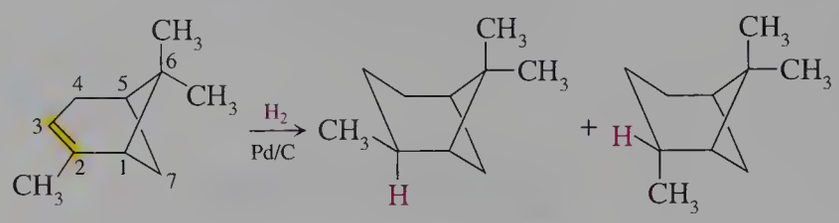


1,2-dimethylcyclopentene *cis*-1,2-dimethylcyclopentane

Syn addition can only occur if the cycloalkene remains attached to the metal surface, allowing the two hydrogen atoms to add to the same side of the double bond.

Stereoselectivity of Hydrogenation

Although catalytic hydrogenation occurs by a syn addition mechanism, the two faces of the planar double bond are not always equivalent. In such cases, the addition of hydrogen could occur at either of the two faces of a molecule, yielding mixtures of stereoisomers. Hydrogenation is **stereoselective**. That is, one of the two stereoisomers forms in greater amount than the other. For example, syn addition of hydrogen to 2,6,6-trimethyl-2-bicyclo[3.1.1]heptene (α-pinene) is highly stereoselective and gives almost 100% cis isomer.

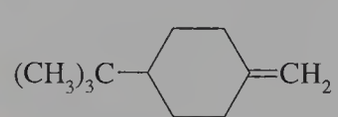


α-pinene | *cis*-pinane (major) | *trans*-pinane (trace)

The stereoselectivity of the reduction of α-pinene, and other alkenes whose two faces differ, is governed by the steric hindrance when the plane of the alkene approaches the catalyst surface. Catalytic hydrogenation occurs at the less hindered face of the reactant. In the case of α-pinene, one of the two methyl groups at the C-6 atom is positioned over the "top" face of the double bond. Thus, the "bottom" face of the double bond is less hindered, and hydrogen adds from that direction. When a hydrogen atom is added from the bottom at the C-2 atom, the methyl group located at that carbon atom is pushed up. In the product, the C-2 methyl group and the C-6 methyl group are on the same side of the six-membered ring, hence the designation cis.

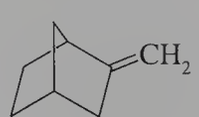
Problem 6.21

Catalytic hydrogenation of the following compound gives a mixture of *cis*- and *trans*-1-*tert*-butyl-4-methylcyclohexanes in a 7:1 ratio. Explain why.



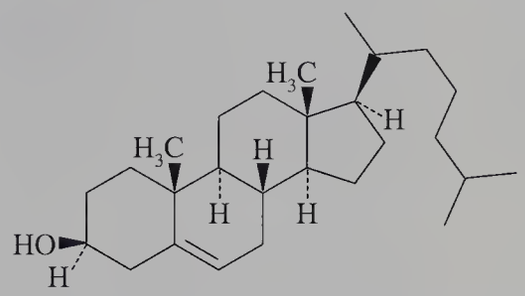
Problem 6.22

Draw the structures of the two products obtained by hydrogenation of the following unsaturated bicyclic compound. Will they be obtained in equal amounts?



Problem 6.23

Predict the stereochemistry of the product obtained by catalytic hydrogenation of cholesterol. The six-membered rings are all in the chair conformation, and the methyl groups at the bridgehead positions are axial. (Refer to Section 4.19 to determine the shape of the steroid.)



6.11 Heats of Hydrogenation

In the hydrogenation of alkenes, the carbon–carbon π bond and the hydrogen–hydrogen bond of the hydrogen molecule break, and two carbon–hydrogen bonds form. The hydrogenation reaction is exothermic because the two carbon–hydrogen bonds formed are stronger than the combined strengths of the bonds broken. The overall heat evolved for the hydrogenation reaction is usually reported as a positive quantity defined as the **heat of hydrogenation** ($\Delta H^\circ_{\text{hydrogn}}$). However, we must remember that ΔH° for the reaction is negative.

Structural Effects on Heats of Hydrogenation

The relative stabilities of isomeric alkenes such as 1-butene, *cis*-2-butene, and *trans*-2-butene can be analyzed by comparing their heats of hydrogenation. This method is possible because the hydrogenation of these alkenes yields the same product (Figure 6.6). The $\Delta H^\circ_{\text{hydrogn}}$ values are easily determined directly from the heat of the hydrogenation reaction. The S°_f values for isomeric alkenes are similar. Therefore, the differences in $\Delta H^\circ_{\text{hydrogn}}$ values for isomeric alkenes are approximately equal to the differences in the $\Delta G^\circ_{\text{hydrogn}}$ values for the isomeric alkenes and are a measure of their relative stabilities.

The heats of hydrogenation of three of the four isomeric C_4H_8 alkenes are shown in Figure 6.6. The thermodynamically more stable compound has the smaller heat of hydrogenation, so we again confirm that the order of increasing stability of the isomers is

1-butene < *cis*-2-butene < *trans*-2-butene

The energy differences as measured by heats of hydrogenation are within the range of experimental error of those obtained from heats of combustion (Section 6.8).

The relative stabilities of nonisomeric alkenes cannot be directly compared using heats of hydrogenation because such alkenes yield different alkanes. However, as shown in Table 6.3, alkenes with similar structures have similar heats of hydrogenation. The heats of hydrogenation of 1-butene and 1-hexene are the same within the range of experimental error. The heat of hydrogenation of a monosubstituted alkene is approximately 126 kJ mole^{-1} (30 kcal mole^{-1}). We saw in Section 6.8 that disubstituted alkenes of the type RCH=CHR are more stable than monosubstituted alkenes. Therefore, they have lower heats of hydrogenation. Furthermore, acyclic trans isomers have lower heats of hydrogenation than cis isomers. In both classes of alkenes, the heats of hydrogenation are within a narrow range for a variety of alkyl groups. Because $\Delta H^\circ_{\text{hydrogn}}$ is reported as a positive quantity, the order of heats of hydrogenation of alkenes is

monosubstituted > disubstituted > trisubstituted > tetrasubstituted

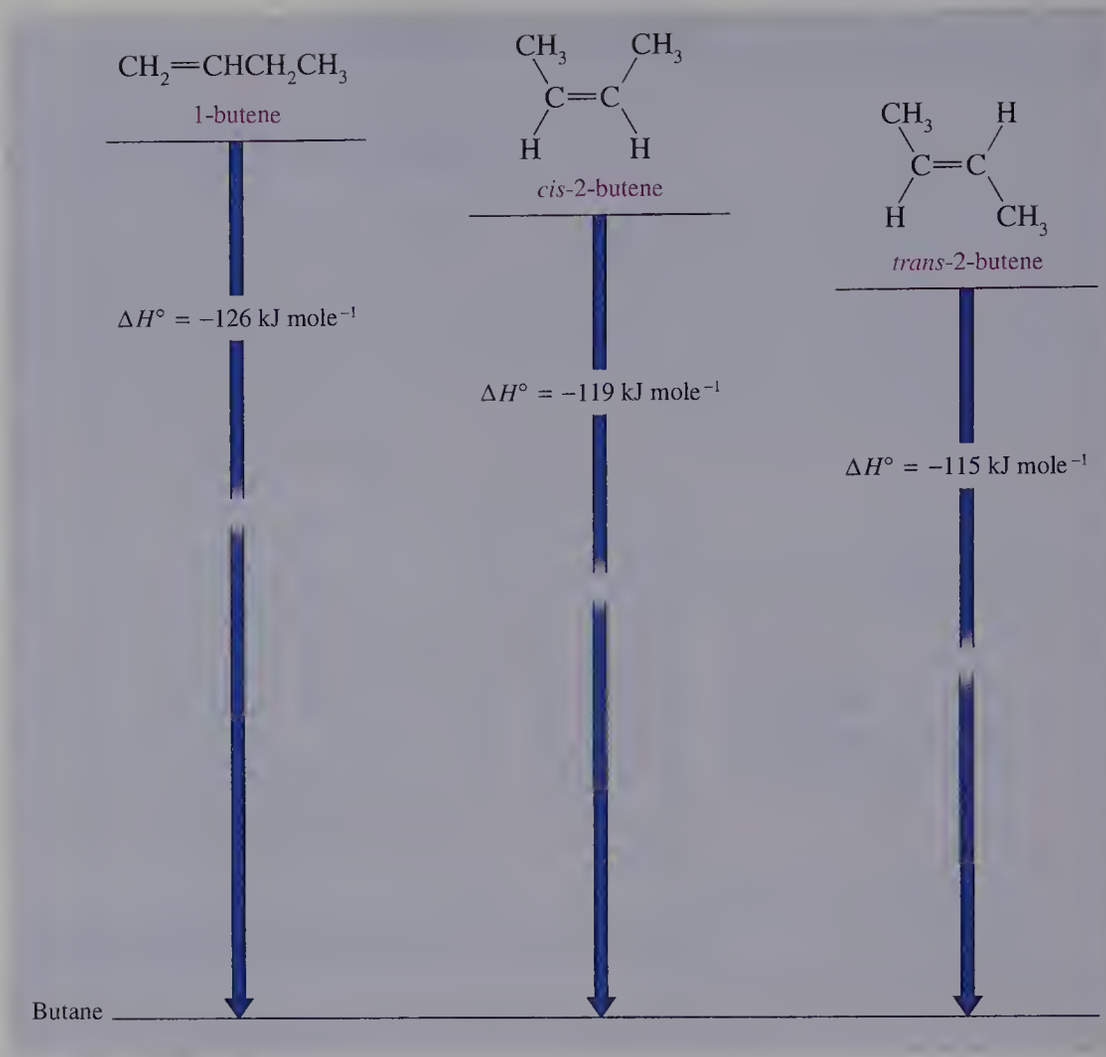


FIGURE 6.6 Heats of Hydrogenation of Isomeric Alkenes
The positions of three isomeric butenes indicate their relative heats of formation. The indicated heat of reaction is the heat of hydrogenation to form butane.

TABLE 6.3
Heats of Hydrogenation of Alkenes

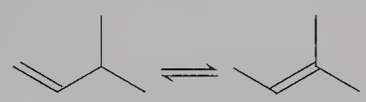
Alkene	$\Delta H°_{hydrogn}$ *(kJ mole^{-1})*	*Alkene*	$\Delta H°_{hydrogn}$ *(kJ mole^{-1})*
Unsubstituted		*Internal disubstituted*	
ethene	136	*cis*-2-butene	119
Monsubstituted		*trans*-2-butene	115
propene	125	*cis*-2-pentene	117
1-butene	126	*trans*-2-pentene	114
1-hexene	126	*cis*-4,5-dimethyl-2-hexene	118
3-methyl-1-butene	127	*trans*-4,5-dimethyl-2-hexene	113
3,3-dimethyl-1-butene	127	*Trisubstituted*	
Terminal disubstituted		2-methyl-2-pentene	112
2-methylpropene	117	2,3-dimethyl-3-hexene	114
2-methyl-1-butene	118	*Tetrasubstituted*	
2,3-dimethyl-1-butene	116	2,3-dimethyl-2-butene	110
2,3-dimethyl-1-hexene	117	2,3-dimethyl-2-hexene	106

Problem 6.24

Explain why the stability of 2-methyl-1-propene can be compared to the stability of the isomeric butenes using heat of combustion data, but these stabilities cannot be directly compared using heat of hydrogenation data.

Problem 6.25

The heats of hydrogenation of 3-methyl-1-butene and 2-methyl-2-butene are 127 and 113 kJ mole^{-1}, respectively. Assuming that the following equilibrium reaction can be established, predict the ΔH°_{rxn}.



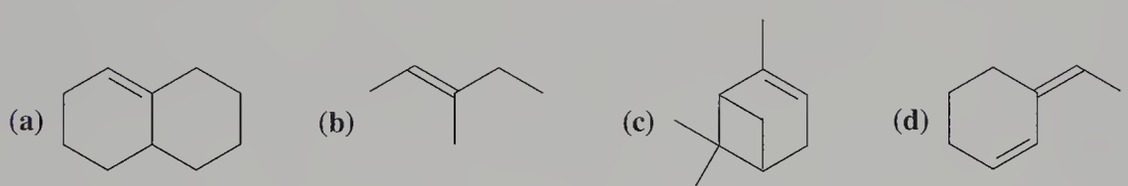
EXERCISES

Molecular Formulas

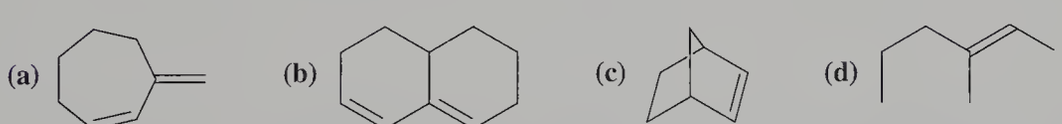
6.1 What is the molecular formula for a compound with each of the following structural features?
(a) six carbon atoms and one double bond
(b) five carbon atoms and two double bonds
(c) seven carbon atoms, a ring, and one double bond

6.2 What is the molecular formula for a compound with each of the following structural features?
(a) four carbon atoms and two double bonds
(b) ten carbon atoms and two rings
(c) ten carbon atoms, two rings, and five double bonds

6.3 Write the molecular formula for each of the following compounds.



6.4 Write the molecular formula for each of the following compounds.



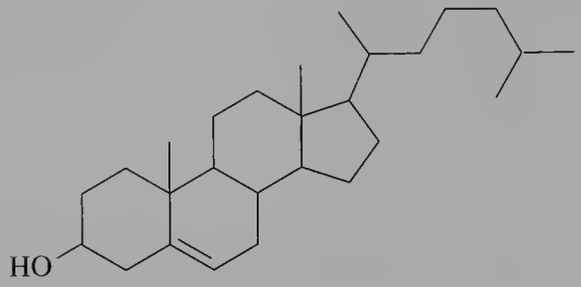
Classification of Alkenes

6.5 Classify each double bond in the alkenes in Exercise 6.3 by its substitution pattern.

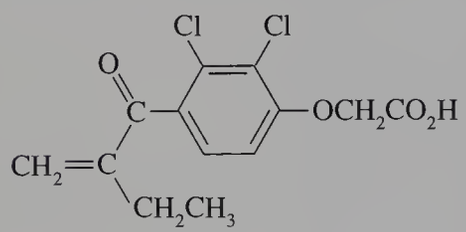
6.6 Classify each double bond in the alkenes in Exercise 6.4 by its substitution pattern.

6.7 Indicate the degree of substitution of the double bond in each of the following compounds.

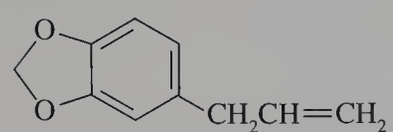
(a) cholesterol, a steroid



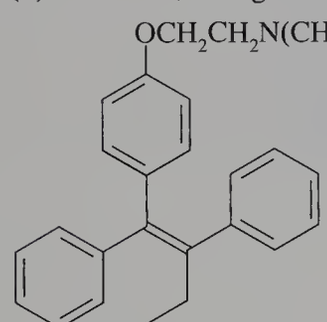
(b) ethacrynic acid, a diuretic



(c) saffrole, a carcinogen found in sassafras root

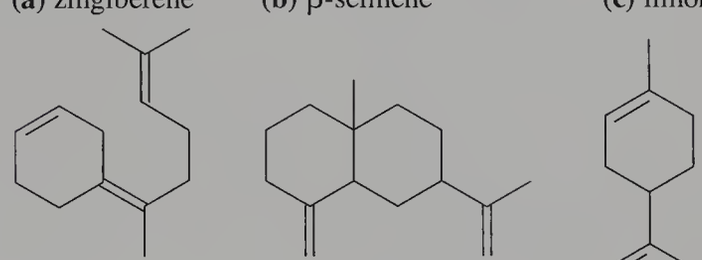


(d) tamoxifen, a drug used in treatment of breast cancer



6.8 Indicate the degree of substitution of all double bonds in each of the following compounds, polyenes found in natural oils.

(a) zingiberene **(b)** β-selinene **(c)** limonene



Unsaturation Number

6.9 Calculate the unsaturation number for each of the following compounds.

(a) camphor, $C_{10}H_{16}O$ **(b)** nicotine, $C_{10}H_{14}N_2$

(c) vitamin B_6, $C_8H_9NO_2$ **(d)** hexachlorophene, $C_{13}H_6O_2Cl_6$

6.10 Calculate the unsaturation number for each of the following compounds.

(a) β-carotene, $C_{40}H_{56}$ **(b)** amphetamine, $C_9H_{13}N$ **(c)** DDT, $C_{11}H_9Cl_5$ **(d)** aspirin, $C_9H_8O_4$

6.11 Calculate the unsaturation number for each of the following compounds.

(a) vitamin A, $C_{20}H_{30}O$ **(b)** sucrose, $C_{12}H_{22}O_{11}$ **(c)** vitamin B_2, $C_{17}H_{20}N_4O_6$ **(d)** saccharin, $C_7H_5NO_3S$

6.12 Calculate the unsaturation number for each of the following compounds.
(a) L-dopa, $C_9H_{11}NO_4$ **(b)** prontosil, $C_{12}H_{13}N_5O_2S$
(c) testosterone, $C_{19}H_{28}O_2$ **(d)** phenobarbital, $C_{12}H_{12}N_2O_3$

Geometric Isomers

6.13 Which of the following molecules can exist as cis and trans isomers?
(a) $CH_3CH{=}CHBr$ **(b)** $CH_2{=}CHCH_2Br$ **(c)** $CH_3CH{=}CHCH_2Cl$ **(d)** $(CH_3)_2C{=}CHCH_3$

6.14 Which of the following molecules can exist as cis and trans isomers?
(a) $CH_3CH{=}CBr_2$ **(b)** $CH_2{=}CHCHBr_2$ **(c)** $CH_3CH{=}CHCHCl_2$ **(d)** $CH_3CH_2CH{=}C(CH_3)_2$

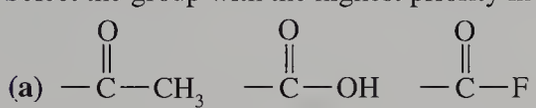
6.15 Which of the following molecules can exist as cis and trans isomers?
(a) 1-hexene **(b)** 3-heptene **(c)** 4-methyl-2-pentene **(d)** 2-methyl-2-butene

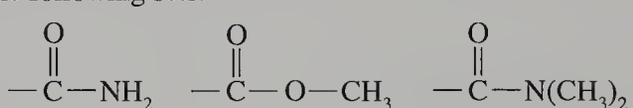
6.16 Which of the following molecules can exist as cis and trans isomers?
(a) 3-methyl-1-hexene **(b)** 3-ethyl-3-heptene **(c)** 2-methyl-2-pentene **(d)** 3-methyl-2-pentene

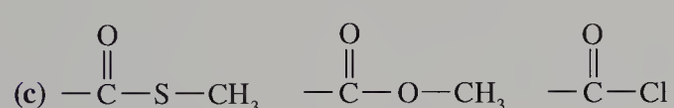
E,Z System of Nomenclature

6.17 Select the group with the highest priority in each of the following sets.
(a) $-CH(CH_3)_2$, $-CHClCH_3$, $-CH_2CH_2Br$
(b) $-CH_2CH{=}CH_2$, $-CH_2CH(CH_3)_2$, $-CH_2C{\equiv}CH$
(c) $-OCH_3$, $-N(CH_3)_2$, $-C(CH_3)_3$

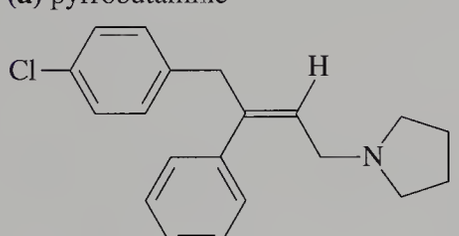
6.18 Select the group with the highest priority in each of the following sets.

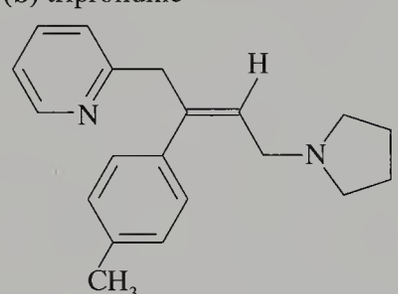
(a) 

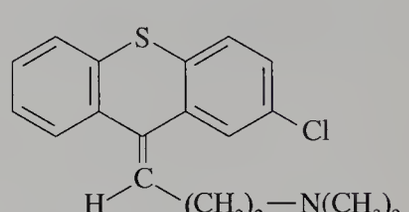
(b) 

(c) 

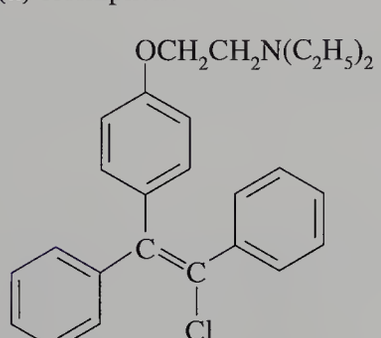
6.19 Assign the *E* or *Z* configuration to each of the following antihistamines.
(a) pyrrobutamine **(b)** triprolidine **(c)** chloroprothixene

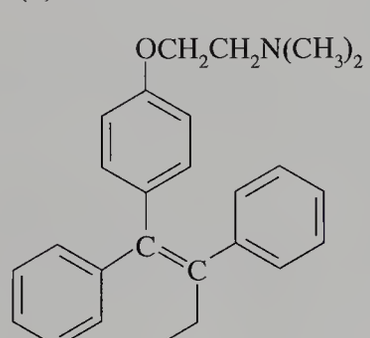


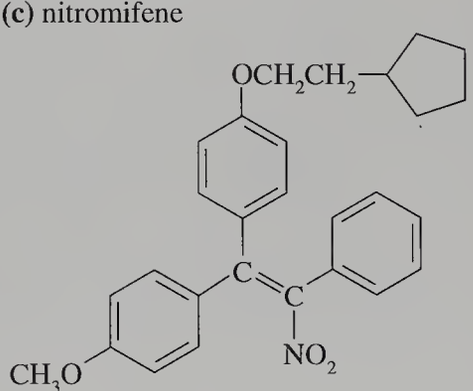




6.20 Assign the *E* or *Z* configuration to each of the following hormone antagonists used to control cancer.
(a) clomiphene **(b)** tamoxifen **(c)** nitromifene







6.21 Draw the structural formula for each of the following pheromones with the indicated configuration.

(a) sex pheromone of Mediterranean fruit fly, *E* isomer

$CH_3CH_2CH{=}CH(CH_2)_4CH_2OH$

(b) sex pheromone of honeybee, *E* isomer

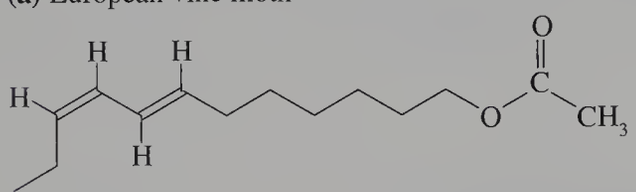
$CH_3\overset{\displaystyle O}{\overset{\|}{C}}(CH_2)_4CH_2CH{=}CHCO_2H$

(c) defense pheromone of termite, *E* isomer

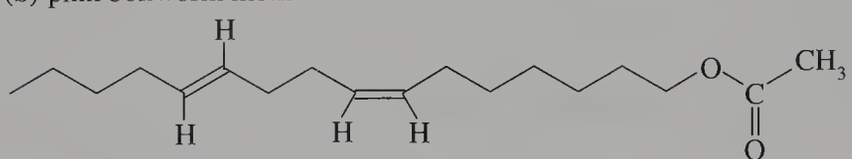
$CH_3(CH_2)_{12}CH{=}CHNO_2$

6.22 Assign the configuration at all double bonds where geometrical isomerism is possible in each of the following sex pheromones.

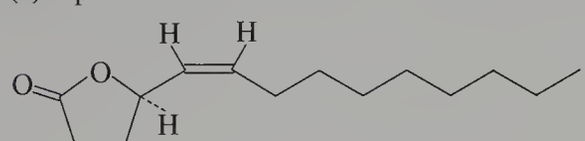
(a) European vine moth



(b) pink bollworm moth

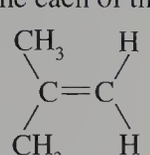


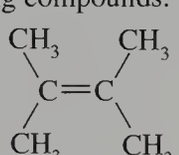
(c) Japanese beetle

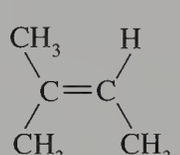


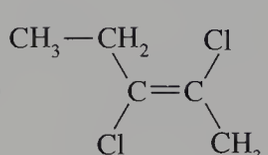
Nomenclature of Alkenes

6.23 Name each of the following compounds.

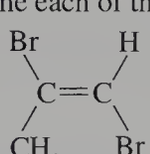
(a) 

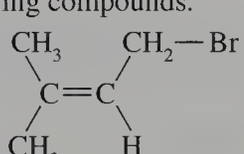
(b) 

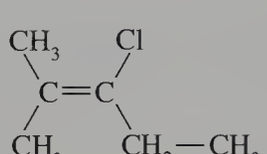
(c) 

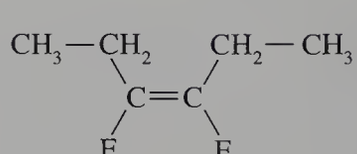
(d) 

6.24 Name each of the following compounds.

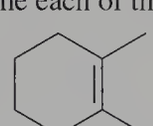
(a) 

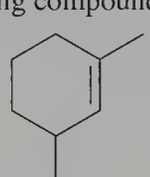
(b) 

(c) 

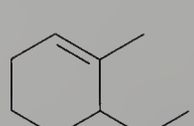
(d) 

6.25 Name each of the following compounds.

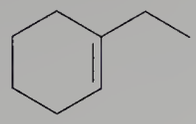
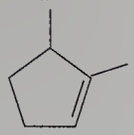
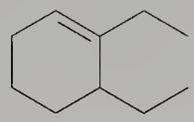
(a) 

(b) 

(c) 

(d) 

6.26 Name each of the following compounds.

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

6.27 Draw a structural formula for each of the following compounds.
(a) 2-methyl-2-pentene **(b)** 1-hexene **(c)** (*Z*)-2-methyl-3-hexene **(d)** (*E*)-5-methyl-2-hexene

6.28 Draw a structural formula for each of the following compounds.
(a) (*E*)-1-chloropropene **(b)** (*Z*)-2,3-dichloro-2-butene
(c) 3-chloropropene **(d)** 4-chloro-2,4-dimethyl-2-hexene

6.29 Draw a structural formula for each of the following compounds.
(a) cyclohexene **(b)** 1-methylcyclopentene
(c) 1,2-dibromocyclohexene **(d)** 4,4-dimethylcyclohexene

6.30 Draw a structural formula for each of the following compounds.
(a) cyclopentene **(b)** 3-methylcyclohexene
(c) 1,3-dibromocyclopentene **(d)** 3,3-dichlorocyclopentene

Physical Properties

6.31 The dipole moment of hexane is 0.09 D, but the dipole moment of 1-hexene is 0.4 D. Explain the reason for the difference.

6.32 Which isomer of 2-butene has the larger dipole moment?

6.33 The dipole moment of 2-methylpropene is 0.5 D, but the dipole moment of 1-butene is 0.3 D. Explain why these values differ.

6.34 The dipole moment of chloroethene is 1.4 D. Predict the dipole moment of *cis*-1,2-dichloroethene.

6.35 *cis*-1-Bromopropene has a higher boiling point than *cis*-1-chloropropene, but has the smaller dipole moment. Explain why.

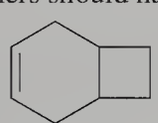
6.36 The boiling points of 1-hexene and 2,3-dimethyl-2-butene are 63.5 and 73 °C, respectively. Suggest a reason for this difference.

Heats of Combustion of Alkenes

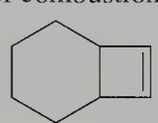
6.37 The difference between the heats of combustion of *cis*- and *trans*-2-butenes is about 4.2 kJ mole^{-1}, but the difference between those of *cis*- and *trans*-4,4-dimethyl-2-pentenes is about 16 kJ mole^{-1}. Explain why these two values differ significantly.

6.38 The difference between the heats of combustion of *cis*- and *trans*-2,2,5,5-tetramethyl-3-hexenes is about 40 kJ mole^{-1}. Explain this very large difference.

6.39 Which of the following two isomers should have the larger heat of combustion? Explain why.

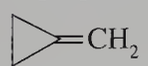


bicyclo[4.2.0]oct-3-ene
I

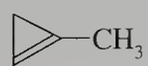


bicyclo[4.2.0]oct-7-ene
II

6.40 Although 1-methylcyclopropene is a trisubstituted alkene and methylenecyclopropane is a disubstituted alkene, the heat of combustion of 1-methycyclopropene is larger by about 42 kJ mole^{-1}. Explain why.



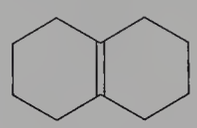
methylenecyclopropane



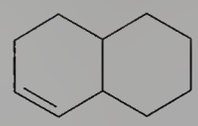
1-methylcyclopropene

6.41 Arrange the following compounds in order of increasing heats of combustion: 3-methyl-1-butene, 2-methyl-1-butene, 2-methyl-2-butene

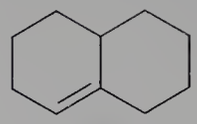
6.42 Arrange the following compounds in order of increasing heats of combustion.



I



II



III

Hydrogenation of Alkenes

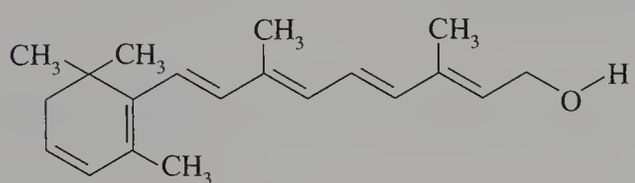
6.43 How many moles of hydrogen gas will react at atmospheric pressure with each of the following compounds?

(a) 1,4-cyclooctadiene **(b)** 4-vinylcyclohexene

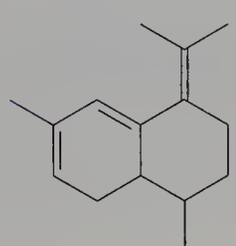
(c) 2,4-dimethyl-1,4-pentadiene **(d)** 2-methyl-1,3-cyclohexadiene

6.44 How many moles of hydrogen gas will react at atmospheric pressure with each of the following compounds?

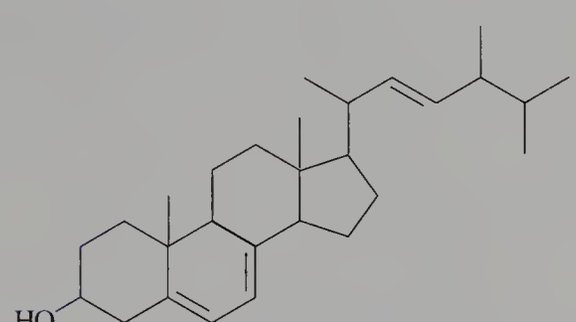
(a) vitamin A_2, contained in freshwater fish



(b) zingiberene, found in oil of ginger



(c) ergosterol, a form of vitamin D

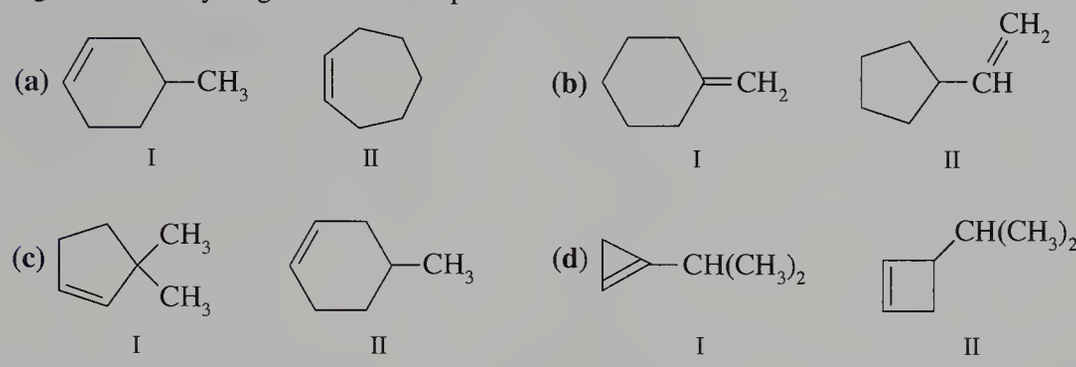


6.45 Oil of marjoram contains α-terpinene, whose molecular formula is $C_{10}H_{16}$. Hydrogenation using the Adams catalyst yields $C_{10}H_{20}$. How many double bonds and how many rings does the α-terpinene contain?

6.46 The wax found on apples contains α-farnesene, whose molecular formula is $C_{15}H_{26}$. Hydrogenation using palladium on charcoal yields $C_{15}H_{32}$. How many double bonds and how many rings does the α-farnesene contain?

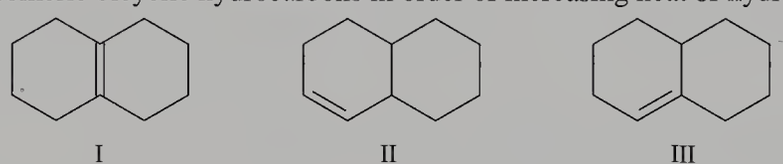
Heats of Hydrogenation

6.47 Consider each compound of the following pairs of isomeric hydrocarbons and determine whether or not there should be a substantial difference in their heats of hydrogenation. Explain why. Indicate the compound with the higher heat of hydrogenation where possible.



6.48 There are three isomeric methylcyclopentenes. Which compound has the smallest heat of hydrogenation?

6.49 Arrange the following isomeric bicyclic hydrocarbons in order of increasing heat of hydrogenation.



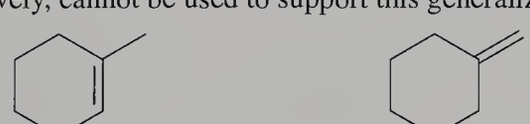
6.50 The $\Delta H^{\circ}_{\text{hydrogn}}$ of bicyclo[4.2.0]oct-7-ene is larger than the $\Delta H^{\circ}_{\text{hydrogn}}$ of the isomeric bicyclo[4.2.0]oct-3-ene. Based on this information, which compound is more stable? What feature of the structures of the two compounds is responsible for this difference in stability?

bicyclo[4.2.0]oct-3-ene bicyclo[4.2.0]oct-7-ene

6.51 Although ethylidenecyclohexane and 1-ethylcyclohexene are both trisubstituted alkenes, the latter compound predominates in an equilibrium reaction. Based on this information, which compound has the larger heat of hydrogenation?

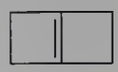
ethylidenecyclohexane 1-ethylcyclohexene

6.52 The data given in Exercise 6.51 support the fact that isomers with double bonds within rings (endocyclic) are more stable than isomers with double bonds between a carbon in the ring and a carbon outside the ring (exocyclic). Explain why the heats of hydrogenation of 1-methylcyclohexane and methylenecyclohexane, which are −107 and −116 kJ mole^{-1}, respectively, cannot be used to support this generalization.

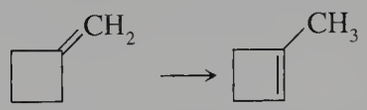


1-methylcyclohexene methylenecyclohexane

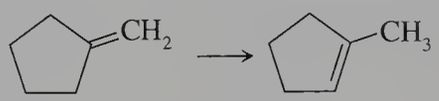
6.53 The heat of hydrogenation of the following bicyclic hydrocarbon is approximately 270 kJ mole^{-1}. Why is this value so much larger than those listed in Table 6.3 for alkenes?



6.54 Explain why the ΔH°_{rxn} for the following two isomerization reactions are negative. Why is the ΔH°_{rxn} for the second reaction more negative than for the first reaction?



$\Delta H^\circ_{rxn} = -3.7$ kJ mole^{-1}



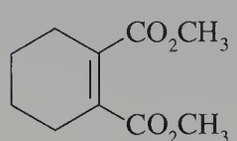
$\Delta H^\circ_{rxn} = -16.2$ kJ mole^{-1}

6.55 The difference between the heats of hydrogenation of (*E*)- and (*Z*)-4,4-dimethyl-2-pentenes is approximately 14.6 kJ mole^{-1}. Compare this difference with the difference between the heats of hydrogenation of (*E*)- and (*Z*)-2-butenes. Why do the two values differ?.

6.56 The heats of hydrogenation of the geometric isomers of 2,2,5,5-tetramethyl-3-hexene differ by 39 kJ mole^{-1}. Explain why this difference is so large compared to other geometric isomers.

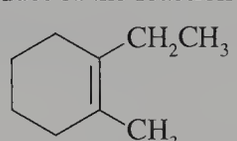
Stereochemistry and Stereoselectivity of Hydrogenation

6.57 Write the structure of the product obtained by hydrogenating the following diester using platinum and hydrogen gas at atmospheric pressure.



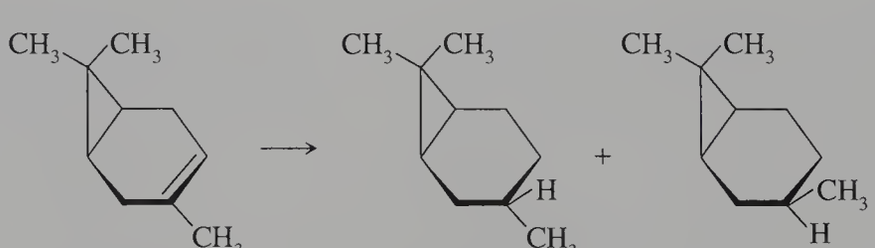
6.58 Write the product obtained by the catalytic hydrogenation of the sex pheromone of the European vine moth at atmospheric pressure. (See structure in Exercise 6.22a.)

6.59 Deuterium gas can be used to deuterate compounds using the Adams catalyst. The reaction proceeds by the same mechanism as for hydrogenation. Write the product of the reaction of 1-ethyl-2-methylcyclohexene with D_2.



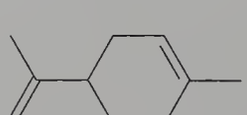
1-ethyl-2-methylcyclohexene

6.60 Which of the two isomeric caranes is the major product of the hydrogenation of 3-carene using the Adams catalyst?



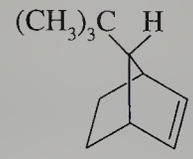
3-carene

6.61 Which of the double bonds of limonene is hydrogenated at the faster rate? Comment on the likelihood that selective hydrogenation may occur.

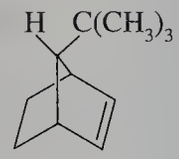


limonene

6.62 The catalytic hydrogenation of compound I occurs at a faster rate than that of compound II. Explain why.

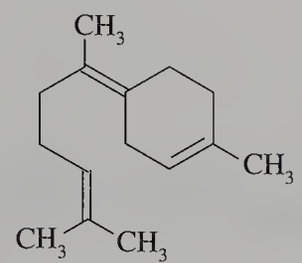


I



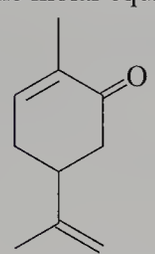
II

6.63 Evaluate the degree of substitution of the double bonds of bisabolene and determine whether stereoselective hydrogenation of a double bond is possible.

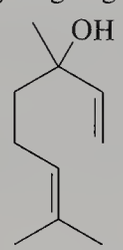


bisabolene

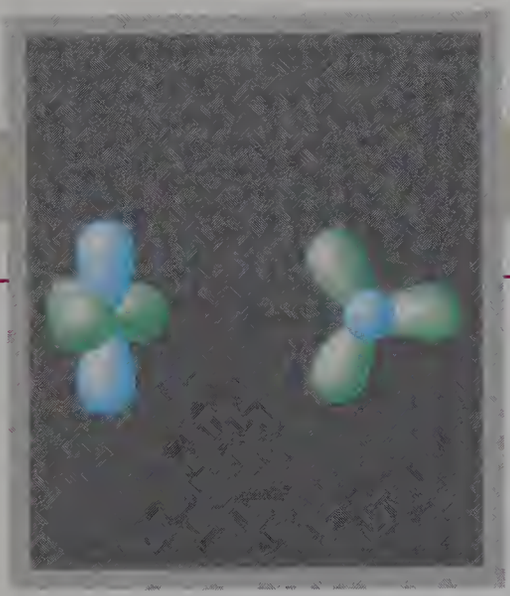
6.64 Write the product obtained from the catalytic hydrogenation of each of the following compounds found in natural oils using the Wilkinson catalyst and one molar equivalent of hydrogen gas.



carvone



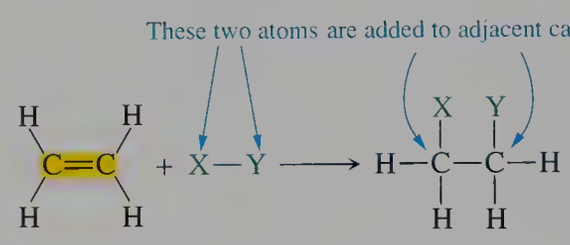
linalool



7 Addition Reactions of Alkenes

7.1 Characteristics of Addition Reactions

The π bonds of alkenes characteristically undergo addition reactions, yielding saturated compounds. For example, the π bond of ethylene reacts with a general reagent, X—Y, by the following equation.



Specific examples of the addition reaction with ethylene include the following.

$$CH_2{=}CH_2 + HBr \longrightarrow CH_3CH_2Br$$

$$CH_2{=}CH_2 + H_2O \xrightarrow{H^+} CH_3CH_2OH$$

$$CH_2{=}CH_2 + Br_2 \longrightarrow BrCH_2CH_2Br$$

The two atoms or groups of atoms add to adjacent atoms of the π bond. This is a common characteristic of addition reactions, which occur by a variety of mechanisms, depending on the reagent.

In this chapter we will first consider reagents such as HBr, H_2O, and Br_2. These react with π bonds by multistep mechanisms involving electrophilic species. Then we will consider reactions of the double bond with oxidizing agents, reactions that occur by concerted mechanisms. Finally, we will consider the mechanism of some free radical addition reactions.

Thermodynamics of Addition Reactions

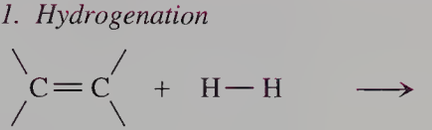
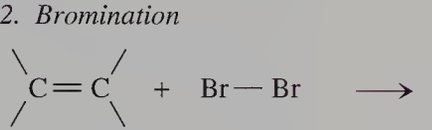
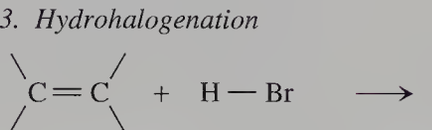
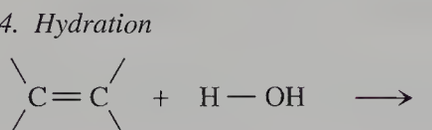
Let's consider the energy changes for all bonds broken and formed in the addition reactions of alkenes. In these reactions, both the π bond and the X—Y bond break. Each of these bond-breaking steps is endothermic ($\Delta H^\circ > 0$). The π bond has a bond dis-

sociation energy of about 240 kJ mole^{-1} (57 kcal mole^{-1}). This value is the difference between the bond dissociation energies of a carbon–carbon double bond and a carbon–carbon single bond. The bond dissociation energy of the X—Y bond, of course, depends on the nature of X and Y, but is also endothermic. The addition of X—Y occurs with the formation of a C—X and a C—Y bond. These bond-making processes are exothermic ($\Delta H^\circ < 0$). The net enthalpy change for the reaction is given by

$$\Delta H^\circ_{rxn} = [DH^\circ_{(\pi\ bond)} + DH^\circ_{(X-Y)}] - [DH^\circ_{(C-X)} + DH^\circ_{(C-Y)}]$$

Using DH° values for the various C—X, C—Y, and X—Y bonds, we can obtain the estimated enthalpy of reaction for several typical addition reactions from the above equation (Table 7.1). The combined strength of the bonds formed for these reactions exceeds the combined strength of the bonds broken. Therefore, the products are more stable than the reactants. Note that ΔH°_{rxn} values for addition of either bromine or hydrogen bromide are significantly negative. Accordingly, we can safely predict that the equilibrium constant for the addition of bromine or hydrogen bromide to an alkene should be very large.

TABLE 7.1
Approximate Enthalpy Change for Addition Reactions

1. Hydrogenation			$\Delta H^\circ = -118$ kJ mole^{-1}
2. Bromination			$\Delta H^\circ = -105$ kJ mole^{-1}
3. Hydrohalogenation			$\Delta H^\circ = -42$ kJ mole^{-1}
4. Hydration			$\Delta H^\circ = -25$ kJ mole^{-1}

The ΔH° value for adding water to an alkene is less negative than ΔH° for adding either bromine or hydrogen bromide. Thus, the reaction with water could lead to an equilibrium mixture, depending on the structural features of the specific alkene. We also must be cautious when we use ΔH° values to estimate the equilibrium constant for a reaction. We recall that the heat of reaction, ΔH°_{rxn}, is a valid approximation of the degree of completeness of a reaction only for reactions in which the numbers of moles of reactants and of products are the same (Section 3.10). For example, a sufficiently large negative entropy change can oppose a favorable enthalpy change in a reaction. In the case of hydration (and the other addition reactions) ΔS°_{rxn} is expected to be negative because two reactant molecules combine to give a single molecule of product. Thus, ΔG°_{rxn} for the addition reaction should be less negative than ΔH°_{rxn}. Finally, we recall that the contributions of enthalpy and entropy changes to the free energy change depend on the temperature. The addition reaction with water ($\Delta S^\circ < 0$) will be less favorable at high temperatures.

Stereochemistry of Addition Reactions

The sp^2-hybridized carbon atoms of an alkene and the atoms directly bonded to them are coplanar. Addition of the two groups X and Y (or identical groups such as X and X) to the carbon atoms of the double bond can occur in either of two ways. Addition to the same face is **syn addition**. Addition to the opposite face is **anti addition**. Do the groups add to the same face of the double bond, or do they add to the opposite face (Figure 7.1)? The stereochemistry of addition reactions can be easily demonstrated using cycloalkenes such as cyclohexene. Consider the reaction of cyclohexene with the general reagent X—Y. Syn addition gives a cis compound (Figure 7.1). Anti addition produces the trans isomer.

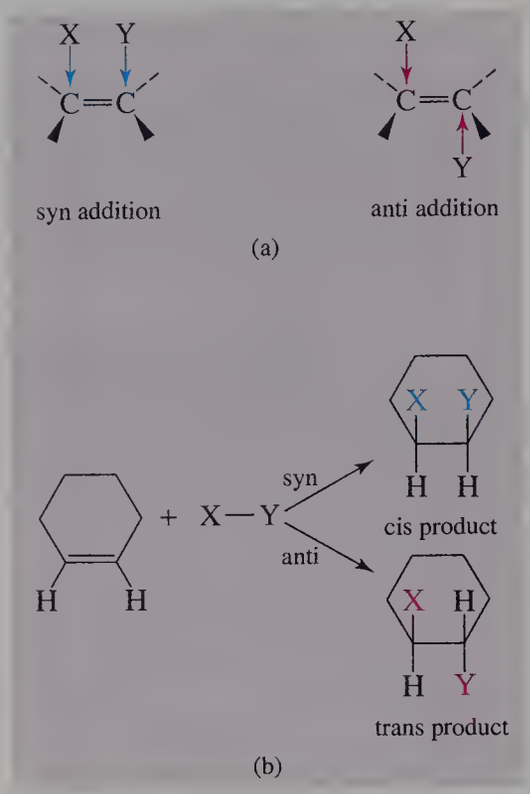


FIGURE 7.1 Syn-Anti Addition to Alkenes
The two possible modes of addition of a reagent X—Y to an alkene are shown in (a). In syn addition, both groups add to the same "face" of the molecule. In anti addition, the groups add to the opposite "faces" of the molecule. The consequences of syn and anti additions are shown in (b). Geometric isomers can result from the addition of a reagent X—Y to the double bond of a cycloalkene. Syn addition produces a cis product, whereas anti addition produces a trans product.

Carbocations in Addition Reactions

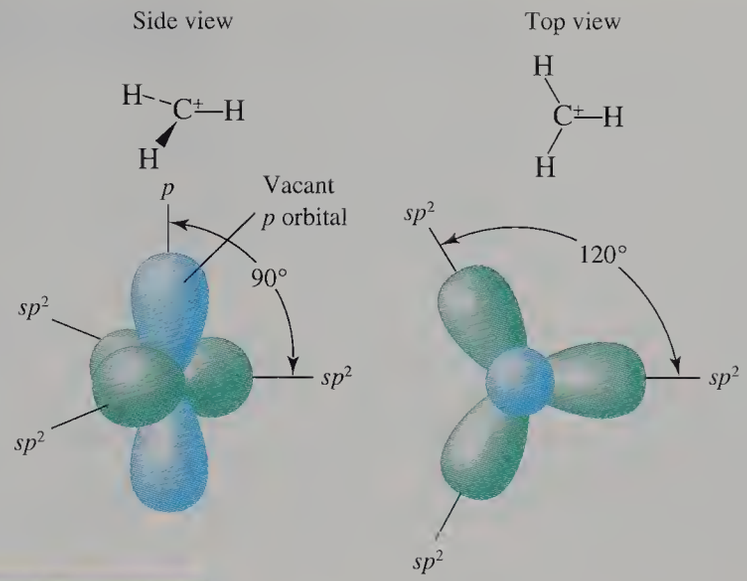
The mechanisms of several addition reactions described in this chapter involve carbocation intermediates. Let's consider again the structure of the simplest carbocation, the methyl cation (CH_3^+), as a representative of the structure of carbocations. The three bonding pairs of electrons are located in a trigonal planar arrangement (Figure 7.2). These bonds involve sp^2 hybrid orbitals of carbon overlapping with the hydrogen 1*s* atomic orbitals to give three σ bonds. The fourth orbital of carbon is an empty *p* orbital located perpendicular to the plane of the three sp^2 orbitals. Because of the planar geometry of a carbocation, attack of a nucleophile to form a bond can occur with equal probability from the top or bottom.

Problem 7.1

The $DH°$ values of S—H and C—S bonds are 342 kJ mole^{-1} (82 kcal mole^{-1}) and 272 kJ mole^{-1} (65 kcal mole^{-1}), respectively. Estimate $\Delta H°$ for the following reaction.

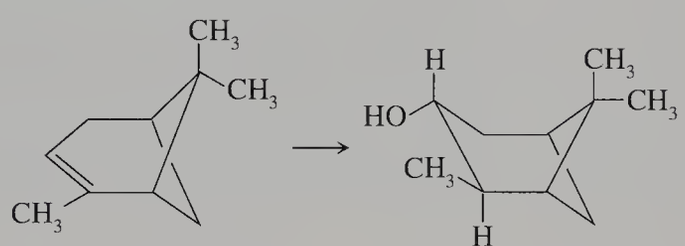
$$CH_2{=}CH_2 + CH_3{-}S{-}H \longrightarrow CH_3{-}CH_2{-}S{-}CH_3$$

FIGURE 7.2 Structure and Hybridization of the Methyl Carbocation



Problem 7.2

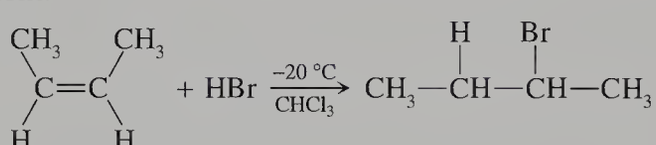
In hydroboration–oxidation, a reaction sequence used to synthesize alcohols, α-pinene is converted to the indicated alcohol. What molecule has been added to the alkene? What is the stereochemistry of the addition reaction?



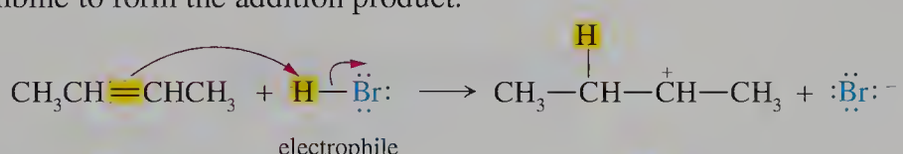
α-pinene

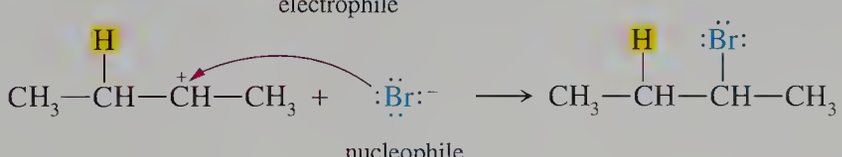
7.2 Addition of Hydrogen Halides

Let's consider the addition reaction of HBr to a symmetrical alkene such as *cis*-2-butene. Only one product is possible because the two carbon atoms of the double bond are equivalent.



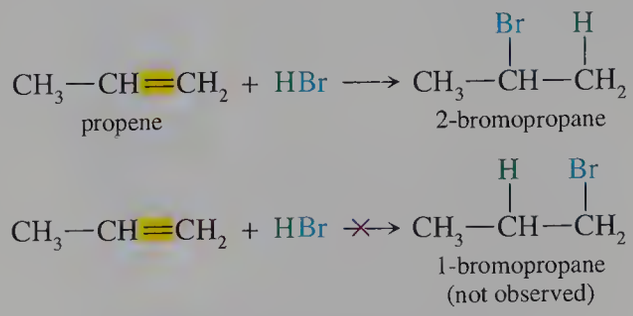
The order of reactivity of hydrogen halides with alkene is HI > HBr > HCl, which corresponds to the order of decreasing acidity. The process is an **electrophilic addition**, in which the proton is the electrophile. The alkene accepts a proton from the acid and forms a carbocation. Then the carbocation and the nucleophilic halide ion combine to form the addition product.





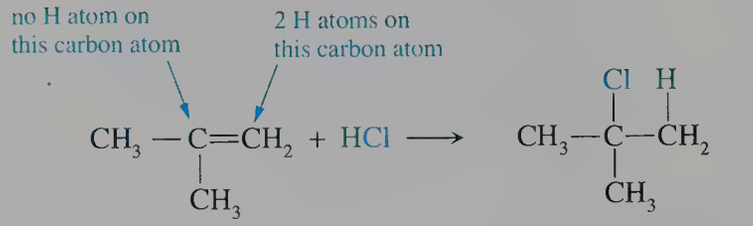
Regiospecificity of Hydrogen Halide Addition

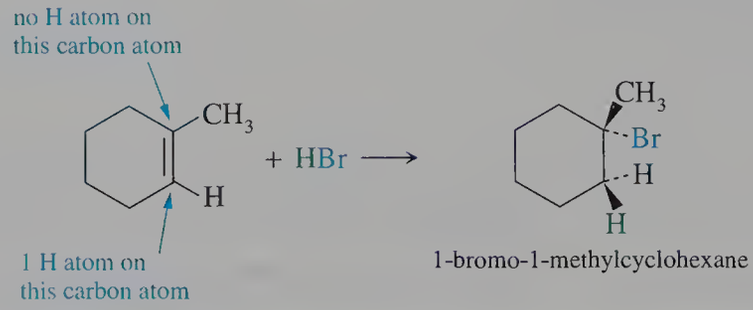
Two products could conceivably result from the addition of HBr to an unsymmetrical alkene, but only one is formed. For example, addition of HBr to propene could yield either 1-bromopropane or 2-bromopropane, but only the latter is formed in the absence of radicals. Thus, the addition of an HBr to an alkene is **regiospecific**. (An alternate reaction described in Section 7.11 occurs under free radical conditions.)



Markovnikov's Rule

In 1870, the Russian chemist Vladimir Markovnikov observed that reagents add to unsymmetrical alkenes in a specific way. **Markovnikov's rule** states that a molecule of the general formula HX adds to a double bond so that the hydrogen atom bonds to a particular unsaturated carbon atom, the one with the largest number of directly bonded hydrogen atoms. This is the less substituted double-bonded carbon atom. The addition reactions of HBr with 2-methylpropene and 1-methylcyclohexene provide two examples of Markovnikov's rule.





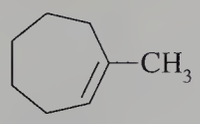
Problem 7.3

Predict the product(s) formed when HCl adds to each of the following.

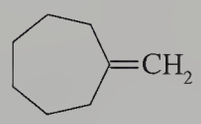
(a) 2-methyl-2-butene (b) (*Z*)-2-butene (c) (*E*)-2-pentene

Problem 7.4

Name each of the following compounds. Predict the product of the addition reaction of HBr with each.



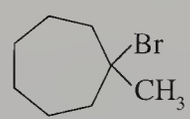
I



II

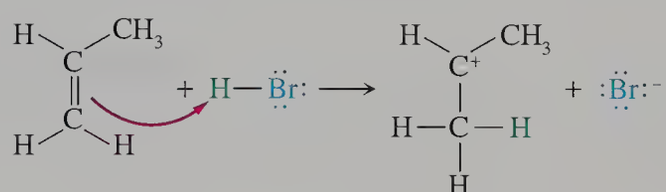
Sample Solution

Compound I is 1-methylcycloheptene. One hydrogen atom is bonded at the C-2 atom and none at the C-1 atom. Thus, hydrogen will add at the C-2 atom and bromine at the C-1 atom. Compound II is methylenecycloheptane. There are two hydrogen atoms at the methylene carbon and none at the C-1 atom. Thus, hydrogen will add at the methylene carbon atom and bromine at the C-1 atom. The product, 1-bromo-1-methylcycloheptane, is the same for both compounds.



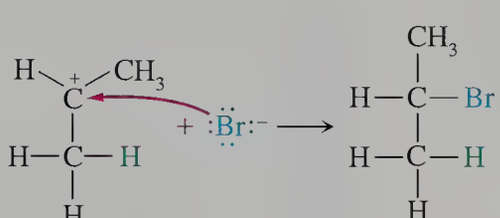
7.3 Mechanistic Basis of Markovnikov's Rule

Markovnikov's rule is explained by the mechanism of the reaction. Consider the reaction of propene with HBr. The π electrons in propene act as a Lewis base and react with a proton. This first step is written with a curved arrow to show the "movement" of two electrons in the π bond to form a σ bond to the proton. The product in this step is an isopropyl cation.

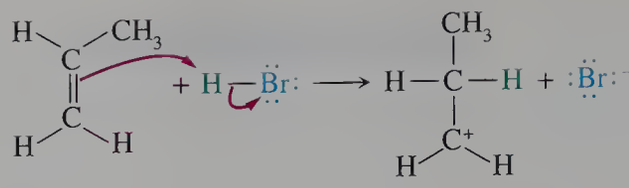


The movement of the π electrons in this step is like the movement of a swinging gate. One end of the gate stays attached, and the other end "swings" free to bond to the electrophile.

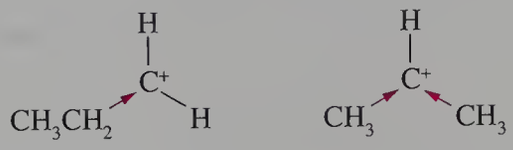
In the second step of the addition reaction, the isopropyl carbocation acts as a Lewis acid and accepts an electron pair from the bromide ion.



This mechanism accounts for the product predicted by Markovnikov's rule. If the hydrogen atom had bonded to the C-2 atom, a propyl carbocation would have formed.



The isopropyl carbocation has the charge on a secondary carbon atom. The propyl carbocation has the charge on a primary carbon atom. The isopropyl carbocation forms, rather than the propyl cation, because the larger number of alkyl groups attached to a positively charged carbon atom help stabilize the charge.



1° carbocation
less stable

2° carbocation
more stable

The order of carbocation stability "explains" Markovnikov's rule. Addition of the electrophile to the less substituted double bonded carbon atom gives the more stable carbocation. The formation of the more stable carbocation controls the product formed, not the number of hydrogen atoms on the carbon atom to which the hydrogen adds.

Hammond Postulate and Electrophilic Addition

Strictly speaking, the regioselectivity in addition of hydrogen halides to alkenes results from the difference in the transition state energies of two competing reactions. We recall that, according to Hammond's postulate, the structure of a transition state resembles that of an intermediate with similar energy (Section 3.17).

The formation of a carbocation by protonation of an alkene is an endothermic process. Thus, the structure of the transition state resembles the intermediate carbocation (Figure 7.3). When a proton reacts with the π bond of an alkene, the π electrons form a bond to hydrogen and the other carbon atom gains a positive charge. Because alkyl groups stabilize carbocations, we can conclude that they also affect the energy of the transition states leading to these intermediates. Increasing the num-

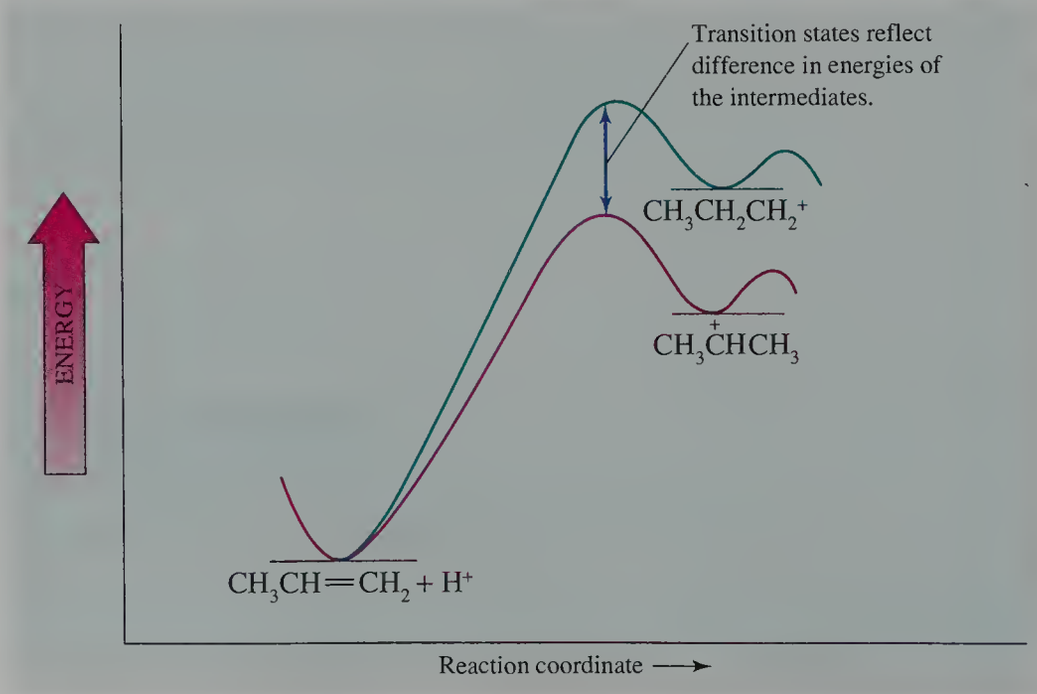


FIGURE 7.3 Reaction Coordinate Diagrams for Addition Reaction
The transition state that leads to the less stable primary carbocation is of higher energy than the transition state that leads to the more stable secondary carbocation. Subsequent reaction of either carbocation with a nucleophile occurs rapidly.

ber of alkyl groups present on the carbon atoms of the original double bond decreases the energy barrier for formation of the transition state leading to the carbocation. Therefore, more highly substituted carbocations form faster than less substituted carbocations. The energy barrier for the second step, the reaction of halide ion with the carbocation, is smaller than the energy barrier for the first step. Hence, the rate of the second step does not contribute to the regiospecificity of the reaction.

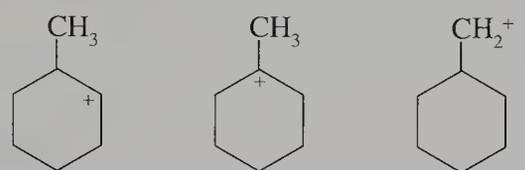
Problem 7.5

Write the structure of the carbocation formed in the addition reaction of HBr with each of the following alkenes.

(a) 1-methylcyclohexene (b) (*Z*)-2-butene (c) 4-methyl-1-pentene

Problem 7.6

Rank the following carbocations in order of their stabilities.



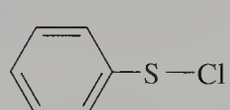
I II III

Problem 7.7

Reaction of either 1-butene or 2-butene with Hr gives the same product, 2-bromobutane. The reaction of 1-butene is faster than the reaction of 2-butene, even though both reactions proceed via a common carbocation intermediate. What is responsible for the difference in the observed rates?

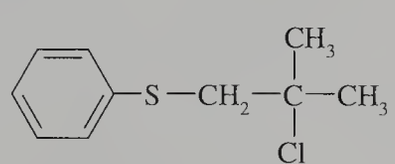
Problem 7.8

Predict the structure of the addition product of the following sulfur compound with 2-methyl-1-propene.



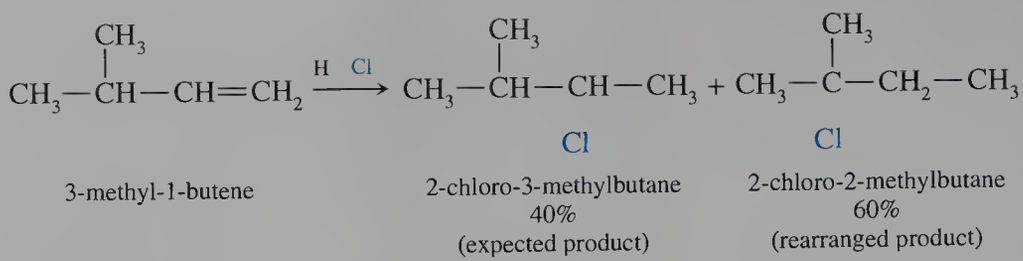
Sample Solution

Chlorine is located to the right of sulfur in period 3 of the periodic table. Thus, chlorine is more electronegative than sulfur. The electrophile is predicted to be a positively charged sulfur species resulting from heterolytic cleavage of the sulfur–chlorine bond. The electrophile should add to the C-1 atom of 2-methyl-1-propene to give a tertiary carbocation, which is then captured by the nucleophilic chloride ion. The product is

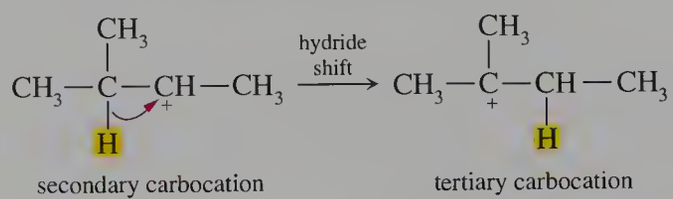


7.4 Rearrangement of Carbocations

Markovnikov's rule allows us to predict the products of most addition reactions, but constitutional isomers occur in some reactions. For example, the addition of HCl to 3-methyl-1-butene gives not only the expected product, 2-chloro-3-methylbutane, but also 2-chloro-2-methylbutane.



The expected product forms from reaction of the nucleophilic chloride ion with the secondary cation, itself formed when a proton adds to the double bond. The isomeric product forms when a nucleophilic chloride ion reacts with a tertiary carbocation. This carbocation forms when the hydrogen atom at C-3 moves, with its bonding pair of electrons, to the adjacent secondary carbocation center (Figure 7.4). This rearrangement is called a **1,2-hydride shift** because a hydride ion (H^-) moves between adjacent carbon atoms.



The 1,2-hydride shift converts the secondary carbocation into a more stable tertiary carbocation. The tertiary carbocation reacts with chloride ion to produce the isomeric rearranged product. Some of the secondary carbocation also reacts with chloride ion without rearranging to give the expected product. The relative amounts of rearranged and unrearranged products depend on how efficiently the carbocation is captured by the nucleophile versus the rate of the rearrangement process.

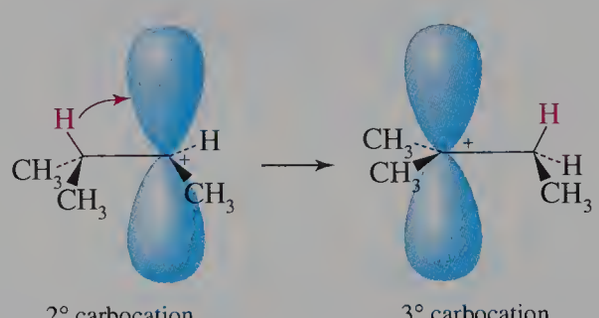
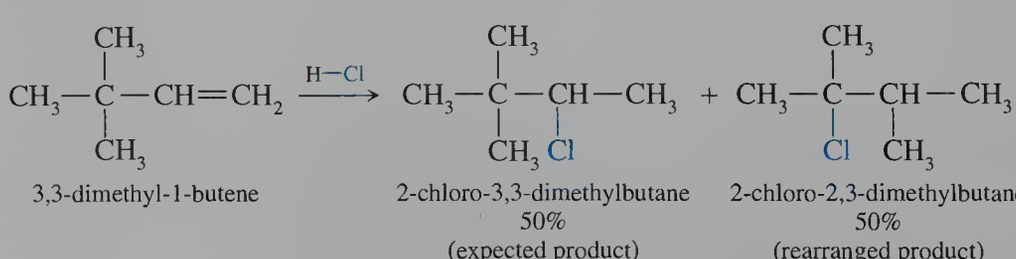
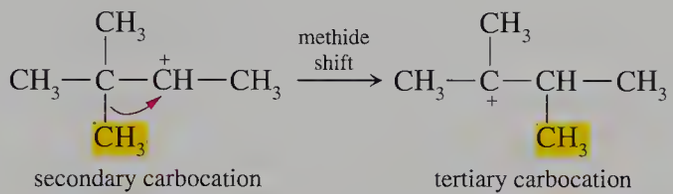


FIGURE 7.4
Rearrangement of a Carbocation
The bonding pair of electrons of the migrating group must be coplanar with the vacant *p* orbital of the carbocation for migration to occur.

A rearrangement analogous to a hydride shift occurs when an alkyl group moves, with its bonding electron pair, to an adjacent carbon atom. This type of rearrangement occurs when a more stable carbocation intermediate is produced. Consider the reaction of 3,3-dimethyl-1-butene with HCl.



Adding a proton to the less substituted carbon atom of the double bond gives a secondary carbocation. This secondary cation reacts with the nucleophilic chloride ion to give the expected product. The rearranged product forms by reaction of the nucleophilic chloride ion with a tertiary carbocation that itself forms by a shift of a methyl group, with its bonding pair of electrons, from the quaternary center to the adjacent secondary carbocation center. This rearrangement is called a **1,2-methide shift** because a CH_3 unit moves between adjacent carbon atoms.



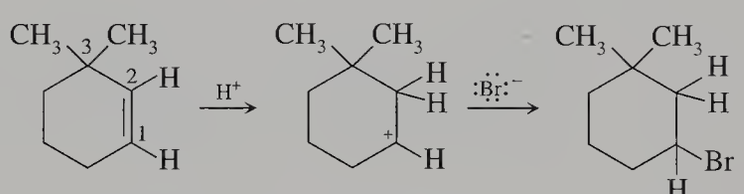
As a result of this shift, a secondary carbocation is converted into a more stable tertiary carbocation. The tertiary carbocation reacts with chloride ion to produce the rearranged product. Some of the secondary carbocation also reacts with a chloride ion without rearranging to give the expected product.

Problem 7.9

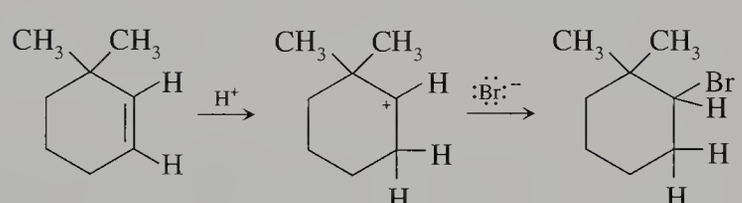
Write the structures of all of the possible addition products of 3,3-dimethylcyclohexene with HBr.

Sample Solution

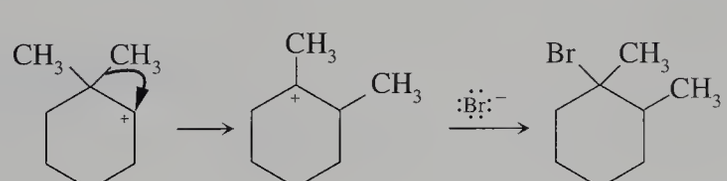
Both carbon atoms of the double bond are bonded to one carbon atom and a hydrogen atom. Thus a proton can add to either carbon atom. Addition at C-2 gives a secondary carbocation at the original C-1 atom. Capture of the carbocation by bromide ion yields 1-bromo-3,3-dimethylcyclohexane.



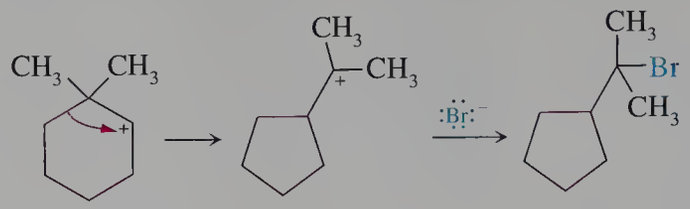
Addition at C-1 gives a secondary carbocation at the original C-2 atom. Capture of the carbocation by bromide ion can give 1-bromo-2,2-dimethylcyclohexane.



However, the secondary carbocation can rearrange to two possible tertiary carbocations. Migration of methyl followed by capture of the carbocation gives 1-bromo-1,2-dimethylcyclohexane.

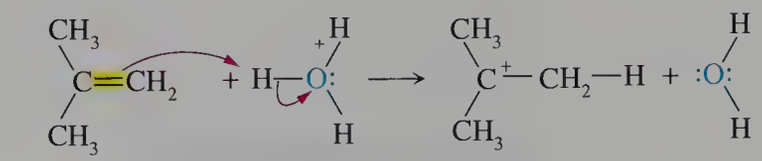


A 1,2-shift of a methylene group of the ring can also occur to give a tertiary carbocation. Capture of the carbocation gives a product containing a cyclopentane ring.



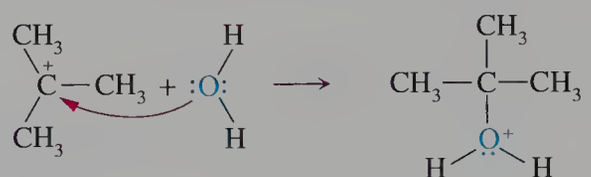
7.5 Hydration of Alkenes

Water adds to a π bond in an acidic medium such as aqueous sulfuric acid. A proton is transferred from H_3O^+ to the π bond to give a carbocation, which then reacts with the nucleophilic oxygen atom of water.



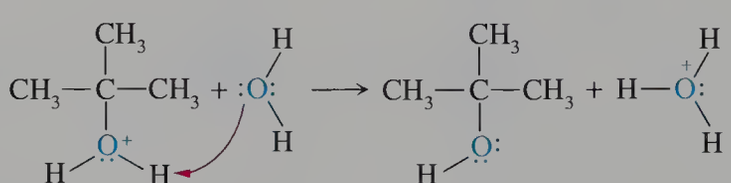
2-methyl-1-propene

tert-butyl carbocation



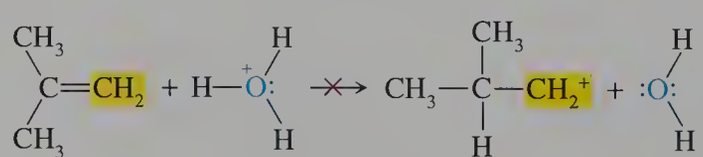
tert-butyl oxonium ion

The *tert*-butyl oxonium ion, which forms in the second step, is the conjugate acid of *tert*-butyl alcohol. This ion transfers a proton to water, regenerating the hydronium ion, the catalyst for the reaction.



tert-butyl alcohol

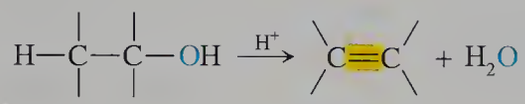
The hydration reaction is regiospecific. It obeys Markovnikov's rule. *tert*-Butyl alcohol is formed, rather than the isobutyl alcohol that would result from addition of a proton to the C-2 atom followed by reaction of water with the C-1 atom. Such a process would proceed via a much less stable primary carbocation.



The structure of the alkene affects the rate of the hydration reaction. The order of reactivity is 2-methylpropene > propene > ethene. This order reflects the effect of the stability of the carbocation intermediate. 2-Methylpropene reacts faster than propene or ethene because a 3° carbocation forms faster than a 2° or a 1° carbocation.

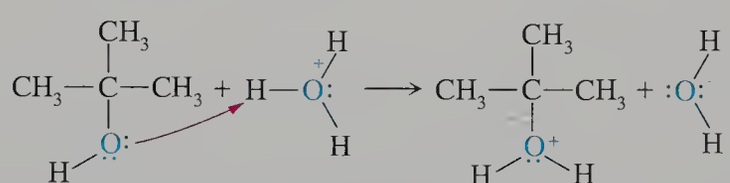
Reversibility of Hydration

Each step in the hydration of an alkene is reversible, so the entire reaction is reversible. The reverse of the hydration reaction is dehydration, an example of an elimination reaction (Section 2.13).

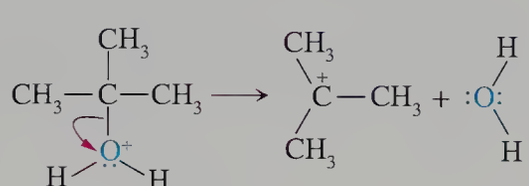


The direction of the reaction—hydration or dehydration—is controlled by the concentration of H_2O. If the H_2O concentration is high, as in dilute H_2SO_4, hydration occurs. If the water concentration is low, as in concentrated (about 98%) H_2SO_4, dehydration occurs. The dehydration reaction is more favorable at higher temperatures because ΔS°_{rxn} is positive.

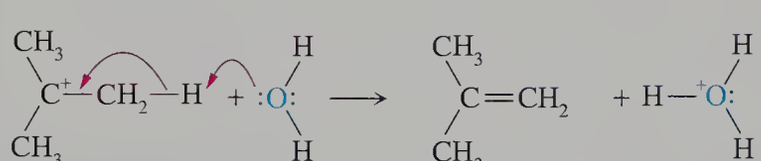
In an equilibrium process, the mechanistic pathways for the forward and reverse reactions are related. This concept is called the **principle of microscopic reversibility**. To write the mechanism for dehydration, start with the last step of the hydration mechanism and proceed "backward" to the second and then the first step. When the reactions are written in reverse the reactants become products and the products become reactants. For the dehydration of an alcohol, the three steps are



tert-butyl alcohol



tert-butyl oxonium ion



tert-butyl carbocation 2-methyl-1 propene

Problem 7.10

One of the steps in the indirect hydration of alkenes (Section 16.8) is the electrophilic addition of mercuric acetate, $Hg(OAc)_2$—a covalent compound—according to the following

equation. What is the electrophile? Predict the structure of the product of the reaction of mercuric acetate with 2-methyl-1-propene.

$$CH_2{=}CH_2 + Hg(OAc)_2 \xrightarrow{H_2O} HO{-}CH_2{-}CH_2{-}Hg{-}OAc$$

7.6 Addition of Halogens

The reaction of an alkene with Br_2 or Cl_2 occurs rapidly at room temperature. The reaction is usually carried out in carbon tetrachloride or methylene chloride as solvent. The product is called a **vicinal** (Latin, *vicinalis*, neighboring) dihalide. Only one product forms.

$$\underset{\text{propene}}{CH_3{-}CH{=}CH_2} + Br_2 \longrightarrow \underset{\text{1,2-dibromopropane}}{CH_3{-}\overset{Br}{\overset{|}{C}}H{-}\overset{Br}{\overset{|}{C}}H_2}$$

Evidence for the addition of bromine to an alkene is easily seen. Bromine is red-orange. It reacts with alkenes to give a colorless product. Hence, the disappearance of the red-orange color of bromine can be used to determine if a compound is unsaturated. Drops of Br_2 dissolved in CCl_4 are added to a compound. If the bromine color disappears, the compound is unsaturated.

$$\underset{\text{(colorless)}}{CH_3(CH_2)_3CH{=}CH_2} + \underset{\text{(red-orange)}}{Br_2} \longrightarrow \underset{\text{(colorless)}}{CH_3(CH_2)_3CHBr{-}CH_2Br}$$

Chlorine also adds to a carbon–carbon double bond, but iodine is not sufficiently reactive to give a good yield of addition product. Fluorine is too reactive to control and several competing reactions also occur if fluorine is used.

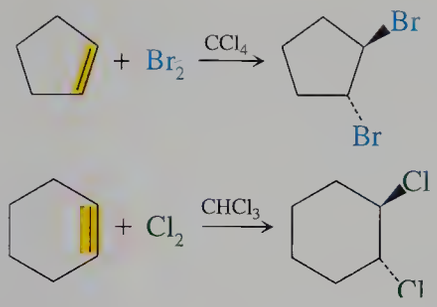
Rearrangement reactions are far less common in the addition of halogens to alkenes. We recall that water adds to 3,3-dimethyl-1-butene to give a rearranged product in addition to the expected product. In contrast, bromine reacts with this alkene to give a single product. This fact suggests that a carbocation similar to that formed in the addition reactions previously discussed is not formed in the addition of bromine.

$$CH_3{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}CH{=}CH_2 \xrightarrow{Br_2} CH_3{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}\underset{Br}{\underset{|}{CH}}{-}CH_2{-}Br$$

expected addition product

Stereochemistry of Halogen Addition

The addition of bromine to cycloalkenes can potentially form two stereoisomeric vicinal dibromides. However, only the trans isomer forms. The reaction is stereospecific.

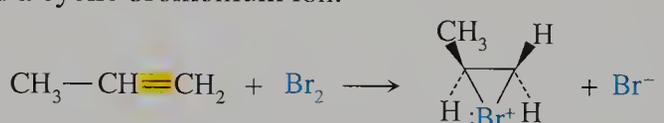


The stereochemistry of the products indicates that the halogen atoms bond from opposite faces of the double bond.

Mechanism of Halogen Addition

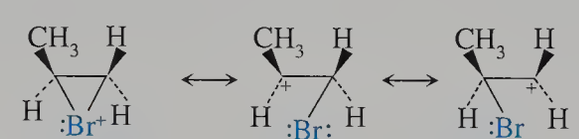
The rate of addition of bromine to alkenes is strongly affected by the degree of substitution of the C=C unit. Alkyl groups increase the rate of the reaction. The relative rates of addition of bromine to ethene, propene, and 2-methylpropene are 1, 60, and 5.5×10^3, respectively. Because alkyl groups can donate electrons and stabilize a positive charge, the transition state must have carbocation character. Increasing the number of alkyl groups lowers the energy barrier.

The absence of rearrangement and the anti stereochemistry of the addition product must be accommodated in a proposed mechanism for the addition of a halogen to an alkene involving a carbocation intermediate. The first step of the reaction mechanism is the electrophilic addition of bromine to the π bond to give a three-membered ring called a cyclic bromonium ion.



bromonium ion

Although the three-membered ring is strained, all atoms have a Lewis octet of electrons. This is a more stable arrangement than an electron-deficient carbocation. The bromine atom bears most of the charge in the bridged ion. However, as shown in the contributing resonance structures, some positive charge is located on the carbon atoms. This charge is stabilized by groups that lower the energy barrier to its formation. The location of most of the positive charge on bromine rather than carbon explains why rearrangement reactions do not occur.



bromonium ion | secondary carbocation | primary carbocation

The cyclic bromonium ion reacts stereospecifically with a nucleophilic bromide ion, as indicated by the formation of *trans*-1,2-dibromocyclopentane from the addition of bromine to cyclopentene. The bromonium ion intermediate has a bromine atom bonded to one face of the molecule. Nucleophilic attack by bromide ion at a carbon atom of the three-membered ring breaks one of the carbon–bromine bonds

of the cyclic intermediate (Figure 7.5). Because the bromine atom in the three-membered ring of the intermediate "shields" one face of the alkene, the bromide ion can attack only at the opposite face and gives only an anti addition product.

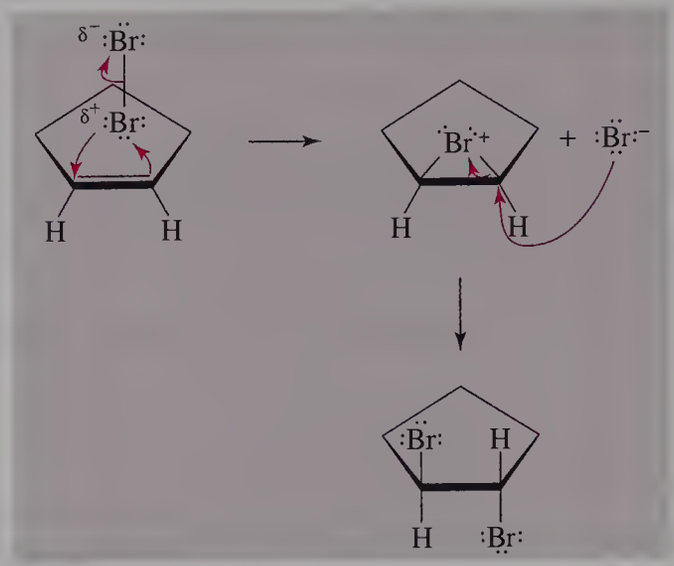
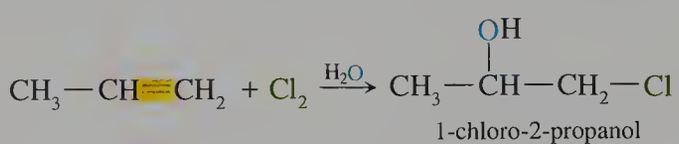


FIGURE 7.5 Anti Addition of Bromine to Alkenes
The π electrons of the alkene act as a nucleophile to displace bromide ion from bromine. The resulting cyclic bromonium ion can be viewed as the addition of Br^+ to the double bond. Bromine has two covalent bonds and a formal 1+ charge in this intermediate. Attack of the nucleophilic bromide ion occurs from the opposite face because the bromine atom that is already there blocks approach from the same face.

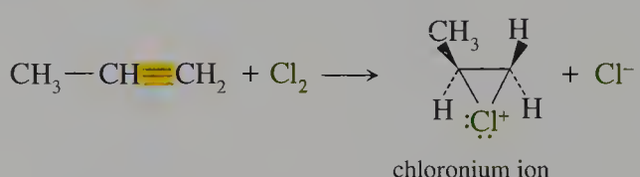
Formation of Halohydrins

An aqueous solution of bromine or chlorine reacts with alkenes to form addition products called **halohydrins**. These compounds have a halogen and a hydroxyl group on adjacent carbon atoms. The reaction of aqueous chlorine with propene is shown below.

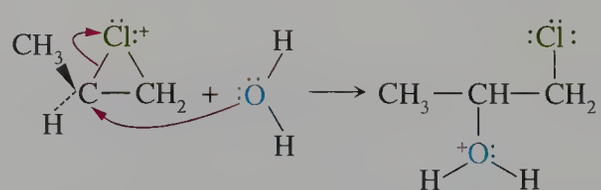


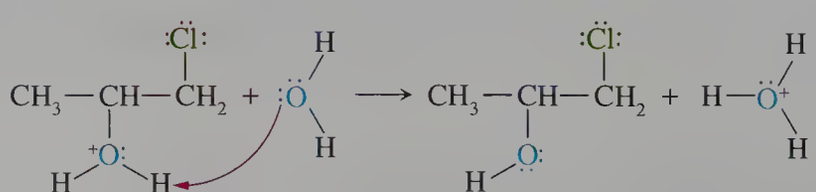
1-chloro-2-propanol

The reaction is regiospecific: The isomeric 2-chloro-1-propanol does not form. This fact implies that the reaction occurs by a mechanism similar to the addition of bromine. The first step of the reaction is formation of a chloronium ion, which is less stable than a bromonium ion. The chloronium ion subsequently reacts with water, which is present in abundance as the solvent. The steps of the mechanism are

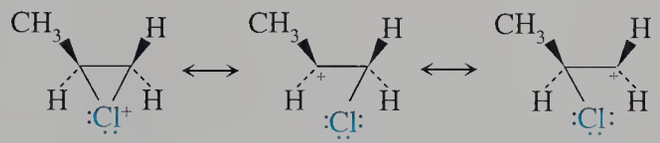


chloronium ion





The chloronium ion has two carbon atoms with some partial positive charge. The more substituted carbon atom is attacked by H_2O. This regiospecificity is explained by the contributing resonance forms for the chloronium ion. The resonance form that is a secondary carbocation is more stable than the resonance form that is a primary carbocation and contributes more strongly to the resonance hybrid.



chloronium ion | secondary carbocation | primary carbocation

Problem 7.11

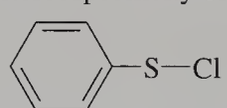
Give the structure of the product formed when 2-methyl-1-butene reacts with bromine in aqueous solution.

Problem 7.12

Give the structure of the product formed when cyclopentene reacts with chlorine in aqueous solution. What is the stereochemistry of the product?

Problem 7.13

Phenylsulfenyl chloride adds stereospecifically to carbon–carbon double bonds. Predict the product of the addition of this compound to 1-methylcyclohexene. Write the structure of an intermediate that accounts for the stereospecificity of the addition reaction.

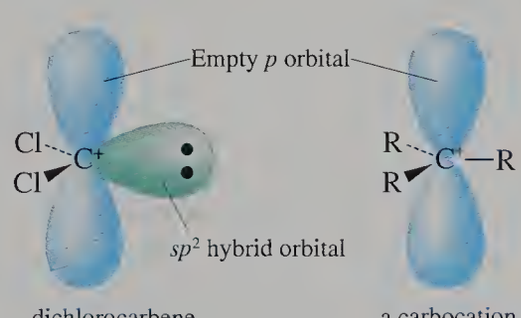


phenylsulfenyl chloride

7.7 Addition of Carbenes

A **carbene** is a divalent carbon species with six electrons in its valence shell and the formula $R_2C{:}$. The groups bonded to the carbon atom may be hydrogen, alkyl groups, aryl groups, or other atoms such as halogens. The structure of a carbene such as dichlorocarbene resembles that of a carbocation (Figure 7.6). Its carbon atom is sp^2 hybridized, with an empty p orbital located perpendicular to the plane containing the sp^2-hybridized orbitals. Two of the sp^2-hybridized orbitals are bonded to the two chlorine atoms. The remaining sp^2-hybridized orbital has an unshared pair of electrons.

FIGURE 7.6 Structure of a Carbene Compared to a Carbocation

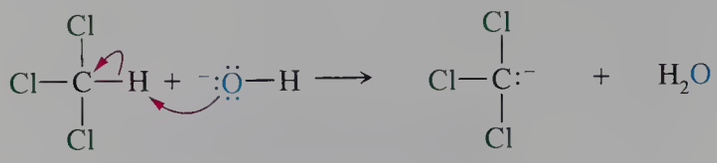


dichlorocarbene | a carbocation

Carbenes have a formal charge of zero because the unshared electron pair in the sp^2-hybridized orbital "belongs" to the carbon atom. Like a carbocation, a carbene is a highly reactive, electrophilic intermediate because it has only six electrons in its valence shell.

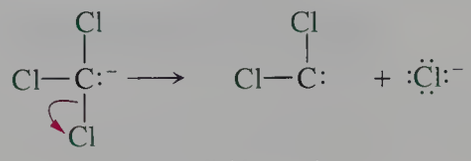
Formation of Dichlorocarbene

Dichlorocarbene (Cl_2C:) can be made from chloroform ($CHCl_3$), and a strong base such as *tert*-butoxide, $(CH_3)_3CO^-$ or potassium hydroxide. Chloroform has three electronegative chlorine atoms, which inductively withdraw electron density from the carbon atom. Thus, the hydrogen atom of $CHCl_3$ is much more acidic than the hydrogen atom of an alkane. The base removes a proton from $CHCl_3$, leaving the electron pair with the carbon atom. The product is a carbanion, the trichloromethanide ion.



trichloromethanide ion

The trichloromethanide ion loses a chloride ion to form dichlorocarbene, which is electrically neutral. Note that the electrons of the C—Cl bond leave with the chloride ion.

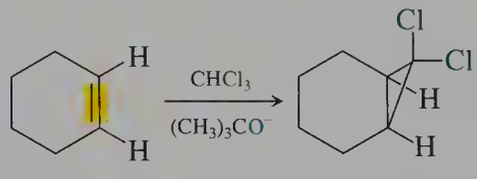


dichlorocarbene

The sum of the two steps corresponds to an elimination reaction (Section 2.13). However, we recall that elimination reactions most often result from the loss of groups bonded to adjacent atoms. These more common elimination reactions are designated β elimination reactions. The loss of two atoms or groups of atoms from the same carbon atom is called an α **elimination** reaction.

Stereospecificity of Carbene Addition Reaction

Carbenes are highly reactive intermediates that cannot be isolated, so they are generated in the presence of a selected reactant. When dichlorocarbene forms in the presence of an alkene, the electrophilic carbene attacks the double bond of the alkene to form a cyclopropane.



We won't discuss the mechanistic details of the addition of a carbene to an alkene. However, we note that a pair of electrons of the π bond and the unshared pair of electrons of the carbene provide the four electrons required to form two C—C bonds of

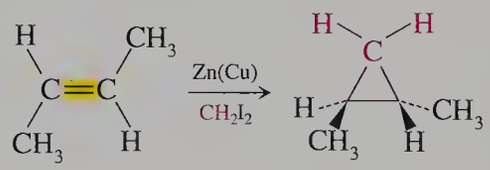
the cyclopropane ring. The reaction shown for cyclohexene and dichlorocarbene is stereospecific. Even with acyclic alkenes, cis alkenes yield cis-substituted cyclopropanes and trans alkenes yield trans-substituted cyclopropanes.

Carbenoid Species

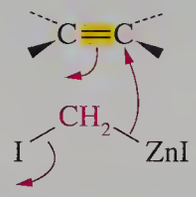
Methylene ($:CH_2$), the simplest carbene, can be prepared by decomposition of the highly toxic and explosive reagent diazomethane (CH_2N_2). However, more easily used reagents have been developed that, while they do not produce methylene, function as methylene transfer agents. They are called **carbenoid** species because they have "carbene-like" reactivity. Iodomethylzinc iodide, known as the Simmons–Smith reagent, is a carbenoid. In the Simmons–Smith method, diiodomethane reacts with a zinc–copper alloy to produce an intermediate ICH_2ZnI compound.

$$CH_2I_2 + Zn(Cu) \xrightarrow{\text{ether}} \underset{\text{Simmons–Smith reagent}}{I{-}CH_2{-}Zn{-}I}$$

The Simmons–Smith reagent transfers a CH_2 unit to the alkene in a stereospecific reaction. For example, *trans*-2-butene reacts with the Simmons–Smith reagent to give only *trans*-1,2-dimethylcyclopropane.



The transition state for the reaction of an alkene with the Simmons–Smith reagent results from a concerted transfer of a methylene unit from the iodomethylzinc iodide.



Problem 7.14

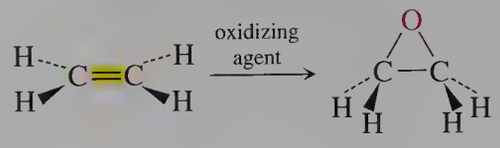
Write the expected product of the reaction of *trans*-2-butene with $CHBr_3$ and potassium *tert*-butoxide. Write the mechanism for the formation of the expected intermediate.

Problem 7.15

1,1-Diiodoethane and Zn(Cu) react with cyclohexene to give a mixture of two isomeric C_8H_{14} compounds. What are the structures of the two isomeric compounds? Explain why two isomers are formed.

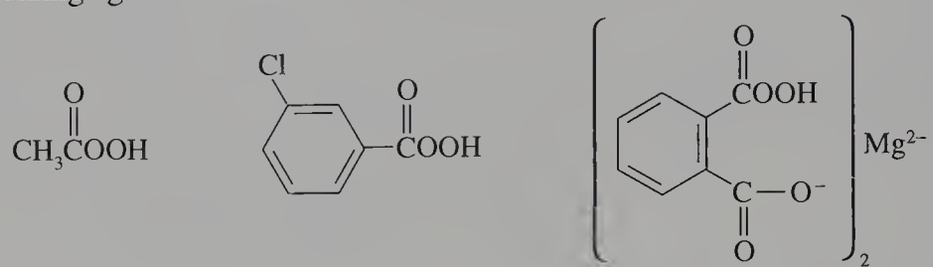
7.8 Epoxidation of Alkenes

The addition of an oxygen atom to an alkene to give a three-membered cyclic ether, called an **epoxide**, is an oxidation reaction because the oxygen content of the molecule increases. The preparation and reactions of epoxides are considered in detail in Chapter 17.



ethylene oxide

Epoxides have a strained three-membered ring, but they are easily prepared by an **epoxidation** reaction using peroxy acids (RCO_3H) such as peroxyacetic acid, m-chloroperbenzoic acid (MCPBA), or magnesium monoperoxyphthalate (MMPP) as the oxidizing agent.

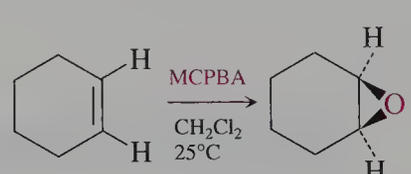


peroxyacetic acid | *m*-chloroperbenzoic acid | magnesium monoperoxyphthalate

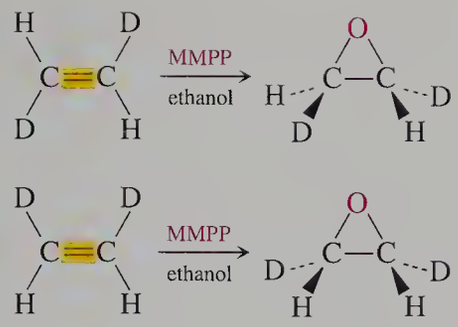
Peroxyacetic acid in an acetic acid solvent is used in industrial epoxidation reactions. Peroxyacetic acid is produced from the reaction of hydrogen peroxide with acetic acid.

$$CH_3—CO_2H + H_2O_2 \longrightarrow CH_3—CO_3H + H_2O$$

Until recently, *m*-chloroperoxybenzoic acid (MCPBA) was used to prepare smaller amounts of epoxides in the laboratory. It has been replaced by magnesium monoperoxyphthalate (MMPP). *m*-Chloroperoxybenzoic acid is soluble in methylene chloride, an excellent solvent for many organic compounds. Magnesium monoperoxyphthalate is used in ethanol as solvent.



In the epoxidation of alkenes with peroxy acids, the stereochemistry of the groups bonded to the double-bonded carbon atoms is retained. The reaction is stereospecific, as we see in the following deuterium-substituted compounds. Groups that are cis in the alkene are cis in the epoxide, and groups that are trans in the alkene remain trans in the epoxide.



Mechanism of Epoxidation

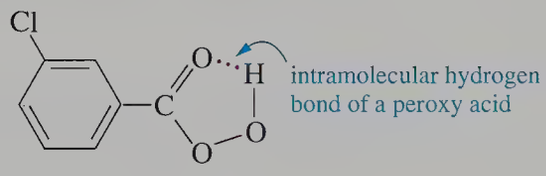
The accepted mechanism of an epoxidation reaction is based on (1) the stereochemistry of the addition product and (2) the effect of substituents on the rate of reaction. Alkyl groups increase the rate of reaction. The order of reactivity for some representative alkenes is

	$CH_2{=}CH_2$	$CH_3{-}CH{=}CH_2$	$(CH_3)_2C{=}CH_2$
relative rate of epoxidation:	1	22	4.8×10^2

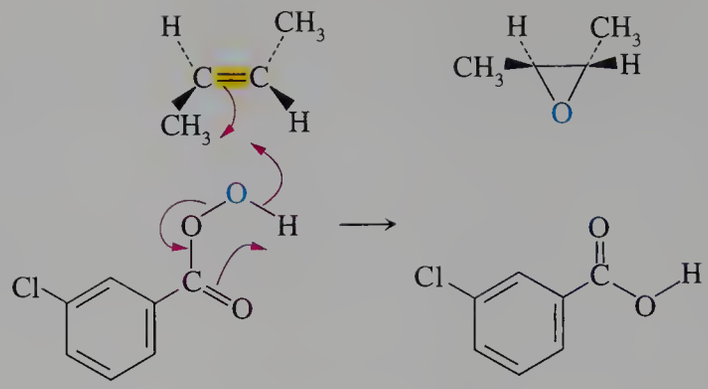
This order of reactivity indicates that some positive charge is developed at a carbon atom in the transition state. Because alkyl groups release electron density, the energy barrier is smaller in the more substituted alkene. The alkene develops a partial positive charge when electrons of the π bond are polarized toward the oxygen atom provided by the peroxy acid. In fact, the reactivity of the representative alkenes toward peroxy acids resembles the data for the addition of bromine to alkenes.

	$CH_2{=}CH_2$	$CH_3{-}CH{=}CH_2$	$(CH_3)_2C{=}CH_2$
relative rate of bromination:	1	60	5.5×10^3

When dissolved in CH_2Cl_2, *m*-chloroperoxybenzoic acid has an intramolecular hydrogen bond between its hydroxyl hydrogen atom and carbonyl oxygen atom.



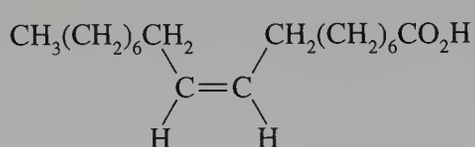
The oxygen–oxygen bond has a low bond energy. The peroxidic oxygen atom bonded to the hydrogen atom is transferred to the alkene in the reaction. This oxygen atom forms a bond with the electron pair of the alkene π bond. The electron pair required for the second carbon–oxygen bond of the epoxide is derived from the O—H bond of the peroxy acid. This electron pair is released as the hydrogen atom is simultaneously transferred to the carbonyl oxygen atom of the peroxy acid.



The reaction mechanism is a concerted process in which several bonds form and break. Although the reaction is concerted, some positive charge develops at the carbon atoms of the alkene as bonds form to the more electronegative oxygen atom. The cyclic arrangement of two carbon atoms and one oxygen atom resembles that of the bromonium ion. However, because two bonds simultaneously form to oxygen, the net stereochemistry of the epoxidation is a syn addition. We recall that bromonium ion also results from syn addition, but a subsequent step gives a net anti addition.

Problem 7.16

Microbial oxidation of oleic acid yields an epoxide. Write the structure of the product.



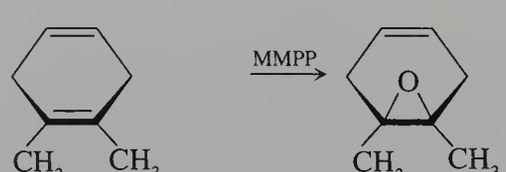
oleic acid

Problem 7.17

Write the structure of the epoxidation product of 1,2-dimethyl-1,4-cyclohexadiene obtained by reaction with one molar equivalent of magnesium monoperoxyphthalate.

Sample Solution

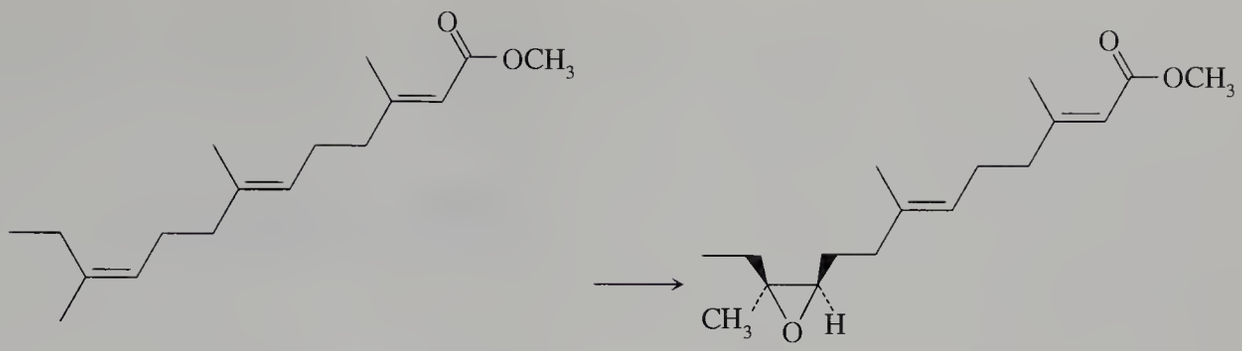
The compound has a disubstituted and a tetrasubstituted double bond. The rate of epoxidation at the tetrasubstituted bond is greater than that at the disubstituted double bond. Thus, the product of the reaction is



1,2-dimethyl-1,4-cyclohexadiene

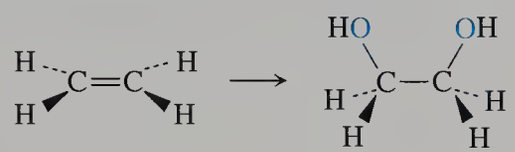
Problem 7.18

Epoxidation of the following compound in a laboratory synthesis gives a 40% yield of the juvenile hormone of insects. Explain why only a 40% yield is obtained.

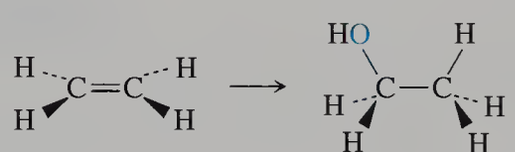


7.9 Dihydroxylation of Alkenes

The dihydroxylation of an alkene occurs by adding one OH group to each of the two alkene carbon atoms. Because two oxygen atoms and two hydrogen atoms are incorporated in the product, the net effect is oxidation. (Recall from Section 2.12 that the addition of one oxygen atom and two hydrogen atoms—which correspond to one water molecule in a hydration reaction—is not an oxidation reaction.)



a diol
(an oxidation product)

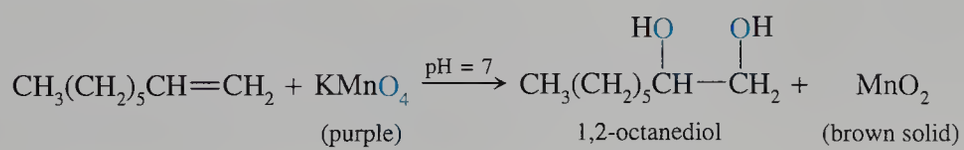


an alcohol
(an addition product)

The products of dihydroxylation are **vicinal diols**, commonly called **glycols**. They are made with either potassium permanganate ($KMnO_4$) or osmium tetraoxide (OsO_4) as the oxidizing agent.

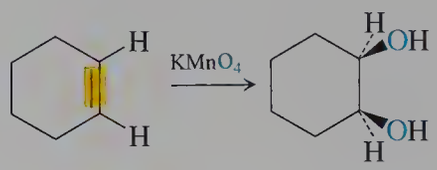
Dihydroxylation with Potassium Permanganate

Potassium permanganate is a readily available and inexpensive reagent. It reacts with alkenes in slightly alkaline conditions to produce vicinal diols. The reaction also gives manganese dioxide, a brown insoluble solid, as a by-product. Potassium permanganate is purple in aqueous solution. Manganese dioxide (MnO_2), the product of the reaction, is a brown solid that precipitates from solution. Since there is a color change, oxidation with potassium permanganate can be used to test visually for the presence of a double bond. Alkanes and cycloalkanes are not oxidized by $KMnO_4$, so the purple color remains.



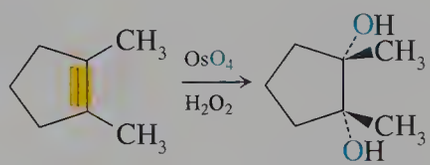
(purple) 1,2-octanediol (brown solid)

The stereochemistry of the dihydroxylation reaction is illustrated by the reaction of cyclohexene with potassium permanganate. The reaction occurs with syn addition of the two —OH groups to give *cis*-1,2-cyclohexanediol. The product is obtained only in modest yield because of side reactions.



Dihydroxylation with Osmium Tetraoxide

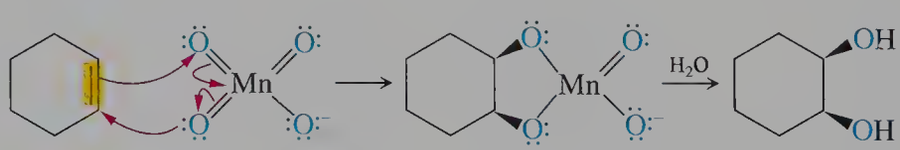
The oxidation of alkenes with osmium tetraoxide gives excellent yields of vicinal diols. However, this reagent is both expensive and highly toxic. Therefore, it is used only in small-scale laboratory syntheses, not in industrial processes. Osmium tetraoxide can, however, be used in a catalytic process in which the oxidizing agent is recycled. Hydrogen peroxide is used to oxidize the reduced osmium back to osmium tetraoxide, which continues to oxidize the alkene to a diol. This process allows the reaction to be carried out with only a small amount of the toxic OsO_4.



The stereochemistry of the dihydroxylation reaction is illustrated by the reaction of 1,2-dimethylcyclopentene. The oxygen atoms are added to the same face of the double bond. Thus, both $KMnO_4$ and OsO_4 form diols by syn addition.

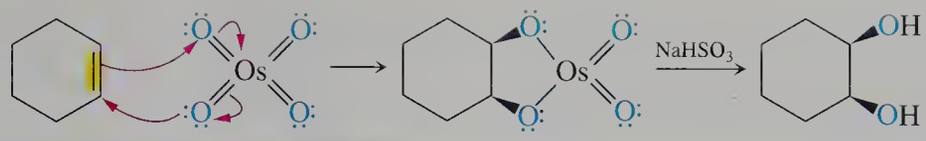
Mechanism of Syn Dihydroxylation

Permanganate ion adds to the double bond of an alkene by a cyclic mechanism in which the two carbon–oxygen bonds form simultaneously. The resulting cyclic permanganate ester has the oxygen atoms bonded to the same face of the original double bond. Then, the manganese–oxygen bonds of the reactive intermediate are hydrolyzed to form the diol.



cyclic manganate ester

The reaction of osmium tetraoxide with alkenes occurs by a similar mechanism to give a cyclic osmate ester. This intermediate is less reactive than the cyclic manganate ester. In fact, it can be isolated as a black solid. However, these intermediates are not usually isolated, but are hydrolyzed by aqueous sodium hydrogen sulfite.



Problem 7.19

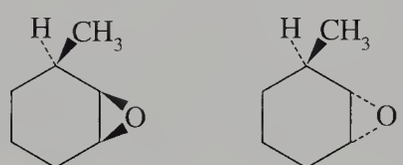
Write the product of the reaction of potassium permanganate with 1-methylcyclohexene under basic conditions.

Problem 7.20

The microbe *Pseudomonas putida* oxidizes 3-methylcyclohexene to produce two epoxides via a syn addition mechanism. Write the structures of the two products.

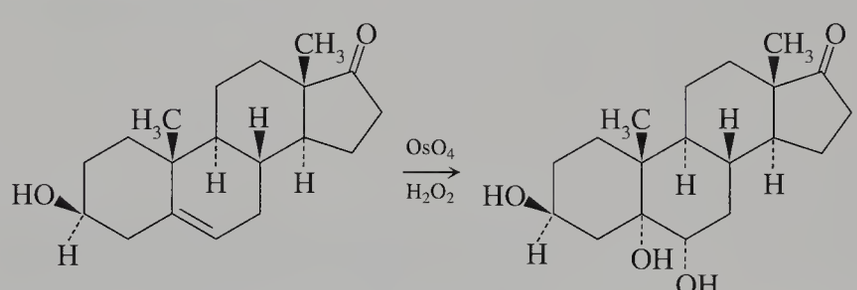
Sample Solution

The oxygen transferred to the double bond can approach from the same side of the ring as the methyl group or the opposite side to give two stereoisomeric products. The epoxide ring may be either cis or trans to the methyl group in the product.



Problem 7.21

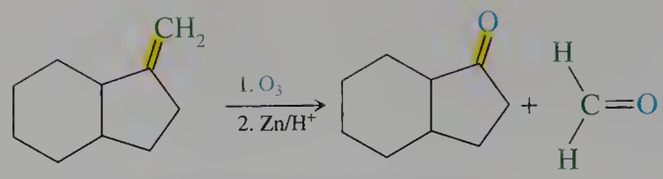
Dihydroxylation of the following steroid gives only the indicated product. Based on the mechanism of the reaction and the indicated stereochemistry, explain why only one diol forms.



7.10 Ozonolysis of Alkenes

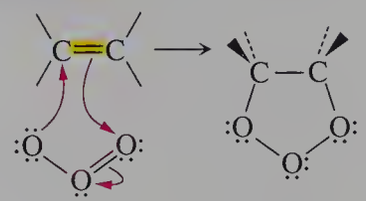
In both epoxidation and dihydroxylation reactions, oxidation occurs at the carbon atoms of the original double bond, but the hydrocarbon skeleton remains intact. Now we consider a reaction in which the products are more highly oxidized. The carbon–carbon double bond is cleaved to produce carbonyl compounds.

Alkenes react rapidly with ozone (O_3) even at −78 °C. Ozone is produced in the laboratory by a device called an ozonator, which forms ozone by passing oxygen gas through an arc discharge. As the ozone forms, oxygen gas containing a few percent ozone is passed through an inert solvent, such as dichloromethane, that contains the alkene. After the reaction is complete, the solution is worked up under reductive conditions such as zinc in acetic acid.



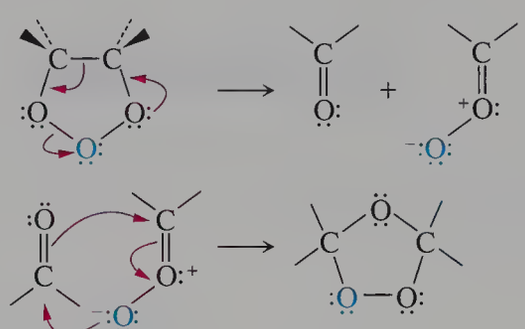
Mechanism of Ozonolysis

Ozonolysis occurs in several steps. First, an unstable intermediate, called a molozonide, forms by a cyclic concerted addition of the terminal oxygen atoms of ozone to the π bond of the alkene. This step requires a total of three electron pair shifts as shown below.



molozonide

In subsequent steps, the molozonide rapidly rearranges when the σ bond of the alkene and an O—O peroxide bond break. The fragments then recombine to give an ozonide. The individual fragments are reoriented to illustrate the addition reaction in the second step shown below.

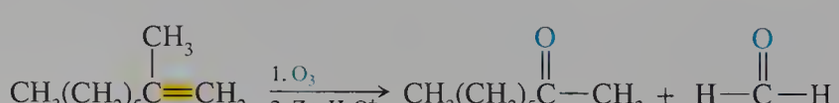


ozonide

The molozonide has two weak peroxide bonds, but the ozonide has only one. This difference accounts for the direction of the reaction. The rearrangement of the molozonide is exothermic. However, ozonides are explosively unstable compounds. For that reason, the reaction mixture is maintained at low temperatures and immediately reduced or oxidized after the reaction is complete.

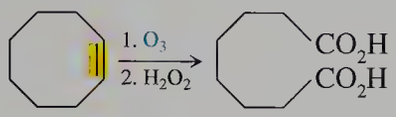
Reductive and Oxidative Workup

The ozonolysis reaction mixture is treated with reducing agents such as zinc metal and aqueous acetic acid or dimethyl sulfide. When zinc is used, the by-product is zinc oxide. When dimethyl sulfide is the reducing agent, dimethyl sulfoxide, $(CH_3)_2SO$, is a by-product. In each case, the reducing agent removes one of the oxygen atoms of the ozonide. The other two oxygen atoms of the ozonide are found as carbonyl oxygen atoms in the product aldehydes or ketones.



2-methyl-1-octene 2-octanone formaldehyde

If the ozonolysis reaction mixture is treated with an oxidizing agent such as hydrogen peroxide, carboxylic acids rather than aldehydes are produced. For example, the ozonolysis of cyclooctene with an oxidative workup yields suberic acid.



octanedioic acid
(suberic acid)

The choice of reducing or oxidizing workup depends on the goal of the synthesis, which may be to prepare aldehydes (or ketones) or carboxylic acids.

Use of Ozonolysis in Structure Determination

Ozonolysis can be used to determine the position of a double bond in an alkene as part of the process of assigning a structure to an unknown compound. Although once a common procedure, ozonolysis as a method of structure determination is not widely used now. Currently, spectroscopic methods, which do not destroy the sample, are used. The sample can be recovered unchanged after its spectrum is determined. However, we will still outline the method to illustrate how the oxidative fragments of ozonolysis can be mentally pieced together to "reconstruct" the original alkene. The carbonyl products of ozonolysis are determined by the degree of substitution of the double bond. The possible combinations of products obtained under reductive workup conditions are

$RCH{=}CH_2$ gives RCHO (aldehyde) + CH_2O (formaldehyde)

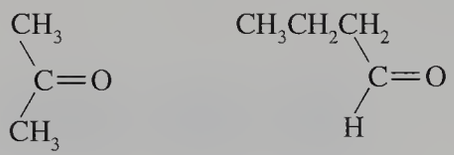
$R_2C{=}CH_2$ gives R_2CO (ketone) + CH_2O (formaldehyde)

$RCH{=}CHR'$ gives RCHO (aldehyde) + R′CHO (aldehyde)

$R_2C{=}CHR'$ gives R_2CO (ketone) + R′CHO (aldehyde)

$R_2C{=}CR'_2$ gives R_2CO (ketone) + R'_2CO (ketone)

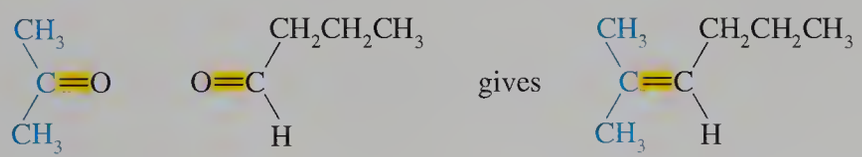
To illustrate the analytical method of determining the structure of an alkene, consider the reaction of an alkene of molecular formula C_7H_{14} with ozone to yield the following two carbonyl compounds.



propanone
(acetone)

butanal

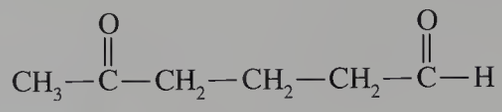
The oxygen atoms mark the carbon atoms that were originally part of the double bond. Place those carbon atoms from the two carbonyl compounds near each other. Mentally remove the oxygen atoms and join the carbon atoms with a double bond.



2-methyl-2-hexene

Problem 7.22

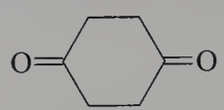
A hydrocarbon of molecular formula C_6H_{10} reacts with ozone followed by treatment with zinc and acetic acid to give 5-ketohexanal. Draw the structure of the hydrocarbon.



5-ketohexanal

Problem 7.23

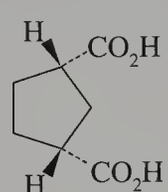
A hydrocarbon of molecular formula C_8H_{12} reacts with O_3 followed by workup with $(CH_3)_2S$ to give formaldehyde and cyclohexane-1,4-dione. Draw the structure of the hydrocarbon.



cyclohexane-1,4-dione

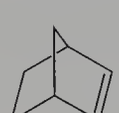
Problem 7.24

A hydrocarbon of molecular formula C_7H_{10} reacts with O_3 followed by an oxidative workup to give only the following dicarboxylic acid. Draw the structure of the hydrocarbon.



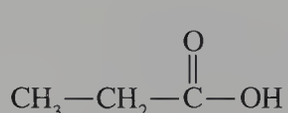
Sample Solution

If both oxidative fragments are contained within a single molecule, the original compound must have been a cycloalkene. Joining the two carbon atoms of the carboxyl groups by a carbon–carbon double bond generates another ring. The original compound is bicyclic.

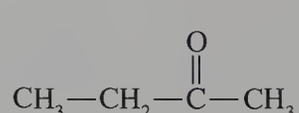


Problem 7.25

A hydrocarbon of molecular formula C_7H_{14} reacts with O_3 followed by an oxidative workup to give propanoic acid and 2-butanone. Does this information unambiguously establish the structure of the hydrocarbon?



propanoic acid



2-butanone

7.11 Free Radical Addition of Hydrogen Bromide

The regiospecificity of the addition of HBr to alkenes was not easily established. Prior to 1933, the addition product obtained followed Markovnikov's rule some of the time, but under apparently identical reaction conditions, the opposite regioselectivity was also observed. Researchers in different laboratories obtained different products for the same reaction. It became clear that the Markovnikov product was obtained only if the reactants were carefully purified. If the reactants contain small quantities of impurities, which produce peroxides (R—O—O—R), the reaction with HBr gives the anti-Markovnikov product. That is, the reaction occurs with the opposite regioselectivity. With purified 1-butene, the Markovnikov product 2-bromobutane always forms. In the presence of peroxides, the anti-Markovnikov product 1-bromobutane forms.

$$CH_3—CH_2—CH=CH_2 + HBr \xrightarrow{\text{no peroxides}} CH_3—CH_2—\underset{\displaystyle Br}{\underset{|}{CH}}—CH_3$$

Markovnikov product

$$CH_3—CH_2—CH=CH_2 + HBr \xrightarrow{\text{peroxides}} CH_3—CH_2—CH_2—CH_2—Br$$

anti-Markovnikov product

Mechanism of Anti-Markovnikov Addition

The mechanism of the addition reaction in the presence of peroxides differs from the electrophilic addition mechanism. A clue to the alternate mechanism is provided by the fact that only a small amount of impurities is required to completely reverse the regioselectivity. Moreover, the alternate reaction occurs very rapidly. Both facts suggest that the peroxides present are a source of free radicals that initiate a free radical chain mechanism. The oxygen–oxygen bond has a low bond energy of about 150 kJ mole^{-1} (36 kcal mole^{-1}). Homolytic cleavage of this weak bond produces alkoxy radicals that abstract a hydrogen atom from HBr in the initiation steps.

$$R—\ddot{O}—\ddot{O}—R \xrightarrow{\text{homolytic cleavage}} 2\,R—\ddot{O}\cdot$$

$$R—\ddot{O}\cdot + H—\ddot{B}r: \xrightarrow{\text{homolytic cleavage}} 2\,R—\ddot{O}—H + :\ddot{B}r\cdot$$

After the bromine radical forms, two chain propagation steps occur. First, a bromine atom adds to the π bond to give an alkyl radical. The carbon–bromine bond is formed using one electron from the bromine atom and one electron from the π bond. The remaining electron of the original π bond is localized on a carbon atom. In the second step, the alkyl radical reacts by abstracting a hydrogen atom from HBr, giving the observed addition product plus another bromine radical.

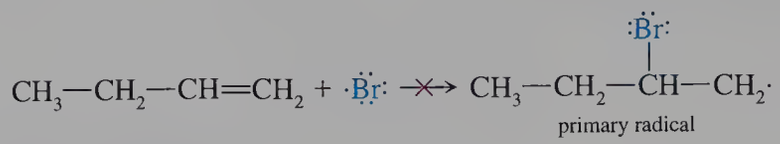
$$CH_3—CH_2—CH=CH_2 + \cdot\ddot{B}r: \longrightarrow CH_3—CH_2—\underset{\displaystyle :\ddot{B}r:}{\underset{|}{CH}}—CH_2$$

secondary free radical

$$CH_3—CH_2—\underset{\displaystyle :\ddot{B}r:}{\underset{|}{CH}}—CH_2 + H—\ddot{B}r: \longrightarrow CH_3—CH_2—\underset{\displaystyle H}{\underset{|}{CH}}—\underset{\displaystyle :\ddot{B}r:}{\underset{|}{CH_2}} + :\ddot{B}r\cdot$$

The chain propagation steps occur sequentially because the product of the first reaction is the reactant in the subsequent step. The two steps occur many times in a chain reaction.

The structure of the product is determined by the first propagation step in which the bromine atom bonds to the primary carbon atom to give a secondary radical. If addition of a bromine atom occurred at C—2, a primary radical would result.



Because a primary radical is less stable than a secondary radical (Section 5.2) the Markovnikov product is not obtained under free radical conditions.

The difference in the structures of the products of Markovnikov addition and anti-Markovnikov addition reflects a difference in the mechanisms of the two reactions. However, in both mechanisms, the regioselectivity reflects the stability of the intermediate. Markovnikov addition of HBr results from protonation of the π bond in a polar addition step that produces the more stable carbocation. Anti-Markovnikov addition of HBr is the result of attack of a bromine atom in a radical reaction to give the more stable alkyl radical.

Absence of Rearranged Products

The free radical addition of HBr to an alkene does not give rearranged constitutional isomers such as are formed in the electrophilic addition of HBr to alkenes. We recall that the differences in the stabilities of radicals are less than the differences in stabilities of carbocations (Section 3.13). Because radicals are less electron deficient than carbocations, the effect of bonded alkyl groups on stability is less. As a result, there is less driving force for the rearrangement of radicals.

7.12 Polymerization of Alkenes

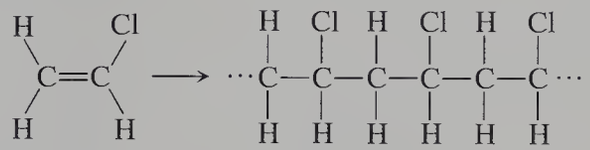
A **polymer** is a high molecular weight molecule created by the repeated addition reactions of many low molecular weight molecules called **monomers**. The process in which monomers join to produce polymers is called **polymerization**. Naturally occurring polymers, called **biopolymers**, include carbohydrates, proteins, and nucleic acids. Cellulose, a polymer of glucose, is the major structural material of plants. Lignin, another carbohydrate polymer, occurs within the spaces between the long fibers of cellulose. Proteins, polymers of amino acids, are major constituents of living matter. Some serve a structural role, others catalyze virtually all metabolic reactions. Nucleic acids, polymers of nucleotides, carry genetic information. We will study some of these classes of compounds in later chapters.

Synthetic polymers are also familiar because we are literally surrounded with these substances. Examples include some of the clothes we wear, containers for foods such as milk, and the computers we use. Football players depend on polymers in helmets for protection; police use bulletproof vests made of a polymer; our cars have many polymers in the interior as well as in the bumpers. In this section, we will discuss the remarkably simple reactions that join monomers together to provide these diverse products.

There are two classes of polymers based on the type of reaction used to join the monomers: addition polymers and condensation polymers. Only addition poly-

merization will be illustrated in this section. Condensation polymerization, giving polyesters and polyamides, is described in Chapters 22 and 25, respectively.

Alkenes can be polymerized by a multiple addition reaction. For example, when $CH_2{=}CHCl$ (vinyl chloride) is polymerized, the product is polyvinyl chloride, commonly known as PVC.



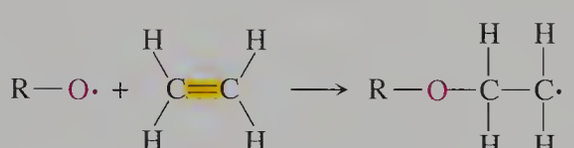
An exact formula for a polymer cannot be written because the size of the molecule depends on how it forms. There is no single "polyvinyl chloride" molecule. PVC is really a mixture of compounds with a range of molecular weights. For this reason, polymers are represented by placing the repeating unit derived from the monomer within a set of parentheses. For polyvinyl chloride, the unit is $(—CH_2CHCl—)$. To show that a large number of units are present, the letter n is added as a subscript. For the polymer of vinyl chloride we write $(—CH_2CHCl—)_n$.

The properties of polymers depend on the monomer used and the molecular weight of the product. A list of some useful addition polymers is given in Table 7.2.

Polymerization of an alkene occurs when a small amount of a suitable initiator is used. The initiator may be a radical, a cation, or an anion, depending on the properties of the monomer. In each case, the initiator reacts with the double bond to form an intermediate that reacts with another double bond to form another reactive intermediate. This process continues and generates the polymeric chain of monomers. The process is eventually terminated by some reaction that destroys the reactive site. Details of termination reactions will be discussed in Chapter 29.

Free Radical Polymerization

Polyethylene is produced by **free radical polymerization** that occurs at pressures of 1000–3000 atm and temperatures of 100–200 °C. A radical initiator is used to generate the radical intermediates responsible for the growth of the polymer chain. The initiator is a peroxide represented as R—O—O—R. Homolytic cleavage of the oxygen–oxygen bond occurs when the peroxide is heated. Reaction of the radical with ethylene in a homogenic reaction forms a carbon radical.



The carbon radical "reactant" continues in a chain reaction with more ethylene units. Each new radical "product" contains one more ethylene unit.

$$ROCH_2CH_2\cdot \xrightarrow{CH_2=CH_2} ROCH_2CH_2CH_2CH_2\cdot \xrightarrow{CH_2=CH_2} ROCH_2CH_2CH_2CH_2CH_2CH_2\cdot$$

Although the polymer consists of a chain of $—CH_2—$ units, the repeating unit, based on the structure of the monomer, is $—CH_2CH_2—$. The polymer is represented by $(—CH_2CH_2—)_n$.

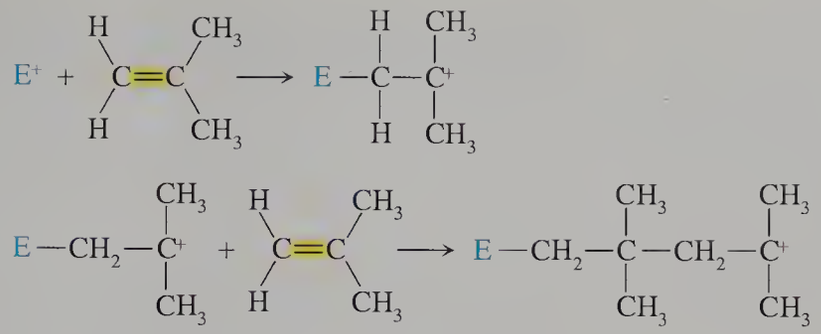
TABLE 7.2
Uses and Structures of Polymers

Monomer	*Polymer*	*Use*
propylene $CH_2{=}CHCH_3$	polypropylene $-CH_2CH(CH_3)CH_2CH(CH_3)-$	carpet fibers, heart valves, bottles
vinyl chloride $CH_2{=}CHCl$	polyvinyl chloride (PVC) $-CH_2CH(Cl)CH_2CH(Cl)CH_2CH(Cl)-$	floor covering, records, garden hoses
dichloroethylene $CH_2{=}CCl_2$	polydichloroethylene $-CH_2CCl_2CH_2CCl_2CH_2CCl_2-$	plastic food wrap
tetrafluoroethylene $CF_2{=}CF_2$	polytetrafluorethylene $-CF_2CF_2CF_2CF_2CF_2CF_2-$	Teflon, bearings
acrylonitrile $CH_2{=}CHCN$	polyacrylonitrile $-CH_2CH(CN)CH_2CH(CN)CH_2CH(CN)-$	Orlon, Acrilan
styrene $CH_2{=}CHC_6H_5$	polystyrene $-CH_2CH(C_6H_5)-CH_2CH(C_6H_5)-CH_2CH(C_6H_5)-$	toys, styrofoam
methyl methacrylate $CH_2{=}C(CH_3)-C(=O)OCH_3$	polymethyl methacrylate $-CH_2C(CH_3)(COOCH_3)-CH_2-C(CH_3)(COOCH_3)-CH_2-C(CH_3)(COOCH_3)-$	Plexiglas, Lucite

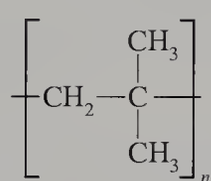
Polyethylene is the world's most common polymer. The United States alone produces more than 8 million tons a year. The properties of the polymer depend on the method of production and its molecular weight. Examples include very flexible sandwich bags (20,000 units/molecule), less flexible milk and soft-drink bottles (30,000 units/molecule), and very stiff plastic bottle caps (40,000 units/molecule).

Cationic Polymerization

Cationic polymerization involves carbocations rather than radicals. A Lewis acid such as BF_3, $Al(CH_2CH_3)_3$, $TiCl_4$, or $SnCl_4$ reacts with the alkene to form a carbocation, which in turn reacts with another alkene molecule to form another cation. Consider the reaction with 2-methylpropene (isobutylene) as the monomer, forming polyisobutylene. The Lewis acid that acts as an electrophile is represented by E^+.



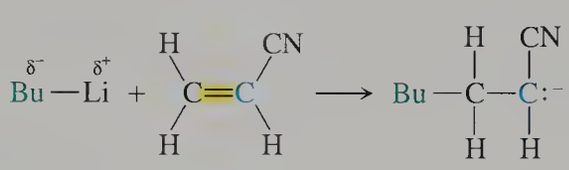
Note that addition occurs in the Markovnikov manner. Subsequent reactions continue with the carbocation adding to the less substituted carbon atom. As a consequence, the more stable tertiary carbocation is formed each time. The structure of the polymer is represented as



Low molecular weight polyisobutylene is used in lubricating oil and adhesives for removable paper labels. Higher molecular weight polyisobutylene is used to produce inner tubes for bicycle and truck tires.

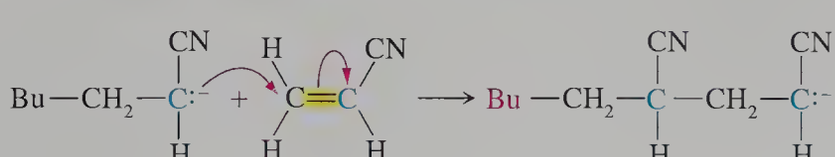
Anionic Polymerization

Anionic polymerization is initiated by a carbanion that behaves as a nucleophile. One example is the butyl anion, provided by butyllithium. The lithium compound has a very polar bond, and the carbon atom has a partially negative charge. In the following reactions, the butyl group is represented by Bu—. The monomer is acrylonitrile.

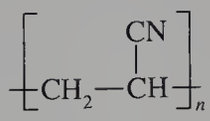


Addition occurs at the less substituted carbon atom because the resulting carbanion is resonance stabilized.

Continued reaction of the nucleophilic carbanion "reactant" gives a carbanion "product", and the length of the polymer chain increases.



Subsequent reactions continue to form the stabilized carbanion. The structure of the polymer is represented as



Polyacrylonitrile is used in fibers that can be spun to give the textiles Orlon or Acrilan. Some rugs are also produced with this polymer.

EXERCISES

Thermodynamics of Addition Reactions

7.1 Calculate ΔH°_{rxn} for the addition of IBr (an interhalogen compound) to ethylene using the following DH° values.

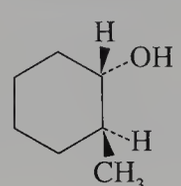
I—Br 279 kJ mole^{-1} (67 kcal mole^{-1})
C—Br 289 kJ mole^{-1} (69 kcal mole^{-1})
C—I 216 kJ mole^{-1} (52 kcal mole^{-1})

7.2 Calculate ΔH°_{rxn} for the addition of HF to ethylene using the following DH° values.

H—F 567 kJ mole^{-1} (136 kcal mole^{-1})
C—F 465 kJ mole^{-1} (111 kcal mole^{-1})
C—H 422 kJ mole^{-1} (101 kcal mole^{-1})

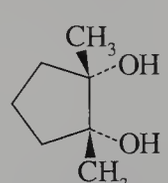
Syn-Anti Addition

7.3 The indirect hydration of an alkene using a procedure called hydroboration–oxidation transforms 1-methylcyclohexene into *trans*-2-methylcyclohexanol. Describe the stereochemistry of the net addition reaction.



trans-2-methylcyclohexanol

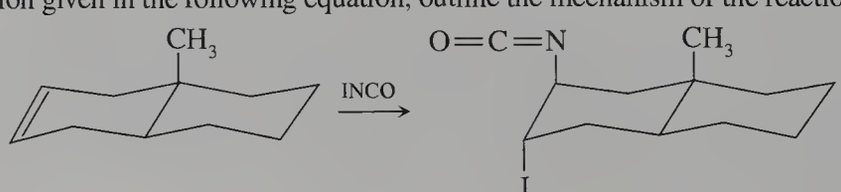
7.4 Reaction of 1,2-dimethylcyclopentene with potassium permanganate yields the following compound. What is the stereochemistry of the net addition reaction?



Electrophiles and Markovnikov's Addition

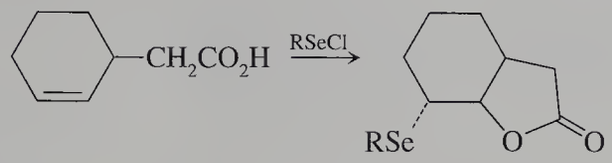
7.5 Predict the structure of the addition product of IN_3 and 1-pentene. The mechanism involves electrophilic attack followed by capture of the carbocation by a nucleophile. The structure of IN_3 is given below.

7.6 Based on the information given in the following equation, outline the mechanism of the reaction of the reagent INCO.



7.7 The reagent N≡C—Se—Cl gives an intermediate formed by heterolysis of the Se—Cl bond. Draw the expected structure of the addition product with 2-methyl-1-propene in methanol as solvent.

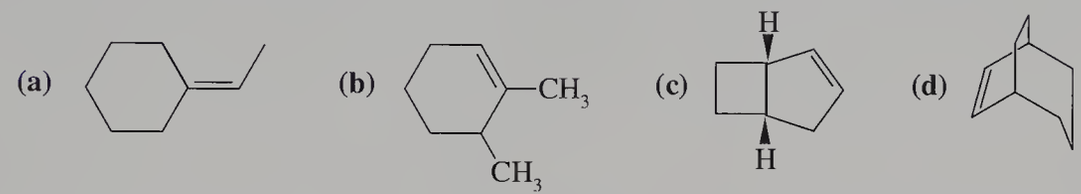
7.8 Selenoyl chlorides (RSe—Cl) add to alkenes. Explain the origin of the product of the following reaction.



Electrophilic Addition of Hydrogen Halide

7.9 Write the product of the reaction of HBr with each of the following compounds.
(a) 2-methyl-1-butene **(b)** 2-methyl-2-butene **(c)** (*Z*)-2-hexene **(d)** (*E*)-3-methyl-2-pentene

7.10 Write the product of the reaction of HBr with each of the following compounds.



7.11 Reaction of 1,6-dimethylcyclohexene with HBr by an electrophilic addition mechanism yields two products. What are the two compounds?

7.12 Reaction of 1,2-dimethylcyclohexene with HCl by an electrophilic addition mechanism yields two products. What are the two compounds?

7.13 The electrophilic addition of HCl to 3,3,3-trifluoropropene gives 1-chloro-3,3,3-trifluoropropane, an anti-Markovnikov addition product. Consider the structure of the intermediate carbocations possible for the two modes of addition and suggest a reason for the observed regioselectivity.

$$CF_3CH{=}CH_2 + HCl \longrightarrow CF_3CH_2CH_2Cl$$

7.14 The electrophilic addition of HCl to vinyl chloride yields 1,1-dichloroethane. Based on resonance structures, account for the observed regioselectivity.

7.15 Reaction of 3,3-dimethyl-1-butene with HI gives a mixture of unrearranged product and rearranged product in the ratio 90:10. Account for the difference in this ratio compared to that for addition of HCl (Section 7.4).

7.16 Reaction of 3,3-dimethyl-1-butene with HBr gives a mixture of two addition products in the ratio 70:30. Based on Exercise 7.15, predict the structures of the two products.

Hydration of Alkenes

7.17 Write the product of hydration of each of the compounds in Exercise 7.9.

7.18 Write the product of hydration of each of the compounds in Exercise 7.10.

7.19 Hydration of either 2-methyl-1-butene or 2-methyl-2-butene yields the same alcohol. What is its structure? Explain why the same compound forms from both alkenes.

7.20 Hydration of 2,3-dimethyl-2-butene is a slower reaction than the hydration of 2,3-dimethyl-1-butene under the same reaction conditions. Suggest a possible explanation.

Addition of Bromine to Alkenes

7.21 Write the structure of the addition product of bromine with each compound given in Exercise 7.9.

7.22 Write the structure of the addition product of bromine with each compound given in Exercise 7.10.

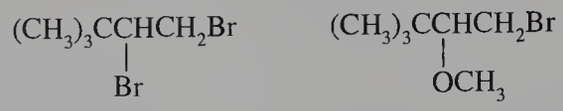
7.23 Reaction of 3-methylcyclohexene with bromine in CCl_4 gives a mixture of two products. Explain why two products result.

7.24 Reaction of 3-bromocyclohexene with HBr gives an "unusual" product— *trans*-1,2-dibromocyclohexane. Explain its origin using an appropriate mechanism and intermediate.

7.25 The reaction of cyclohexene with bromine in water as the solvent yields the alcohol *trans*-2-bromocyclohexanol. Explain why.

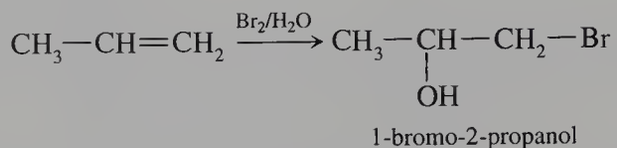
7.26 Reaction of cyclohexene with an aqueous bromine solution saturated with sodium chloride gives a mixture of *trans*-2-bromocyclohexanol and a compound with the molecular formula $C_6H_{10}BrCl$. What is the structure of the latter compound?

7.27 Bromination of 3,3-dimethyl-1-butene in methanol (CH_3OH) gives a mixture of the expected dibromo compound and a bromoether. Explain the origin of the two products.

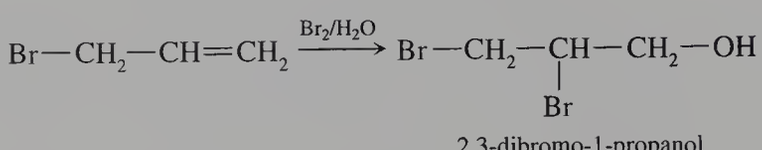


7.28 Based on the information given in Exercise 7.25, predict the structure of the chloroalcohol formed in the reaction of methylenecyclohexane with an aqueous chlorine solution.

7.29 Reaction of propene with aqueous bromine gives the expected product 1-bromo-2-propanol, but reaction of 3-bromo-1-propene with aqueous bromine gives 2,3-dibromo-1-propanol. Suggest a reason for this difference in regioselectivity.

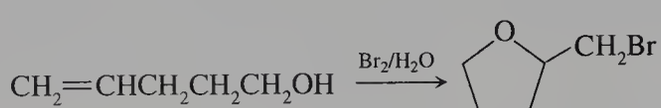


1-bromo-2-propanol



2,3-dibromo-1-propanol

7.30 Reaction of 4-penten-1-ol with aqueous bromine gives the indicated cyclic bromoether. Write a mechanism for its formation.

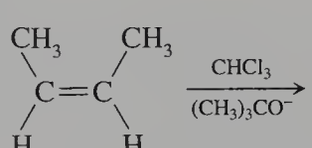


Carbene Additions

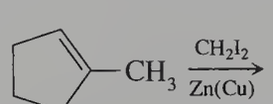
7.31 Chlorocarbene (CHCl) can be produced from dichloromethane using butyl lithium ($CH_3CH_2CH_2CH_2^-Li^+$) but cannot be produced using potassium tert-butoxide. Suggest a reason why not.

7.32 Addition of chlorocarbene to *cis*-2-butene gives a mixture of two isomeric compounds. Explain why.

7.33 Write the products of the following reaction.



7.34 Write the product of the following reaction.

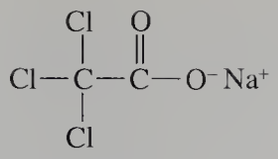


7.35 Based on the stated electrophilicity of dichlorocarbene, predict the relative reactivities of 1-butene and *trans*-2-butene with dichlorocarbene.

7.36 Predict the relative electrophilicities of dichlorocarbene and chlorocarbene.

7.37 Reaction of 1,1-dichloroethane with butyllithium does not give a carbene. Why?

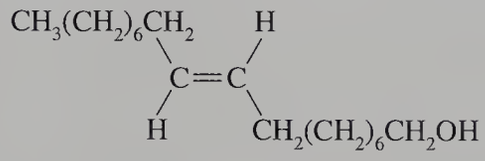
7.38 Dichlorocarbene can be formed by heating sodium trichloroacetate. Propose a mechanism for the reaction. What are the by-products?



sodium trichloroacetate

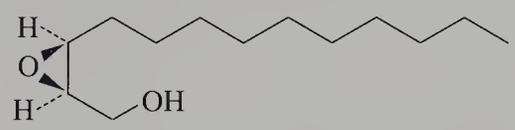
Epoxidation of Alkenes

7.39 Write the structure of the epoxide obtained from the reaction of *trans*-9-octadecen-1-ol with MCPBA.

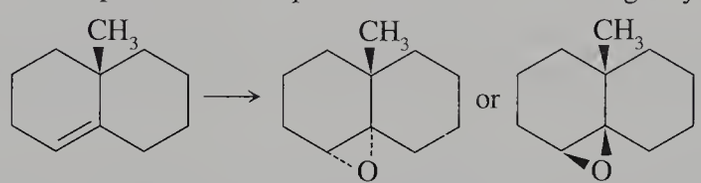


trans-9-octadecen-1-ol

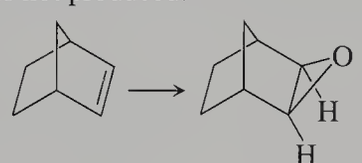
7.40 The following epoxide is an intermediate in the synthesis of disparlure, the sex attractant of the gypsy moth. Write the structure of the unsaturated alcohol used to produce the epoxide.



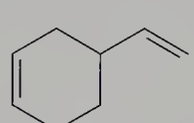
7.41 Predict which of the two isomeric epoxides will be produced from the following bicyclic unsaturated compound.



7.42 Oxidation of bicyclo[2.2.1]hept-2-ene gives the indicated epoxide. Write the structure of an alternative epoxide product and explain why this compound is not produced.



7.43 Write the structure of the epoxide expected from the reaction of the following diene with one molar equivalent of MCPBA.



7.44 Arrange the following compounds in order of increasing rate of reaction with MCPBA.

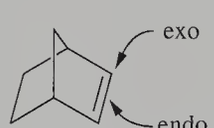
I: 5-methyl-1-hexene II: 3-methyl-2-hexene III: 4-methyl-2-hexene IV: 2,3-dimethyl-2-pentene

Dihydroxylation of Alkenes

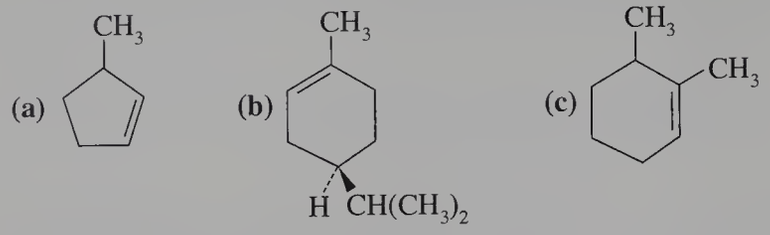
7.45 Describe the observation that is made when *cis*-2-pentene reacts with potassium permanganate. How could this reagent be used to distinguish between the isomers *cis*-2-pentene and cyclopentane?

7.46 Write the product of the reaction of vinylcyclohexane with potassium permanganate.

7.47 The exo face of bicyclo[2.2.1]hept-2-ene (norbornene) is less sterically hindered than the endo face. Based on this information, write the product of reaction of norbornene with $KMnO_4$.

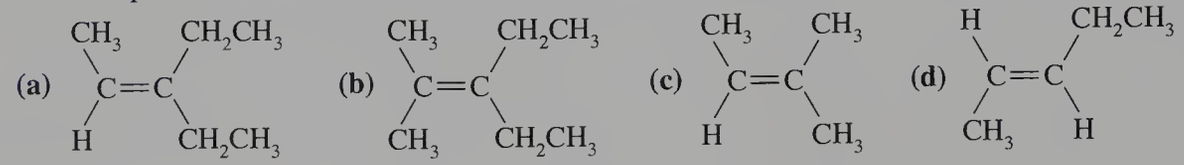


7.48 Write the structure of the diol obtained from the reaction of OsO_4 with each of the following alkenes.

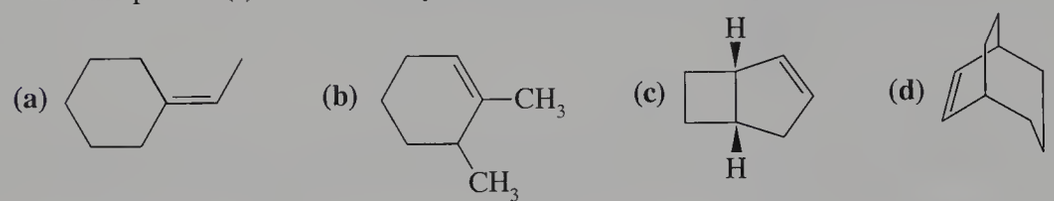


Ozonolysis of Alkenes

7.49 Write the product(s) of the ozonolysis of each of the following compounds under reductive workup conditions.



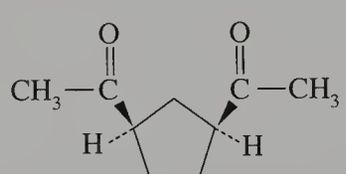
7.50 Write the product(s) of the ozonolysis of each of the following compounds under oxidative workup conditions.



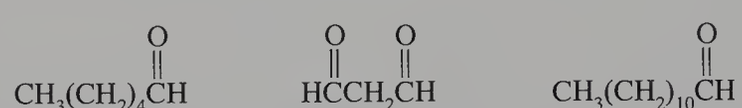
7.51 How can you distinguish between 1,3-cyclohexadiene and 1,4-cyclohexadiene based on their ozonolysis products?

7.52 Write the products of ozonolysis using reductive workup conditions for each of the three isomeric methylcyclohexenes and classify the carbonyl group present in each product.

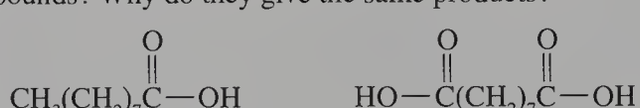
7.53 A hydrocarbon of molecular formula C_9H_{14} is found in sandalwood oil. Ozonolysis of the hydrocarbon followed by oxidative workup gives the following diketone. Draw the structure of the hydrocarbon.



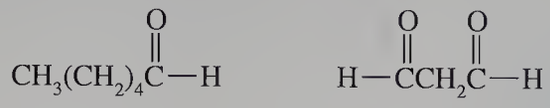
7.54 A hydrocarbon component of a pheromone of a species of moth reacts with ozone followed by reductive workup to give the following compounds. Draw a structure of the hydrocarbon. How many geometric isomers are possible with this structure?



7.55 Two isomeric unsaturated carboxylic acids, oleic acid and elaidic acid, melt at 13 and 45 °C, respectively. Ozonolysis of either compound under oxidative conditions yields the following two compounds. What are possible structures of the two compounds? Why do they give the same products?



7.56 An unsaturated fatty acid contained in brain tissue has the molecular formula $C_{24}H_{40}O_2$. Hydrogenation yields an unbranched carboxylic acid of molecular formula $C_{24}H_{48}O_2$. Ozonolysis of the fatty acid under reductive conditions yields 2 equivalents of 1,3-propanedial and 1 equivalent each of hexanal and an aldehydic acid with the formula $C_{12}H_{22}O_3$. Write the structure of the most stable isomer that is consistent with these data. How many other isomeric compounds are also consistent with the data?



hexanal

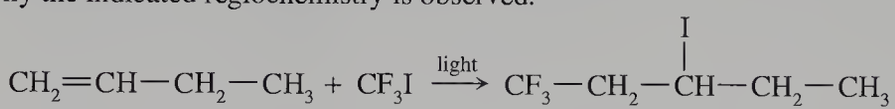
1,3-propanedial

Radical Reactions

7.57 Write the product of the free radical addition of HBr to each of the compounds given in Exercise 7.9.

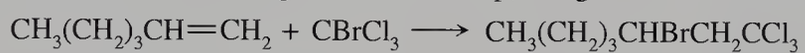
7.58 Write the product of the free radical addition of HBr to each of the compounds given in Exercise 7.10.

7.59 Trifluoroiodomethane reacts with 1-butene according to the following equation. Suggest the mechanism for the reaction. Explain why the indicated regiochemistry is observed.



7.60 Based on the information given in Exercise 7.59, predict the products of the reaction of CF_3I with 2-methyl-1-pentene and with 3-methyl-1-pentene. Which reaction will occur more rapidly?

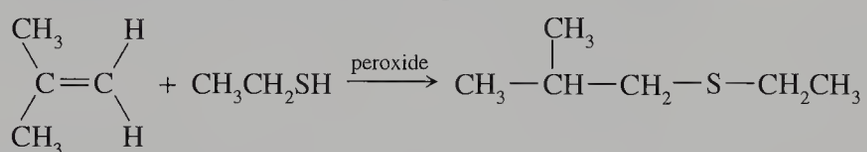
7.61 Bromotrichloromethane adds to 1-hexene in the presence of free radical initiators to give the indicated product. Write the mechanism of the reaction, including the initiation step, using In· as the free radical initiator.



7.62 Based on the information given in Exercise 7.61, predict the product of the free radical reaction of $CBrCl_3$ with 2-methyl-1-pentene. Will this reaction be faster or slower than the reaction with 1-hexene?

7.63 Reaction of 3-bromocyclohexene with HBr in the presence of peroxides gives a mixture of four isomeric products. Write the structures of the products.

7.64 Ethanethiol adds to 2-methyl-1-propene in the presence of peroxides according to the following equation. Write the mechanism of the reaction including the initiation step.



Polymers

7.65 Propene polymerizes more easily than ethylene under free radical conditions. Explain why.

7.66 Anionic polymerization of acrylonitrile ($CH_2{=}CH{-}C{\equiv}N$) can be initiated by amide ion (NH_2^-). Write the structure of the product of the initial step in the polymerization.

8

Haloalkanes and Alcohols

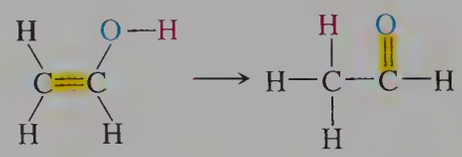
8.1 Functionalized Hydrocarbons

We introduced the concept of functional groups and their role in the organization of the study of organic chemistry in Chapter 2. But so far we have considered in detail only the chemistry of one functional group, the multiple bond of alkenes, which is part of the hydrocarbon skeleton. Now we will start to examine the first of many functional groups containing electronegative atoms. In this chapter we consider haloalkanes (alkyl halides) and alcohols.

Compounds with a halogen atom bonded to an sp^3-hybridized carbon atom are called haloalkanes. Halogens can also bond to an sp^2-hybridized carbon atom of an aromatic compound or an alkene, but because the chemistry of these compounds is very different, they are not considered in this chapter. Compounds with the halogen atom bonded to an *sp*-hybridized carbon atom, which are very unstable, are seldom encountered.

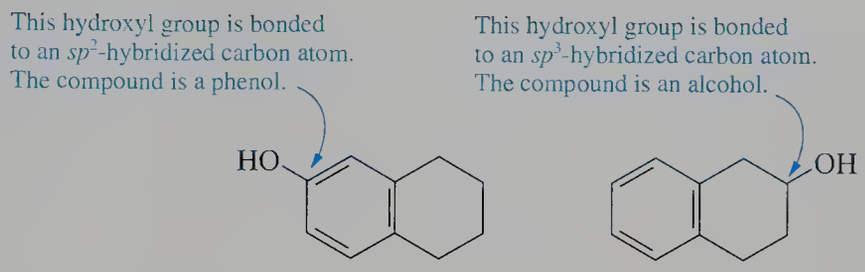
We will primarily focus on the chemistry of chloro and bromo compounds. Iodo compounds are less stable. The chemistry of fluoro compounds is somewhat different from the other halogen compounds and will not be discussed in this text.

Alcohols contain a hydroxyl group bonded to an sp^3-hybridized carbon atom. Compounds in which an —OH is bonded to the sp^2-hybridized carbon atom of an alkene are called **enols**. An enol is unstable, existing only at low concentration in equilibrium with an isomeric carbonyl compound (Chapter 17).



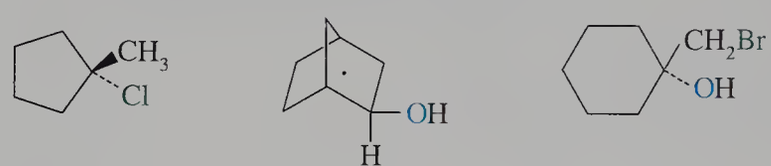
enol (unstable) aldehyde (stable)

Phenols have a hydroxyl group bonded to an sp^2-hybridized carbon atom of an aromatic ring. The distinction between an alcohol and a phenol is illustrated by the two isomeric structures shown below. The chemistry of phenols, which is different from that of alcohols, is considered in Chapter 27.



Classification of Haloalkanes and Alcohols

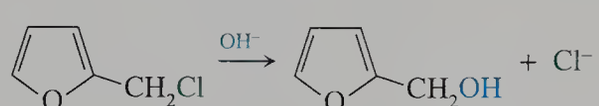
Haloalkanes and alcohols are classified by the number of alkyl groups bonded to the carbon atom bearing the functional group. You may wish to review the classification of carbon atoms in Chapter 4. Haloalkanes and alcohols are classified as primary (1°), secondary (2°), or tertiary (3°) according to the number of alkyl groups bonded to the carbon atom bearing the halogen or hydroxyl group.



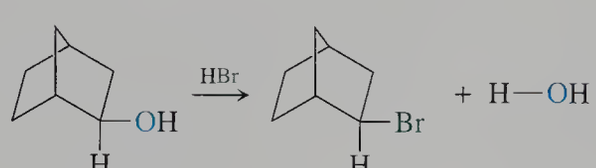
tertiary chloride | secondary alcohol | primary bromide tertiary alcohol

Interconversion of Haloalkanes and Alcohols

Alkyl halides and alcohols are important starting materials used for preparation of compounds with other functional groups. Compounds containing halogen atoms or the hydroxyl group can also be interconverted. Alkyl halides can be converted into alcohols by a substitution reaction with hydroxide ion, although we will see that there are competing elimination reactions in the case of secondary and tertiary compounds.

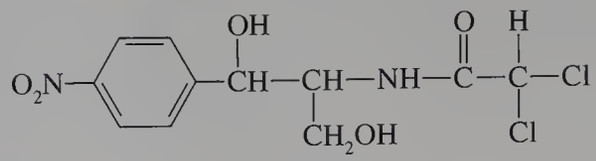


Alcohols react with hydrogen halides to form alkyl halides. The rate of the reaction depends on the classification of the carbon atom bonded to the hydroxyl group.



Problem 8.1

Classify the alcohol functional groups in the broad-spectrum antibiotic chloramphenicol.



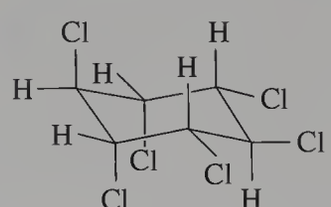
chloramphenicol

Sample Solution

First locate the oxygen atoms in the structure. There are five, but only two are found in hydroxyl groups. Two oxygen atoms are bonded to a nitrogen atom in a group bonded to the benzene ring. One oxygen atom is contained in an amide group. The hydroxyl group in the middle of the structure is bonded to a carbon atom that has two hydrogen atoms and a carbon atom bonded to it; this is a primary alcohol. The hydroxyl group to the left in the molecule is bonded to a carbon atom with two other carbon atoms bonded to it; one carbon atom is part of a substituted alkyl group, the other carbon atom is part of the benzene ring. This alcohol is secondary.

Problem 8.2

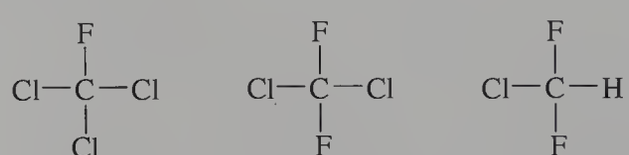
Classify the carbon centers containing chlorine in the insecticide lindane.



8.2 Uses of Haloalkanes

Most of the haloalkanes that we encounter in everyday life were produced in large quantities by the chemical industry. Many haloalkanes are potentially dangerous substances. For example, trichloromethane (chloroform) and tetrachloromethane (carbon tetrachloride), while still used as solvents in the laboratory, are no longer used for general commercial applications because they are on the Environmental Protection Agency's list of suspected carcinogens.

Another group of haloalkanes, collectively known as Freons, contain fluorine and chlorine, but no hydrogen. Freons are also called chlorofluorocarbons (CFCs). They are used as refrigerants, and until recently they were used as propellants in aerosol cans. The CFCs are nontoxic and nonflammable. Under most conditions, they are unreactive, but in the upper atmosphere they react to deplete the ozone layer, which protects us from ultraviolet radiation. Freon use is now severely restricted, and a search for substitute compounds is underway.



CFC-11 CFC-12 CFC-22

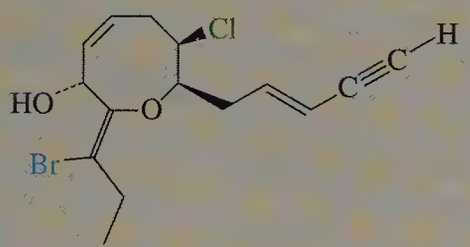
Halogen Compounds and Life in the Ocean

Although halogen-containing compounds are not common in terrestrial plants and animals, they do occur in marine organisms such as algae, sponges, and mollusks. The compounds made by these species have unusual structures, and some of them are clinically useful as antimicrobial, antifungal, and antitumor agents.

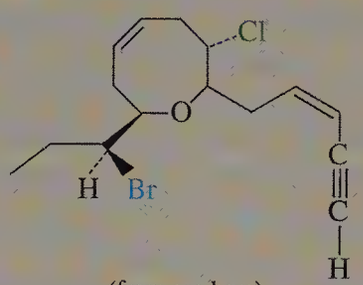
Some marine organisms use haloalkanes as part of a chemical defense mechanism to avoid predators. Thus, they can survive in an environment where virtually every organism is simultaneously predator and prey.

Marine algae produce halogen-containing metabolites to defend themselves against intense feeding by herbivores. For example, red algae produce halogen compounds that repel most herbivores and provide a chemical "shield". However, the sea hare, a soft-bodied, shell-less mollusk, is not repelled by compounds from the red algae, which it uses as a source of food.

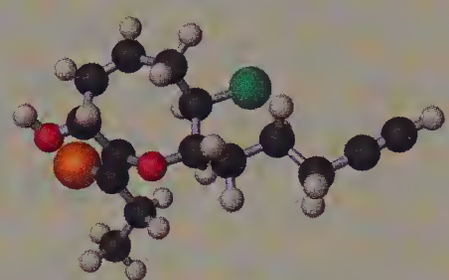
Most mollusks are protected from predators by a hard shell. The shell-less sea hare might therefore seem to have little prospect of survival in the face of large carnivores. However, the sea hare converts the haloalkanes in red algae into closely related substances that it uses for its own chemical defense. The sea hare coats itself with a mucus containing the halogenated compounds. These compounds protect its soft body against carnivorous fish. The structures of two of the closely related haloalkanes produced by red algae and the sea hare are shown below.



(from red algae)

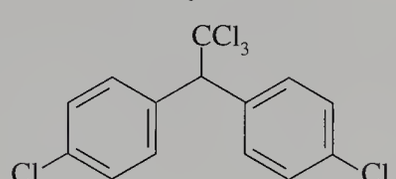


(from sea hare)



algal haloalkane

Certain chlorinated hydrocarbons are effective insecticides. DDT was introduced during World War II to control mosquitoes, which carry the malarial parasite responsible for millions of deaths each year.

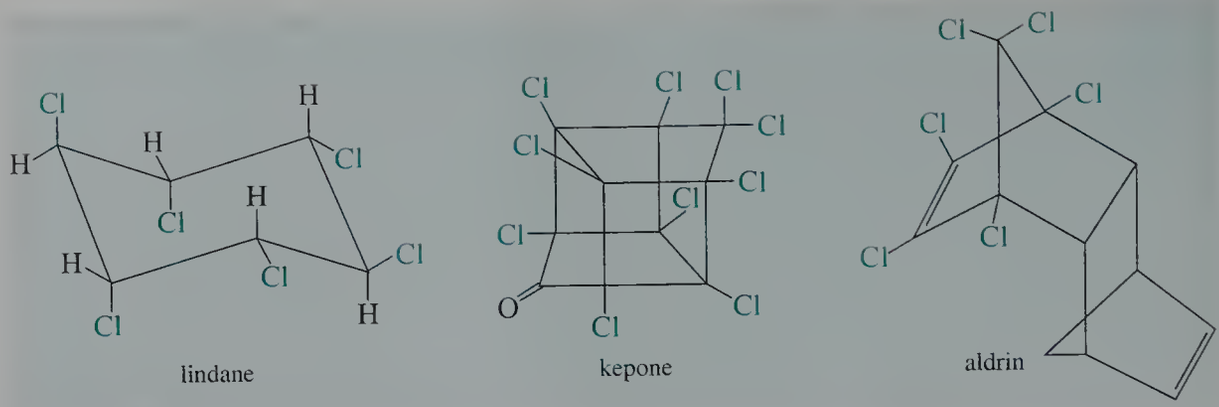


DDT
1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane

DDT is only slowly degraded in nature, making it a **persistent pesticide**. Although not toxic to humans, DDT is not easily metabolized in animals and tends to accumulate in fatty tissue. As a consequence, birds of prey—such as the eagle, osprey, and peregrine falcon—that feed on other animals and fish build up substantial quantities of DDT in their tissues. DDT alters calcium metabolism in these birds, and they produce eggs with thin, fragile shells that break before the baby bird hatches. DDT is now banned in the United States to protect these birds.

Many other chlorinated hydrocarbons were once used in agriculture, but these have also been banned because they are environmentally unsafe. Figure 8.1 shows the structures of some of these compounds. Chlorinated hydrocarbons used as insecticides have been replaced by other classes of compounds.

FIGURE 8.1 Chlorine-Containing Insecticides



8.3 Uses of Alcohols

Methanol

Methanol (CH_3OH) is toxic. Temporary blindness, permanent blindness, or death can result from consumption of methanol, even the small amount present as an impurity in improperly produced ethanol. As little as 15 mL of pure methanol can cause blindness; 30 mL will cause death. Prolonged breathing of methanol vapors is also a serious health hazard.

Methanol is used in car windshield washer fluids. It has been used as a fuel in racing cars for many years. It burns more efficiently than gasoline, but has some limitations as an alternative fuel for general use. Methanol provides only one-half as much energy for the same volume as gasoline because the carbon in methanol is already partially oxidized. Thus, the fuel tank in a methanol-fueled car would need to be twice as large or it would have to be refilled twice as often.

Ethanol

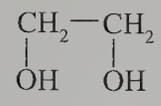
Ethanol (CH_3CH_2OH) is the substance popularly known as "alcohol". It can be produced by fermentation of almost any substance containing sugar, but only in concentrations up to about 14%. The rate of the reaction carried on by yeast cells is inhibited as the alcohol concentration increases. For this reason, most red, white, or rose table wines are 12% alcohol. The alcohol concentration can be increased to 95% by distillation of alcohol–water mixtures. Distillation with a small amount of benzene is required to increase the concentration to 100%. The resultant 100% alcohol is called absolute alcohol, but it contains trace quantities of benzene. The benzene is not detrimental for reactions in the laboratory. However, because the body cannot easily metabolize benzene, ingestion of absolute alcohol can result in liver and kidney damage.

Ethanol is widely used as an industrial solvent. Special tax-free permits are issued for this use. To ensure the proper use of untaxed alcohol, substances are added in small amounts to render such alcohol unfit for drinking. Alcohol containing adulterants that are difficult to remove is called **denatured alcohol**.

Ethanol is a depressant, and acts as a general anesthetic. In fact, in the days before modern anesthetics, alcohol was used to deaden pain during surgery. Ethanol acts in the brain by inhibiting the firing of certain neurons. These neurons are also inhibited by tranquilizers and sedatives such as Valium. Valium and ethanol bind to the same protein, and there is a strong cooperative interaction between them. If Valium and ethanol are consumed at the same time, the effect is potentially lethal.

Polyhydroxy Alcohols

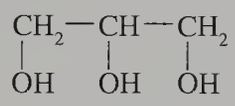
Ethylene glycol contains two hydroxyl groups, one on each of the adjacent carbon atoms of ethane.



ethylene glycol

It is the major component of automobile antifreeze. One of the largest commercial uses of ethylene glycol is in the production of a polyester used in Dacron fibers and Mylar film (Chapter 21). The latter is used in tapes for recorders and computers.

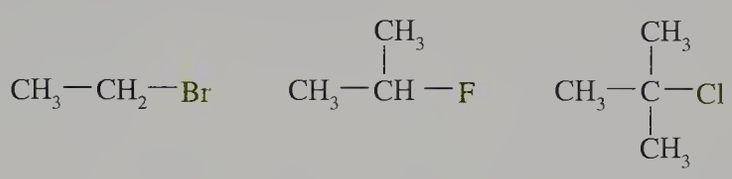
Glycerol, also known as glycerin, contains three hydroxyl groups, one on each of the three carbon atoms of propane. Because it retains moisture, it is useful in skin lotions, inks, and pharmaceuticals.



glycerol

8.4 Nomenclature of Haloalkanes

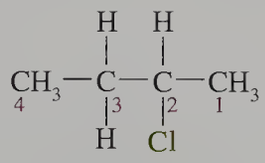
Haloalkanes with low molecular weights are often given a common name consisting of the name of the alkyl group followed by the name of the halide.



ethyl bromide | isopropyl fluoride | *tert*-butyl chloride

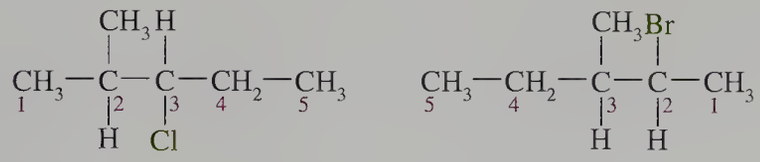
Haloalkanes are named in the IUPAC system by an extension of the rules outlined for alkanes and alkenes.

1. Select the longest continuous chain of carbon atoms as the parent. If the parent chain has no branching alkyl groups, number the carbon chain so that the carbon atom bearing the halogen atom has the lowest number.



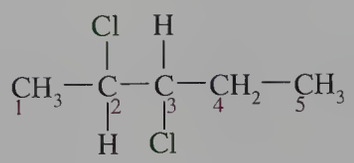
This is 2-chlorobutane, not 3-chlorobutane.

2. If the parent chain has branching alkyl groups, number the chain from the end nearer the first substituent whether it is an alkyl group or a halogen atom.

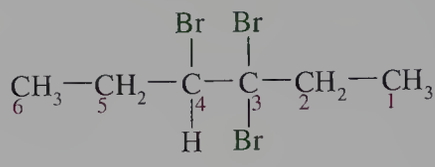


3-chloro-2-methylpentane | 2-bromo-3-methylpentane

3. If the compound contains two or more halogen atoms of the same type, indicate them with the prefixes di-, tri-, etc. Give each halogen atom a number that corresponds to its position in the parent chain.

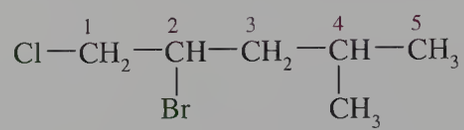


2,3-dichloropentane



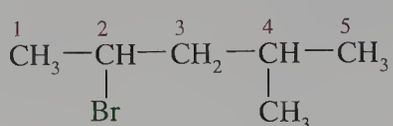
3,3,4-tribromohexane

4. If a compound contains different halogen atoms, number them according to their positions on the chain, and list them in alphabetical order.



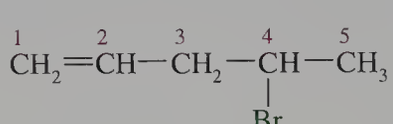
2-bromo-1-chloro-4-methylpentane

5. If the chain can be numbered from either end based on the location of the substituents, begin at the end nearer the substituent that has alphabetical precedence, whether it is an alkyl group or a halogen atom.

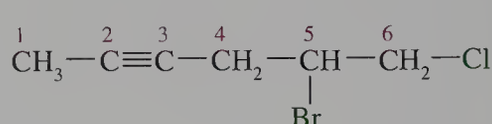


2-bromo-4-methylpentane

6. In a halogen-containing compound with a double or triple bond, the unsaturated unit takes precedence in numbering the carbon chain. Place the number indicating the position of the multiple bond in front of the name of the alkene (or alkyne). Use the number that indicates the position of the halogen group as a prefix to the name of the alkene (or alkyne).

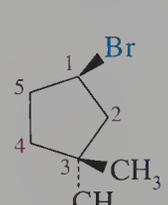


4-bromo-1-pentene

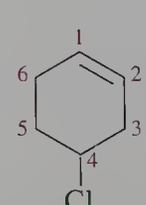


5-bromo-6-chloro-2-hexyne

7. Number halocycloalkanes from the carbon atom bearing the halogen atom unless another functional group, such as a double bond, takes precedence. Number carbon atoms in the ring to give the lower number to the substituent.



1-bromo-3,3-dimethylcyclopentane



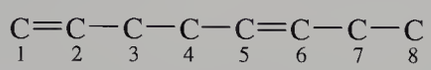
4-chlorocyclohexene

Problem 8.3

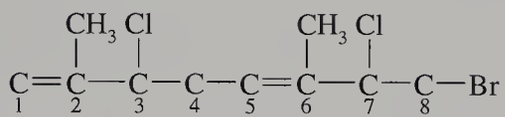
(*E*)-8-Bromo-3,7-dichloro-2,6-dimethyl-1,5-octadiene is produced by a species of red alga. Draw its structure.

Sample Solution

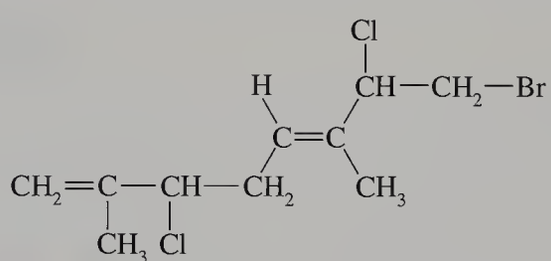
Draw the eight-carbon-atom parent chain, and select a direction for numbering it. Place double bonds between the C-1 and C-2 atoms and between the C-5 and C-6 atoms.



Next, place a bromine atom at the C-8 atom, chlorine atoms at the C-3 and C-7 atoms, and methyl groups at the C-2 and C-6 atoms.



The C-1 atom must have two attached hydrogen atoms; no geometric isomers are possible about this double bond. Arrange the configuration about the double bond between the C-5 and C-6 atoms. The higher priority groups at both the C-5 and C-6 atoms are the alkyl groups that are part of the parent carbon chain. Place the atoms of the carbon chain on the opposite sides of the double bond to obtain the (*E*) configuration. Finally, fill in the requisite hydrogen atoms.



Problem 8.4

Assign the IUPAC name of the following cyclic fluorine-containing compound.

8.5 Nomenclature of Alcohols

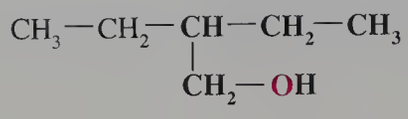
Alcohols that contain one to four carbon atoms have common names consisting of the name of the alkyl group followed by the term "alcohol". For example, CH_3CH_2OH is ethyl alcohol and $CH_3CH(OH)CH_3$ is isopropyl alcohol. Other common names are allyl alcohol and benzyl alcohol, whose structures are shown below.

allyl alcohol

benzyl alcohol

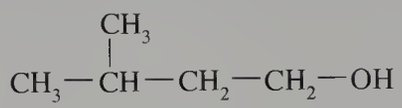
The IUPAC system of naming alcohols is as follows.

1. Designate the longest continuous chain of carbon atoms that includes the hydroxyl group as the parent chain.



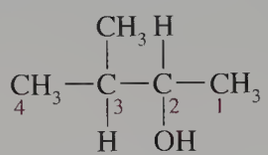
The longest chain that contains the hydroxyl group has 4 carbon atoms, although the longest chain has 5 carbon atoms.

2. Name the parent by substituting the suffix *-ol* for the final *-e* of the corresponding alkane.



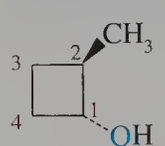
The parent alkane is butane. This is a substituted butanol. A methyl branch is attached to the butanol chain.

3. Indicate the position of the hydroxyl group using the number of the carbon atom to which it is attached. Number the chain so that the carbon atom bearing the hydroxyl group has the lower number.

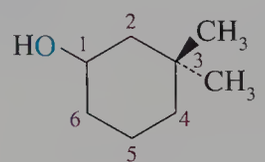


This is 3-methyl-2-butanol, not 2-methyl-3-butanol.

4. When the hydroxyl group is attached to a ring, number the ring starting with the carbon atom bearing the hydroxyl group. Continue numbering in the direction that gives the lowest numbers to carbon atoms with substituents such as alkyl groups. Do not use the number 1 in the name to indicate the position of the hydroxyl group.

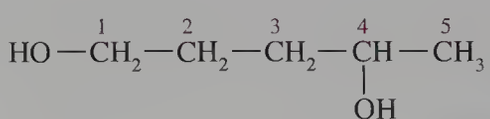


trans-2-methylcyclobutanol



3,3-dimethylcyclohexanol

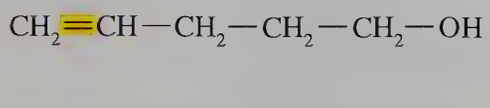
5. Alcohols that contain two or more hydroxyl groups are called diols, triols, and so on. Retain the terminal *-e* in the name of the parent alkane, and add the suffix *-diol* or *-triol*. Indicate the positions of the hydroxyl groups in the parent chain by numbers.



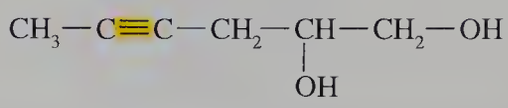
1,4-pentanediol

6. When an alcohol contains a double or triple bond, the hydroxyl group takes precedence in numbering the carbon chain. Place the number that

indicates the position of the multiple bond in front of the name of the alkene (or alkyne) and drop the final *-e*. Append the number that indicates the position of the hydroxyl group to the name of the alkene (or alkyne) along with the suffix *-ol*.



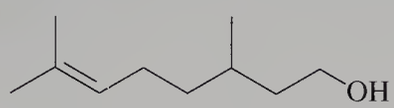
4-penten-1-ol



4-hexyn-1,2-diol

Problem 8.5

Assign the IUPAC name for citronellol, a compound found in geranium oil and used in perfumes.



citronellol

Sample Solution

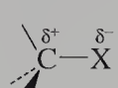
The longest carbon chain that contains the hydroxyl group has eight carbon atoms. The hydroxyl group is on the carbon atom located on the right side of the chain. This carbon atom is C-1. Numbering the chain from right to left, the methyl groups are at the C-3 and C-7 atoms. The double bond is located at the C-6 atom. The name is 3,7-dimethyl-6-octen-1-ol.

Problem 8.6

Menthol is the most stable stereoisomer of 2-isopropyl-5-methylcyclohexanol. Draw the chair conformation of this compound.

8.6 Structure and Properties of Haloalkanes

We recall that the halogens are more electronegative than carbon. As a result, the carbon atom of a carbon–halogen bond bears a partial positive charge. The halogen atom has a corresponding partial negative charge.



where X = F, Cl, Br, I

Because the carbon atom in a C—X bond has a partial positive charge, it is electrophilic. It reacts with nucleophiles, which have a full or partial negative charge.

The atomic radii of the halogens increase going from top to bottom in the periodic table. This trend is reflected in the bond lengths of the carbon–halogen bond.

	CH_3—F	CH_3—Cl	CH_3—Br	CH_3—I
bond length (pm)	139	178	193	214

We recall from Section 2.8 that the polarizability of an atom is a measure of the ease with which its electrons can be distorted in an electric field. The polarizability of the halogen atoms increases as we move down the periodic table: F < Cl < Br < I. Highly polarizable atoms interact more strongly by London forces than less polarizable atoms. Therefore, intermolecular forces for haloalkanes increase in the

order RF < RCl < RBr < RI. The effect of intermolecular forces is reflected in the boiling points of haloalkanes, which increase in the same order as the polarizability of their halogen components.

	CH_3CH_2—F	CH_3CH_2—Cl	CH_3CH_2—Br	CH_3CH_2—I
boiling point (°C)	–37.7	12.7	38.4	72

Fluoroalkanes and chloroalkanes containing a single halogen atom are less dense than water. Compounds with two or more chlorine atoms are denser than water. All bromoalkanes and iodoalkanes are denser than water (Table 8.1).

TABLE 8.1
Boiling Points and Densities of Haloalkanes

Compound	*Boiling Point (°C)*	*Density (g mL)*
CH_3F	–78	
CH_3Cl	–24	
CH_3Br	4	
CH_3I	42	2.28
CH_2Cl_2	40	1.34
$CHCl_3$	61	1.50
CCl_4	77	1.60
CH_3CH_2F	–38	
CH_3CH_2Cl	12	
CH_3CH_2Br	38	1.46
CH_3CH_2I	72	1.94
$CH_3CH_2CH_2F$	3	
$CH_3CH_2CH_2Cl$	47	0.89
$CH_3CH_2CH_2Br$	71	1.35
$CH_3CH_2CH_2I$	102	1.75

8.7 Structure and Properties of Alcohols

The C—O—H bond angle in methyl alcohol is 108.9°, approximately the tetrahedral bond angle (Figure 8.2). According to VSEPR theory, the lone pair electrons in the remaining two sp^3 hybrid orbitals of the oxygen atom are directed to the remaining corners of a tetrahedron. The radius of the oxygen atom is smaller than the radius of a carbon atom. As a result, the O—H bond length (96 pm) is shorter than the C—H bond length (110 pm) and the C—O bond length (140 pm) is shorter than a C—C bond length (154 pm).

The dipole moments of ethanol and propane are 1.69 and 0.08 D, respectively. Alcohols are much more polar than alkanes because they have both a polar C—O bond and a polar O—H bond. Alcohols form strong intermolecular hydrogen bonds, and these bonds have an enormous influence on their physical properties.

Boiling Points of Alcohols

Alcohols boil at much higher temperatures than alkanes of comparable molecular weight. For example, propane boils at −42 °C, whereas ethanol boils at 78 °C. Although ethanol has strong dipole–dipole forces of attraction, the dramatic difference in boiling points is largely due to hydrogen bonding between alcohol molecules.

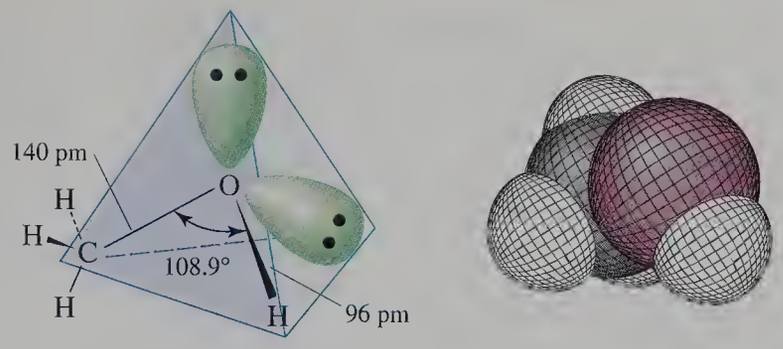
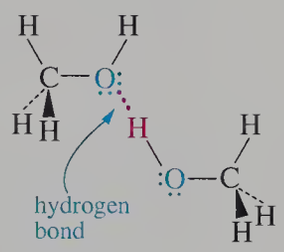


FIGURE 8.2 Structure of Methanol
The oxygen atom of alcohols is sp^3 hybridized. The C—O—H bond angle is close to the tetrahedral angle. The two sets of lone pair electrons are in sp^3 hybrid orbitals that are directed to two of the corners of a tetrahedron.

The hydroxyl group of an alcohol can serve as both a hydrogen bond donor and a hydrogen bond acceptor. As a consequence, much more energy is needed to separate hydrogen-bonded alcohol molecules than is required to disrupt the relatively weak London forces in alkanes.



The boiling points of the alcohols and alkanes of approximately the same molecular weight are compared in Figure 8.3. As the molecular weights of alkanes and alcohols increase, the two curves approach each other. In alcohols having high molecular weights, hydrogen bonding is still possible, but interactions due to London forces increase because the carbon chain is longer. Hence the difference in boiling points between an alcohol and an alkane of comparable molecular weight decreases.

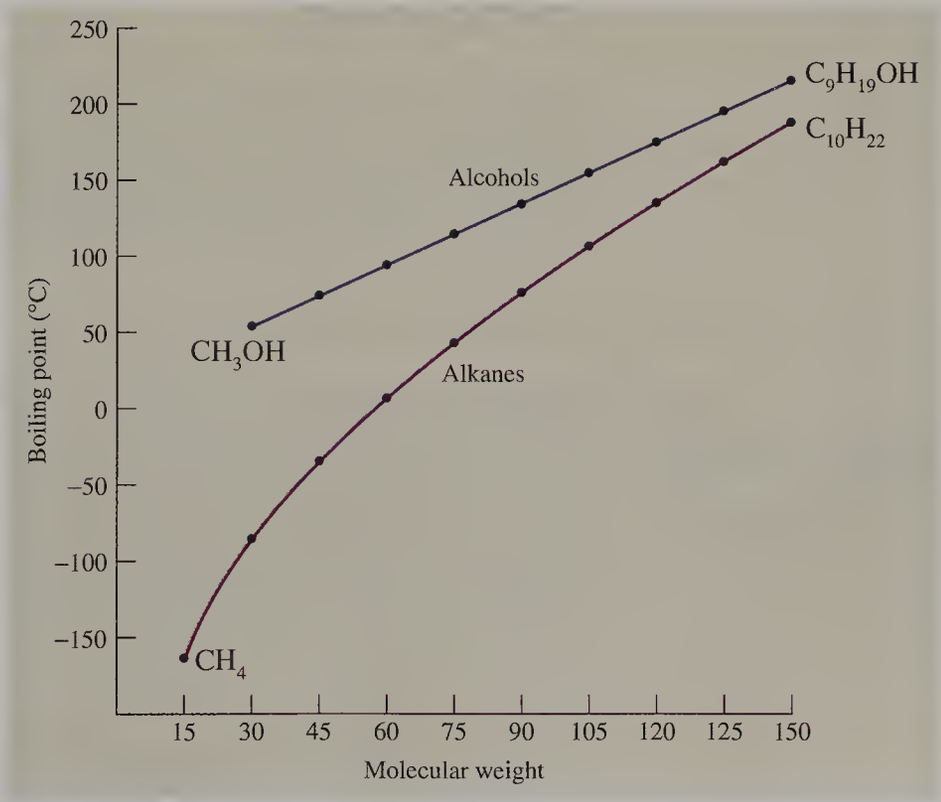


FIGURE 8.3 Comparison of the Boiling Points of Alcohols and Alkanes
The boiling points of both alkanes and normal alcohols increase with increasing chain length. Alcohols have higher boiling points than alkanes of similar molecular weight.

Solubility of Alcohols in Water

The ability of alcohols to form hydrogen bonds has an important effect on their solubilities in water. Table 8.2 lists the solubilities of some alcohols that contain normal alkyl groups. The lower molecular weight alcohols are completely soluble in water. These molecules, like water, are highly polar, and we know that "like dissolves like." Water and alcohols can hydrogen-bond to one another. However, as the size of the alkyl group increases, alcohols more closely resemble alkanes, and the hydroxyl group has less effect on their physical properties. Water can still form hydrogen bonds to the hydroxyl group. However, the long chain interferes with other water molecules, and prevents them from hydrogen-bonding to each other. The formation of a hydrogen bond between an alcohol and water releases energy. However, the energy released is not sufficient to compensate for disrupting the extensive hydrogen-bonding network of water. As a result, the solubility of alcohols decreases with increasing size of the alkyl group.

TABLE 8.2
Boiling Points and Solubilities of Alcohols

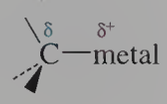
Name	*Formula*	*Boiling Point (°C)*	*Solubility (g/100 mL water)*
methanol	CH_3OH	65	miscible
ethanol	CH_3CH_2OH	78	miscible
1-propanol	$CH_3CH_2CH_2OH$	97	miscible
1-butanol	$CH_3CH_2CH_2CH_2OH$	117	7.9
1-pentanol	$CH_3CH_2CH_2CH_2CH_2OH$	137	2.7
1-hexanol	$CH_3(CH_2)_4CH_2OH$	158	0.59
1-heptanol	$CH_3(CH_2)_5CH_2OH$	176	0.09
1-octanol	$CH_3(CH_2)_6CH_2OH$	194	insoluble
1-nonanol	$CH_3(CH_2)_7CH_2OH$	213	insoluble
1-decanol	$CH_3(CH_2)_8CH_2OH$	229	insoluble

Alcohols as Solvents

Ethanol is an excellent solvent for many organic compounds, especially those with lone pair electrons that are hydrogen bond acceptors. Polar compounds dissolve readily in the "like" polar solvent. Nonpolar compounds dissolve in alcohols to some extent, but the solubility is often limited because the extensive hydrogen-bonding network of the alcohol must be broken to accommodate the solute.

8.8 Organometallic Compounds

Organic halogen compounds are widely used to prepare reactive compounds containing a carbon–metal bond and known as **organometallic compounds**. The only example thus far presented is the Simmons–Smith reagent, which contains a carbon–zinc bond (Section 7.7). Metals that form organic derivatives include lithium, magnesium, zinc, mercury, and copper. Although each type of organometallic compound has unique properties, there are also some common features. Many are nucleophiles because the polarity of the carbon–metal bond places some negative charge on the carbon atom.



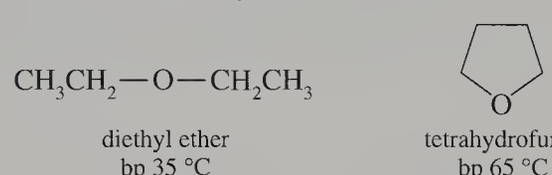
Only the preparation of organometallic compounds containing magnesium and copper compounds is given in this chapter. A limited number of reactions is presented, but the chemistry of these important synthetic intermediates will be discussed in several later chapters.

Grignard Reagents

Haloalkanes and other compounds with the halogen atom bonded to either sp^3-hybridized or sp^2-hybridized carbon atoms (aryl and vinyl halides), when dissolved in ether solvents, react with magnesium metal to yield organomagnesium halides called **Grignard reagents**. Grignard reagents are usually prepared in diethyl ether ($CH_3CH_2OCH_2CH_3$). The French chemist Victor Grignard discovered this reaction. He received the 1912 Nobel Prize in chemistry for his work.

$$\underset{\text{1-bromobutane}}{CH_3CH_2CH_2CH_2{-}Br} + Mg \xrightarrow{\text{diethyl ether}} \underset{\text{butylmagnesium bromide}}{CH_3CH_2CH_2CH_2{-}MgBr}$$

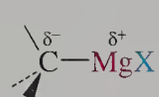
Grignard reagents form easily from 1°, 2°, and 3° alkyl halides, although there are differences in reactivity. Aryl and vinyl halides react somewhat more slowly, and the cyclic ether tetrahydrofuran (THF) is required to prepare Grignards of these compounds. The higher boiling point of the cyclic ether provides more vigorous reaction conditions, but the rate of the reaction is also increased because THF solvates the Grignard reagent better than diethyl ether.



diethyl ether
bp 35 °C

tetrahydrofuran
bp 65 °C

The order of reactivity of the halogens in haloalkanes is I > Br > Cl ≫ F. Organofluorides are so unreactive that they are never used to prepare Grignard reagents. Organohalogen compounds of bromine and chlorine are readily available, and are commonly used to prepare Grignard reagents. Grignard reagents are used synthetically to form new carbon–carbon bonds. A Grignard reagent has a very polar carbon–magnesium bond in which the carbon atom has a partial negative charge and the metal a partial positive charge.



This bond polarity is opposite that of the carbon–halogen bond of haloalkanes. Because the carbon atom in a Grignard reagent has a partial negative charge, it resembles a carbanion, and it reacts with electrophilic centers such as the carbonyl carbon atom of aldehydes, ketones, and esters. We will discuss this chemistry extensively in later chapters.

Grignard reagents react rapidly with acidic hydrogen atoms in molecules such as alcohols and water. When a Grignard reagent reacts with water, the product is an alkane. The Grignard reagent therefore provides a pathway for converting a haloalkane to an alkane in two steps.

$$R{-}X \xrightarrow[\text{ether}]{Mg} R{-}Mg{-}X \xrightarrow{HOH} R{-}H + HOMgX$$

Problem 8.7

Devise a synthesis of $CH_3CH_2CHDCH_3$ starting from 1-butene and heavy water (D_2O).

Sample Solution

Reaction of a Grignard reagent, RMgBr, with D_2O will yield R—D. The necessary Grignard reagent is obtained from the corresponding bromoalkane, RBr.

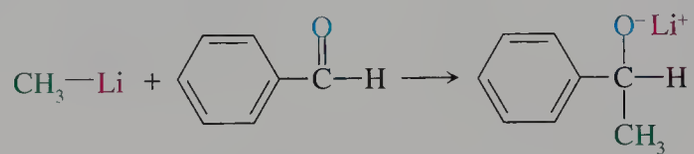
$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow{Mg} CH_3CH_2\underset{\displaystyle MgBr}{\underset{|}{C}}HCH_3 \xrightarrow{D_2O} CH_3CH_2\underset{\displaystyle D}{\underset{|}{C}}HCH_3$$

The required 2-bromobutane can be prepared from 1-butene by adding HBr. This reaction occurs according to Markovnikov's rule, so that a hydrogen atom adds to the less substituted carbon atom of the double bond.

$$CH_3CH_2CH{=}CH_2 + HBr \longrightarrow CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

Organolithium Reagents

The organic portion of the organometallic compound behaves as a carbanion. For example, methyllithium can be prepared by the reaction of bromomethane with lithium. It reacts with carbonyl compounds to place the "methyl carbanion" at the carbon atom of a carbonyl group, as in benzaldehyde.



benzaldehyde

Organolithium compounds are used as bases to remove protons from very weak acids. The pK_a of methane is about 50, making the methyl carbanion one of the strongest bases encountered in organic chemistry. Organolithium compounds, such as methyllithium, are used to prepare conjugate bases of a variety of organic compounds. For example, amines react with methyllithium in an acid–base reaction to form amide salts. The equilibrium constant for the reaction of methyllithium with diisopropylamine is approximately 10^{14}.

$$CH_3Li + (CH_3)_2\underset{\displaystyle CH(CH_3)_2}{\underset{|}{C}}H{-}N{-}H \longrightarrow CH_4 + (CH_3)_2\underset{\displaystyle CH(CH_3)_2}{\underset{|}{C}}H{-}N^-Li^+$$

diisopropylamine
$K_a = 10^{-36}$

$K_a = 10^{-50}$

lithium diisopropylamide

Gilman Reagents

Reaction of an alkyllithium with copper(I) iodide in ether solvent produces a Gilman reagent (also known as the Corey–House reagent). For example, methyllithium reacts with CuI to give lithium dimethylcopper.

$$2\,CH_3Li + CuI \longrightarrow (CH_3)_2Cu^-Li^+ + LiI$$

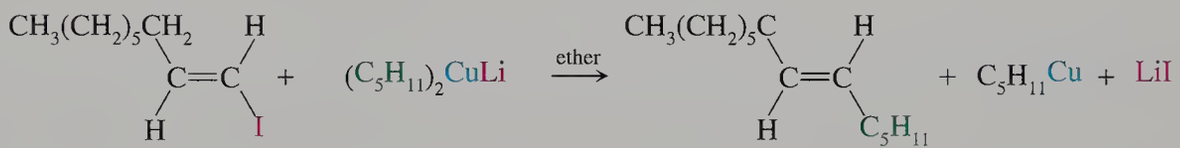
methyllithium — lithium dimethylcopper (a Gilman reagent)

One of the alkyl groups of the Gilman reagent replaces a halogen from a haloalkane to give a "coupled" product that results from joining two alkyl groups.

$$(CH_3)_2Cu^-Li^+ + CH_3(CH_2)_6CH_2I \longrightarrow CH_3(CH_2)_6CH_2CH_3 + CH_3Cu + LiI$$

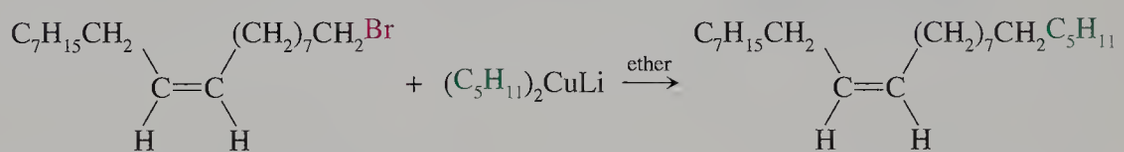
1-iodooctane — nonane

Of course Gilman reagents are not used to synthesize simple hydrocarbons, which are readily available from petroleum. They are used to make more complex compounds that are not available from petroleum. For example, a Gilman reagent will couple with organohalogen compounds that have the halogen bonded to the sp^2-hybridized carbon atom.



trans-1-iodononene — lithium dipentylcopper — *trans*-6-tetradecene

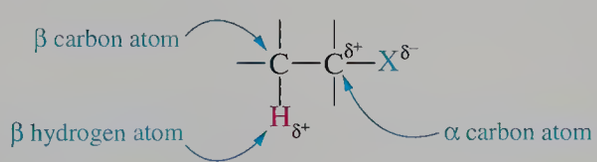
The Gilman reagent has been used in the industrial synthesis of muscalure, the sex attractant of the common housefly. Muscalure is added to fly bait that also contains an insecticide. When the fly eats the bait, the attraction is fatal.



cis-1-bromo-9-octadecene — *cis*-9-tricosene (muscalure)

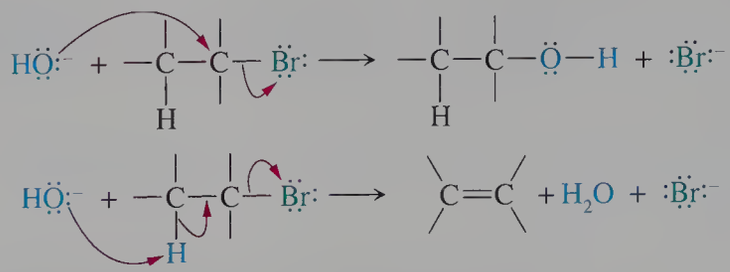
8.9 Reactions of Haloalkanes

This chapter concentrates on chemistry of two sites of reactivity of halolkanes. One is the carbon atom bonded to the halogen atom. Because this carbon atom is electropositive, it attracts reactants having a negative or partial negative charge. That is, the electropositive carbon—called the α carbon atom—reacts with nucleophiles. The second site of reactivity in a haloalkane is the hydrogen atom bonded to the adjacent carbon atom, called the β carbon atom. The hydrogen on the β carbon atom is more acidic than the hydrogen atoms in alkanes because the halogen atom on the adjacent carbon atom withdraws electron density by an inductive effect.



First, let's consider the reaction of the nucleophile hydroxide ion with an electropositive carbon atom bonded to a halogen atom. Hydroxide ion can displace

the halide ion in a substitution reaction. However, the hydroxide ion is not only a nucleophile, it is also a strong base that can remove a proton from the β carbon atom. When the proton is extracted, the halide ion can simultaneously or subsequently depart, and a double bond forms in an elimination reaction.



The substitution and elimination reactions usually occur concurrently, and mixtures of products result. In this chapter we will first consider the substitution reaction and then the elimination reaction. In Chapter 10, we will evaluate the conditions that cause one reaction to be favored over the other.

8.10 Nucleophilic Substitution Reactions of Haloalkanes

In a nucleophilic substitution reaction, the nucleophile donates an electron pair to the electrophilic carbon atom to form a carbon–nucleophile bond. The nucleophile may be either negatively charged, as in the case of OH^-, or neutral, as in the case of NH_3. These two types of nucleophiles are commonly represented as $Nu:^-$ and $Nu:$, respectively. If the nucleophile is negatively charged, the product has no net charge. If the nucleophile is neutral, the product is positively charged. The haloalkane is called the **substrate** because it is the compound upon which the reaction occurs.

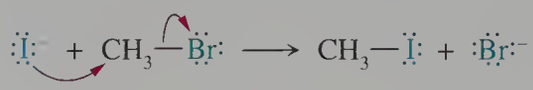
$$Nu:^- + R{-}X \longrightarrow R{-}Nu + X:^-$$

$$Nu: + R{-}X \longrightarrow R{-}Nu^+ + X:^-$$

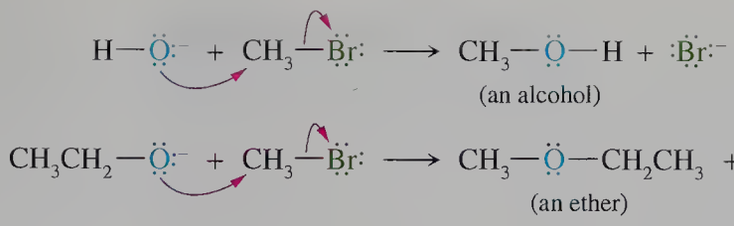
The nucleophile displaces an atom or group of atoms in the reaction, and this group—called the **leaving group**—has an electron pair that was originally part of the C—X bond. The leaving group may be negatively charged, as in the case of halide ions. Water, an example of a neutral leaving group, results from the protonation of the oxygen atom of alcohols.

Haloalkanes are substrates in an extremely broad range of nucleophilic substitution reactions. They react with nucleophilic anions derived from the halogens, oxygen, sulfur, and even carbon. They also react with neutral nucleophiles that contain nitrogen, such as NH_3 or amines.

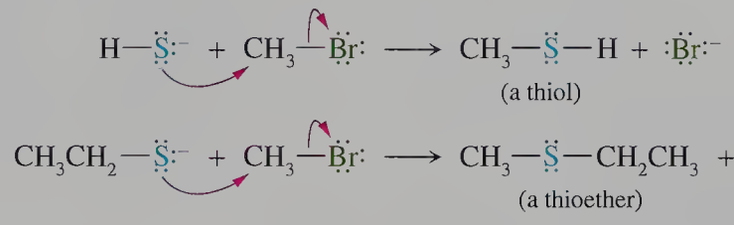
First, let's consider the nucleophilic substitution of iodide ion for chloride or bromide ion in a haloalkane such as chloromethane or bromomethane.



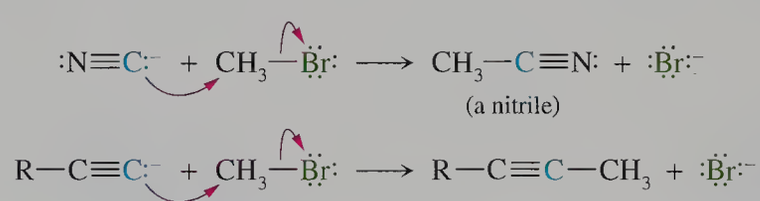
A similar reaction occurs when the hydroxide ion replaces the halide ion to produce an alcohol. When the oxygen-containing nucleophile is an alkoxide ion (RO^-), the product is an ether. This reaction will be discussed in Chapter 17.



Haloalkanes also undergo nucleophilic substitution reactions with sulfur-containing nucleophiles such as hydrogen sulfide ion (HS^-) and thiolate ions (RS^-). These reactions yield sulfur analogs of alcohols and ethers—namely, thiols and thioethers (Chapters 16 and 17).



Haloalkanes also react with carbon nucleophiles. These reactions increase the length of the carbon chain. One carbon-containing nucleophile is cyanide ion (CN^-), which reacts with haloalkanes to give nitriles with the formula R—CN. Nitriles can be transformed into carboxylic acids and amines. Carbon-containing nucleophiles derived from alkynes are called **alkynide** ions. These nucleophiles, the conjugate bases of alkynes (Chapter 11), react to form alkynes containing the carbon atoms of both the haloalkane and the alkynide.

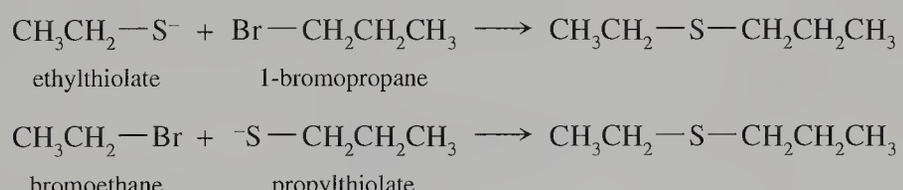


Problem 8.8

Using compounds containing no more than three carbon atoms, propose two ways to prepare $CH_3CH_2—S—CH_2CH_2CH_3$.

Sample Solution

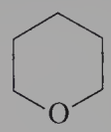
This thioether can be prepared by reaction of a thiolate with a haloalkane. It has two different alkyl groups bonded to sulfur. One alkyl group can be bonded to the sulfur atom in the thiolate, and the other can be in the haloalkane. Thus, two possible combinations of reactants can yield the product.



Problem 8.9

Write a sequence of steps that accounts for the following reaction of 1,5-dibromopentane to give tetrahydropyran.

$$BrCH_2CH_2CH_2CH_2CH_2Br + NaOH \longrightarrow$$



tetrahydropyran

8.11 Mechanisms of Nucleophilic Substitution Reactions

We shall see that there are two mechanisms of nucleophilic substitution reactions described by the symbols S_N2 and S_N1, where the term S_N means substitution, nucleophilic. The numbers 2 and 1 refer to the number of reactant molecules present in the transition state for the rate-determining step. The observed mechanism depends on the structure of the haloalkane.

The S_N2 Mechanism

The S_N2 mechanism is a one-step process in which the nucleophile attacks the substrate and the leaving group, L, departs simultaneously. Because the reaction occurs in one step, it is said to be **concerted**. The substrate and the nucleophile are both present in the transition state for this step. Because two molecules are present, the reaction is **bimolecular**, as indicated by the number 2 in the S_N2 symbol. Hence it is first order in the substrate and first order in the nucleophile. If the substrate concentration is doubled, the reaction rate doubles. Similarly, if the concentration of the nucleophile is doubled, the rate again doubles. This relationship between the rate and the concentration of the reactants exists because the reactants must collide for reaction to occur. The probability that the nucleophile will collide with the substrate increases if the concentration of either species is increased or if the concentrations of both are increased.

Let's consider the S_N2 reaction of hydroxide ion with chloromethane to give methanol and chloride ion. This reaction is shown with the reaction coordinate diagram in Figure 8.4. We see that the transition state contains hydroxide ion and the substrate. As the reaction proceeds through the transition state, a bond forms between carbon and hydroxide ion, and the bond between carbon and chlorine breaks. In the transition state, neither the nucleophile nor the leaving group is fully bonded to carbon. As we will establish in Chapter 10, the partial bonds to the nucleophile and leaving group must be collinear.

The rate of reaction for haloalkanes by the S_N2 mechanism is methyl > primary > secondary > tertiary. This order of reactivity is attributed to steric hindrance. Adding alkyl groups to the carbon atom of the carbon–halogen bond shields the carbon atom from attack by nucleophiles in the direction required for the transition state (Figure 8.5). Furthermore, the carbon atom bearing the nucleophile and the leaving group is pentacoordinate in the transition state. As a consequence, there is more crowding in the transition state. The energy barrier for formation of the transition state increases with the steric size of the groups bonded to the reactive center.

The S_N1 Mechanism

Now let us turn to the other pathway for nucleophilic substitution reactions, which proceeds in two steps and is known as the S_N1 mechanism. It is experimentally distinguished from the S_N2 mechanism in part by a different rate law. In the rate-deter-

FIGURE 8.4 Activation Energy and the S_N2 Reaction Mechanism
The reaction of chloromethane with hydroxide ion occurs in a single step. The activation barrier reflects the stability of the transition state, which in turn is related to the structures of the alkyl group, the nucleophile, and the leaving group.

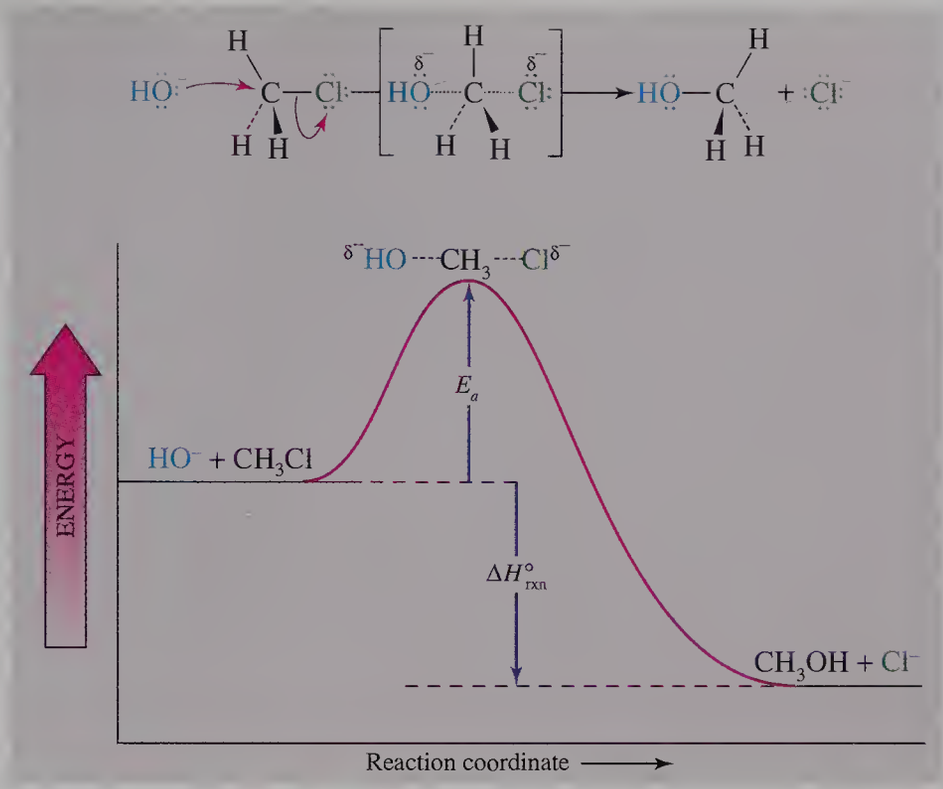
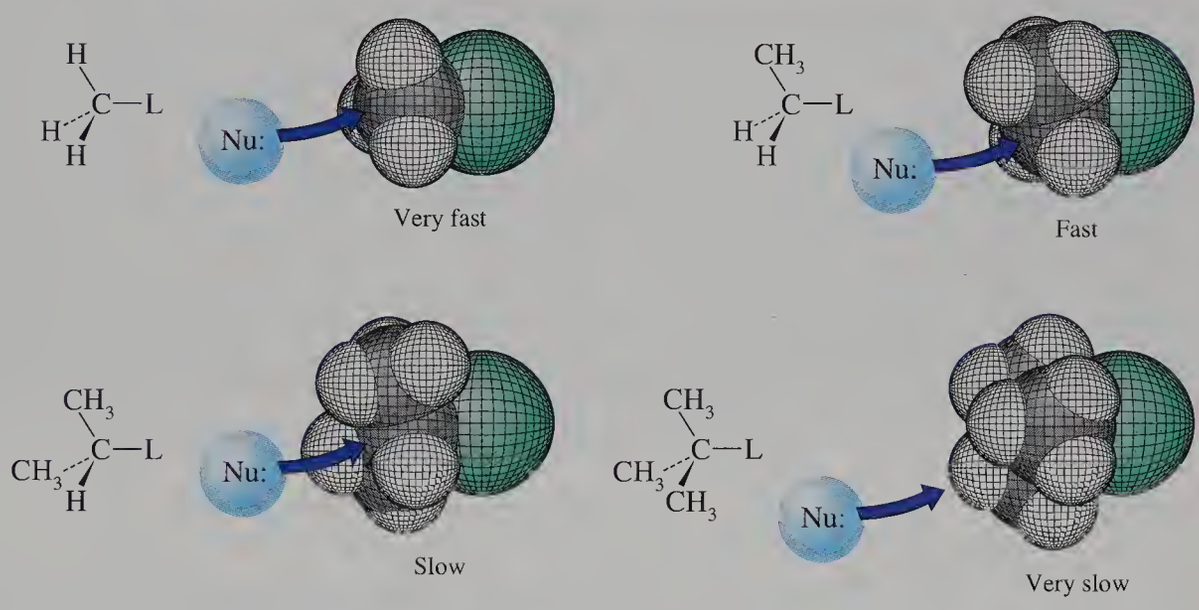
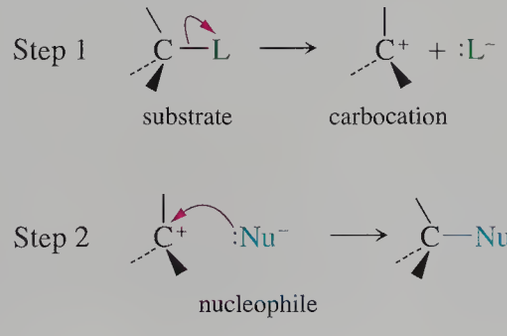


FIGURE 8.5 Effect of Steric Hindrance on the S_N2 Reaction
As hydrogen atoms are replaced by methyl (or alkyl) groups, the reaction becomes slower because the nucleophile cannot as easily attack the carbon atom. The rate of reaction is methyl > primary > secondary > tertiary.

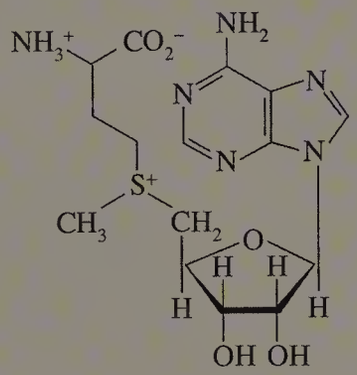


mining step, the bond between the carbon atom and the leaving group breaks to produce a carbocation and, most commonly, an anionic leaving group. In the subsequent step, the carbocation reacts with the nucleophile to form the product. The two-step process is shown below.



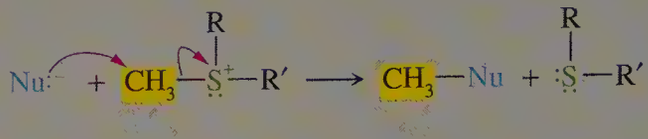
Biological Methylation by an S_N2 Reaction

An S_N2 reaction occurs in living cells in which a methyl group is transferred from a methylating agent called *S*-adenosylmethionine (SAM) to various biological substrates.

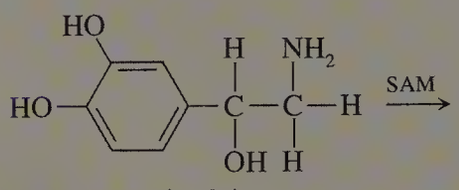


S-adenosylmethionine

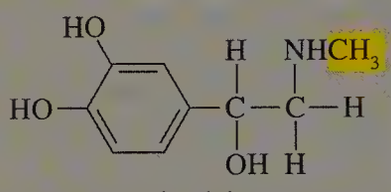
Three carbon atoms are bonded to the positively charged sulfur atom, which is known as a sulfonium ion. It is part of a leaving group called *S*-adenosylhomocysteine. In short, SAM reacts with nucleophiles, which displace *S*-adenosylhomocysteine so that the methyl group is transferred from SAM to the nucleophile. This nucleophilic substitution reaction is shown at top right with a generic nucleophile ($Nu:^-$) and an abbreviated representation of SAM.



An important example of methyl group transfer from SAM to a nucleophile occurs in the biosynthesis of the neurotransmitter epinephrine. In this reaction, an amino group of norepinephrine attacks the methyl group of *S*-adenosylmethionine in an S_N2 reaction to produce epinephrine. The leaving group is *S*-adenosylhomocysteine, the compound that results from the loss of a methyl group from *S*-adenosylmethionine.



norepinephrine



epinephrine

The formation of a carbocation is the slow, or rate-determining, step. The subsequent step, formation of a bond between the nucleophile and the carbocation, occurs very rapidly. Because the slow step of the reaction involves only the substrate, the reaction is **unimolecular**. Because only the substrate is present in the transition state, the rate of the reaction depends only on its concentration and not on the concentration of the nucleophile.

A reaction coordinate diagram for the S_N1 mechanism is shown in Figure 8.6. The rate of the reaction depends on the energy barrier to formation of the carbocation intermediate. The energy barrier in the second step, bonding of the nucleophile to the carbocation, is much smaller, so step 2 is very fast. The rate of the second step has no effect on the net rate of the reaction.

The rates of S_N1 reactions decrease in the order tertiary > secondary > primary > methyl. This trend is exactly the reverse of the trend observed in S_N2 reactions. The relative reactivity of haloalkanes in S_N1 reactions corresponds to the relative stability of carbocation intermediates that form during the reaction. We recall from Chapter 7 that the order of stability of carbocations is tertiary > secondary > primary >

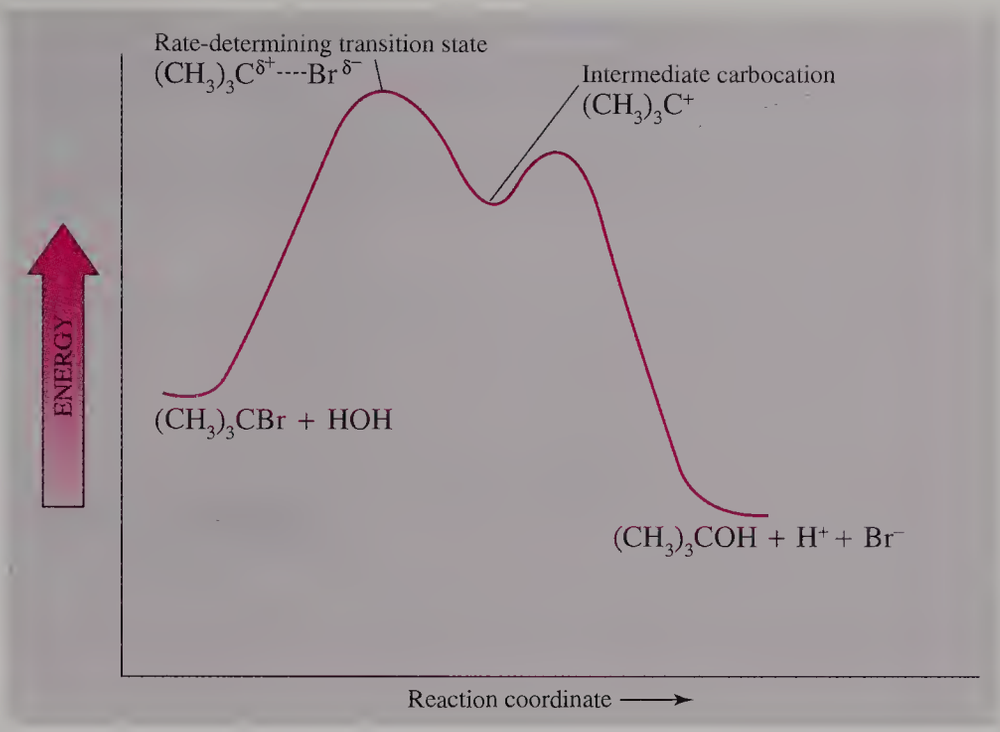
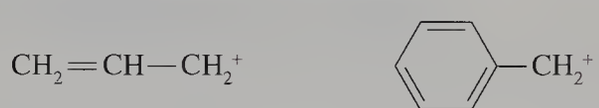


FIGURE 8.6 Activation Energy and the S_N1 Reaction Mechanism
The reaction of 2-bromo-2-methylpropane occurs via a tertiary carbocation that is formed in a rate-determining step that does not involve a nucleophile. In the second, faster step the carbocation reacts with water to form the product alcohol.

methyl. A relatively stable tertiary carbocation forms faster than a less stable secondary carbocation, which in turn forms very much faster than a highly unstable primary carbocation. However, S_N1 mechanisms are possible at primary centers that are resonance stabilized, such as allyl and benzyl.

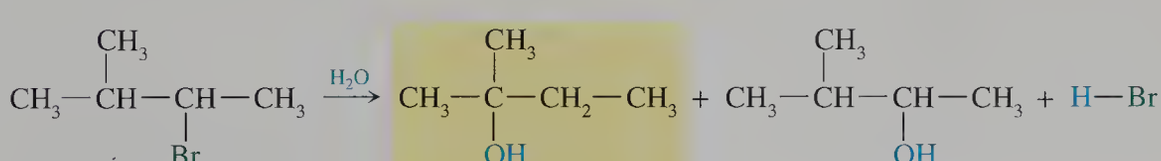


allyl carbocation　　benzyl carbocation

Carbocation Rearrangements in S_N1 Reactions

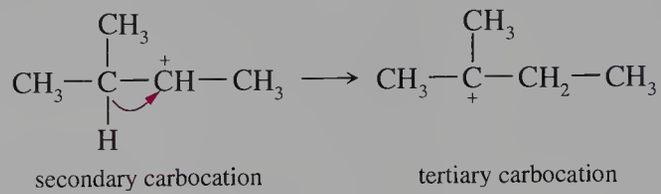
Although the products of most nucleophilic substitution reactions result from replacement of a leaving group by a nucleophile, there are examples of rearranged products. We first encountered this phenomenon in Chapter 7, where we saw that the carbocation intermediate produced by adding a proton to an alkene may rearrange to form a more stable carbocation. Because substitution reactions that occur by an S_N1 mechanism produce carbocation intermediates, we should not be surprised to find that rearranged substitution products occur.

Let's look at an example of an S_N1 reaction that gives rearranged products. The reaction of 2-bromo-3-methylbutane with water gives a rearranged product, 2-methyl-2-butanol, not the direct substitution product, 3-methyl-2-butanol.



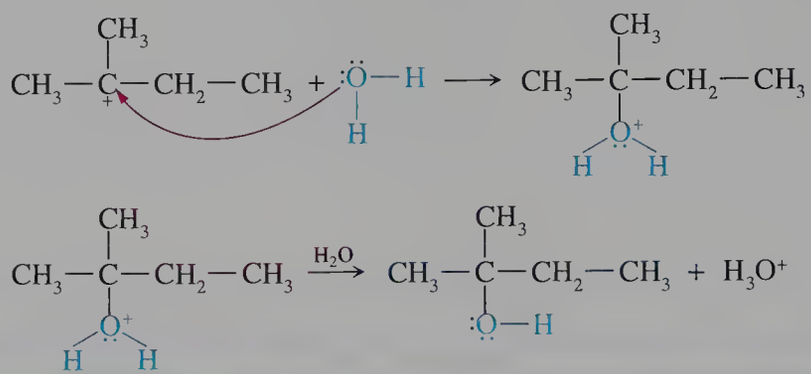
2-bromo-3-methylbutane　　2-methyl-2-butanol (actual product)　　3-methyl-2-butanol (none obtained)

The product forms by reaction of the nucleophile water with a tertiary carbocation. We recall that such a tertiary carbocation results from the movement of a hydrogen atom, with its bonding pair of electrons, from the tertiary center to the adjacent secondary carbocation. The rearrangement is a 1,2-hydride shift because a hydride ion (H^-) moves between adjacent carbon atoms.



secondary carbocation tertiary carbocation

This shift converts a secondary carbocation into a more stable tertiary carbocation, which reacts with water to produce the rearranged tertiary alcohol.

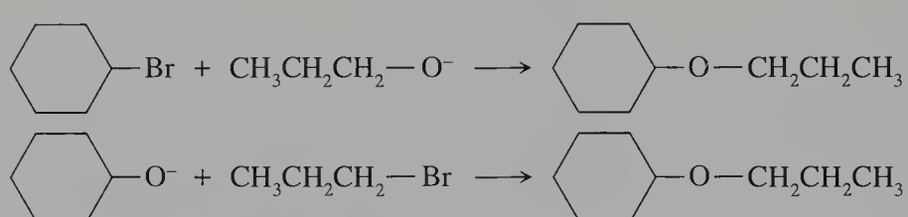


Problem 8.10

The rates of S_N2 reactions of primary haloalkanes can differ substantially. The rate of reaction of 1-bromopentane with a nucleophile is approximately 4×10^6 times as fast as the reaction of the isomeric 2,2-dimethyl-1-bromopropane. Explain why.

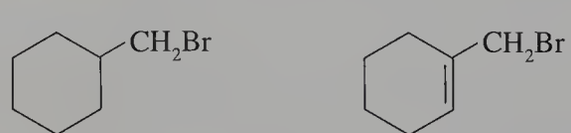
Problem 8.11

Consider the following two possible reactions to produce the ether propoxycyclohexane. Which of the two reactions should proceed at a faster rate?



Problem 8.12

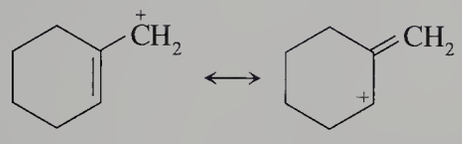
Explain why compound I reacts with methanol via an S_N2 mechanism, whereas compound II reacts at a much faster rate via an S_N1 mechanism.



I II

Sample Solution

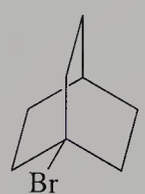
Both substrates are primary bromides. The reaction with methanol, a neutral nucleophile, with I will tend to occur by an S_N2 process because a primary carbocation is unlikely to form. However, the carbocation derived from II is a resonance-stabilized allylic carbocation. Resonance stabilization enhances the rate of its formation in an S_N1 process. No such stabilization can occur in the reaction of I.



resonance-stabilized allylic carbocation

Problem 8.13

Although 1-bromobicyclo[2.2.2]octane is a tertiary bromide, it cannot react via an S_N1 mechanism. Suggest a reason for its lack of reactivity.

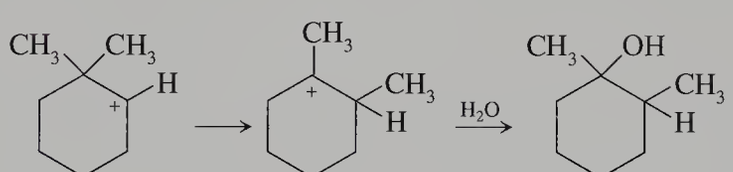


Problem 8.14

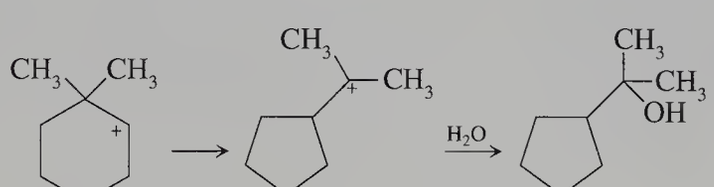
One of the rearranged products in the hydration reaction of 1-bromo-2,2-dimethylcyclohexane with water is 1,2-dimethylcyclohexanol. Explain how this product is formed. What other rearranged alcohol can form?

Sample Solution

The secondary carbocation can rearrange to two possible tertiary carbocations. Migration of a methyl group followed by capture of the carbocation gives 1,2-dimethylcyclohexanol.



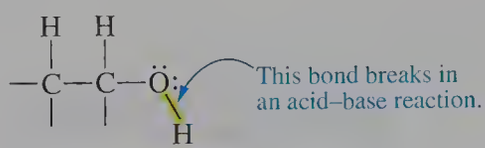
A 1,2-shift of a methylene group of the ring can also occur to give a tertiary carbocation. Capture of the carbocation gives a product containing a cyclopentane ring.



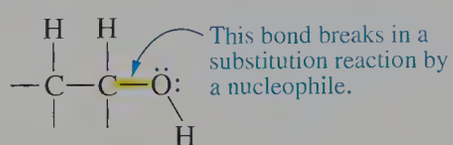
8.12 Reactions of Alcohols

Alcohols undergo reactions in which several different bonds can break, depending on experimental conditions. In some reactions, the O—H bond breaks; in others, the C—O bond breaks. The C—H bond on the carbon atom bearing the hydroxyl group or the C—H bond on the carbon atom adjacent to that carbon atom bearing the OH group also react under some conditions. We will divide our discussion of the reactions of alcohols into four classes based on the bonds that break. Examples of the first three classes of reactions are presented in this chapter. We will discuss the fourth in Chapter 16.

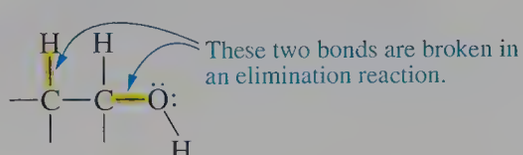
1. Breaking the oxygen–hydrogen bond.



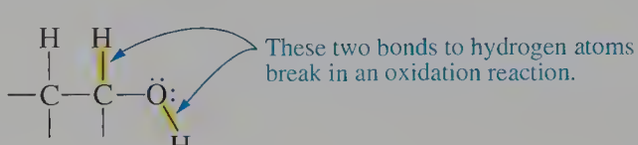
2. Breaking the carbon–oxygen bond.



3. Breaking both the carbon–oxygen bond and the carbon–hydrogen bond at a carbon atom adjacent to the carbon atom bearing the hydroxyl group.



4. Breaking both the oxygen–hydrogen bond and the carbon–hydrogen bond at the carbon atom bearing the hydroxyl group.



8.13 Acid–Base Reactions of Alcohols

We know that water can act as a proton donor (an acid) in some reactions and as a proton acceptor (a base) in other reactions depending on conditions. Alcohols can also act as acids or bases. That is, alcohols are amphoteric substances.

Alcohols are slightly weaker acids than water; the K_a of ethanol is 1.3×10^{-16} ($pK_a = 16$) and the K_a of water is 1.8×10^{-16} ($pK_a = 15.7$). The pK_a values of some common alcohols are listed in Table 8.3. We recall that a strong acid has a large K_a and a small pK_a.

$$CH_3CH_2OH + H_2O \rightleftharpoons \underset{\text{ethoxide ion}}{CH_3CH_2O^-} + H_3O^+ \qquad K_a = 1.3 \times 10^{-16}$$

$$H_2O + H_2O \rightleftharpoons HO^- + H_3O^+ \qquad K_a = 1.8 \times 10^{-16}$$

TABLE 8.3
Effect of Structure on the Acidity of Alcohols

Compound	K_a	pK_a
CH_3OH	3.2×10^{-16}	15.5
CH_3CH_2OH	1.3×10^{-16}	15.9
$(CH_3)_2CHOH$	1×10^{-18}	18.0
$(CH_3)_3COH$	1×10^{-19}	19.0
$ClCH_2CH_2OH$	5×10^{-15}	14.3
CF_3CH_2OH	4×10^{-13}	12.4
$CF_3CH_2CH_2OH$	2.5×10^{-15}	14.6
$CF_3CH_2CH_2CH_2OH$	4×10^{-16}	15.4

The acidity of alcohols increases when electronegative substituents are added to the carbon atoms near the hydroxyl group. Such substituents withdraw electron density from the oxygen atom by an inductive effect that weakens the O—H bond and destabilizes the alcohol. The substituents also stabilize the negative charge of the conjugate base. Replacing a hydrogen atom at the C-2 atom of ethanol with a chlorine atom decreases the pK_a from 15.9 to 14.3, which means that K_a increases by a factor of 50. Replacing all three hydrogen atoms at the C-2 atom of ethanol with the more electronegative fluorine atoms decreases the pK_a to 12.4, which corresponds to an increase in acidity of more than 1000 fold. The effect of the electron-withdrawing CF_3 group decreases with distance from the oxygen atom. The pK_a of 4,4,4-trifluorobutanol, for example, is similar to the pK_a of a primary alcohol such as ethanol.

When an alcohol loses a proton, an **alkoxide ion** forms. Because alcohols are weaker acids than water, alkoxides are stronger bases than hydroxide ion. Alkoxides are used as bases in organic solvents because they are more soluble than hydroxide salts. Alkoxide ions can be easily prepared by adding an alkali metal to an alcohol.

$$2\,Na + 2\,CH_3OH \longrightarrow H_2 + 2\,CH_3O^- + 2\,Na^+$$

$$2\,K + 2\,(CH_3)_3COH \longrightarrow H_2 + 2\,(CH_3)_3CO^- + 2\,K^+$$

These oxidation–reduction reactions resemble the reaction of alkali metals with water. Alcohols react somewhat less vigorously with alkali metals than does water. However, the evolution of hydrogen gas is a qualitative test for the presence of an —OH group in an organic molecule.

Alcohols can act as bases because they have two lone pairs of electrons on the oxygen atom. But alcohols are very weak bases and can only be protonated to form the conjugate acid, an **alkyloxonium ion**, by a strong acid. The formation of an alkyloxonium ion is analogous to the reaction of water with a strong acid to give the hydronium ion. Alkyloxonium ions are intermediates in many reactions catalyzed by strong acids.

$$CH_3CH_2OH + HA \rightleftharpoons \underset{\text{(an alkyloxonium ion)}}{CH_3CH_2OH_2^+} + A^-$$

$$H_2O + HA \rightleftharpoons \underset{\text{(hydronium ion)}}{H_3O^+} + A^-$$

8.14 Substitution Reactions of Alcohols

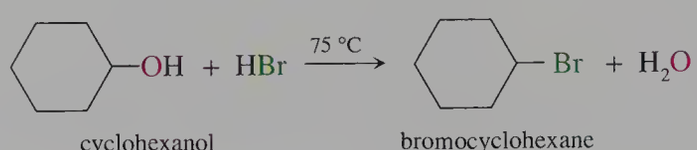
The hydroxyl group of an alcohol can be replaced by a halogen in a reaction using a hydrogen halide. For example, treating a primary alcohol with hydrogen bromide (HBr) produces a bromoalkane. Similarly, treating a primary alcohol with HCl in the presence of $ZnCl_2$, which is required as a catalyst, produces an alkyl chloride.

$$CH_3CH_2CH_2OH + HBr \longrightarrow CH_3CH_2CH_2Br + H_2O$$

$$CH_3CH_2CH_2CH_2OH + HCl \xrightarrow{ZnCl_2} CH_3CH_2CH_2CH_2Cl + H_2O$$

These reactions also occur when secondary and tertiary alcohols are the substrates. Their relative rates depend on the type of alcohol, decreasing in the order tertiary > secondary > primary alcohols. For example, a typical reaction temperature for a primary alcohol such as 1-hexanol is about 125 °C, whereas a secondary alcohol such as cyclohexanol reacts at about 75 °C.

$$\underset{\text{1-hexanol}}{CH_3(CH_2)_4CH_2OH} + HBr \xrightarrow{125\ ^\circ C} \underset{\text{1-bromohexane}}{CH_3(CH_2)_4CH_2Br} + H_2O$$

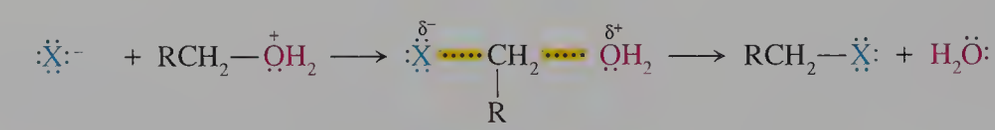


cyclohexanol bromocyclohexane

Reaction Mechanisms

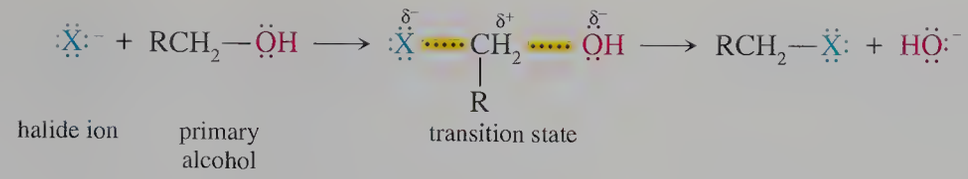
Like the reaction of alkyl halides with nucleophiles such as the hydroxide ion, alcohols react with nucleophiles by two reaction mechanisms. The mechanism depends on the structure of the alkyl group. Primary alcohols react by an S_N2 mechanism. Tertiary alcohols react by an S_N1 mechanism. The mechanism for secondary alcohols is often, but not always, S_N1. In every class of alcohol, the leaving group is a water molecule, not hydroxide ion. An acid catalyst is required to form the conjugate acid of the alcohol, an alkyloxonium ion.

The alkyloxonium ions of primary alcohols react with hydrogen halides via an S_N2 mechanism in which a water molecule is displaced by the halide ion, X^-. In the transition state, the charge of the two reagents is partly neutralized.



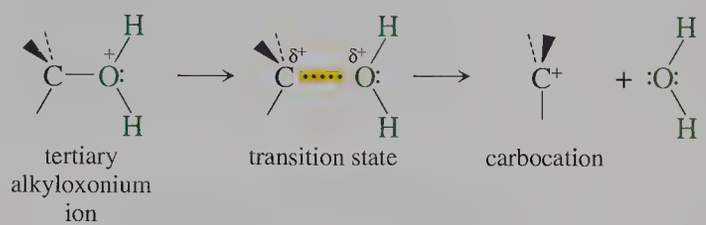
halide ion primary alkyloxonium ion transition state

Now consider an alternative S_N2 mechanism in which a hydroxide ion is displaced from the alcohol by a halide ion. Because both the leaving group and nucleophile are negatively charged, the competition for bonding electrons leaves the carbon atom more positive than in the reaction of the alkyloxonium ion. The departure of a neutral leaving group from a developing carbocation center requires less energy than the departure of a negatively charged leaving group such as the hydroxide ion.

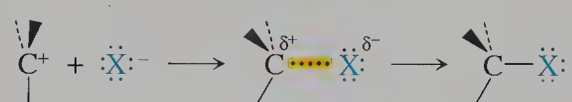


The activation barrier for the displacement of water as a leaving group is smaller than for the displacement of hydroxide ion. For that reason we say that water is a better leaving group than hydroxide ion. In fact, there is a general correlation between basicity and leaving-group ability. A weak base is a better leaving group than a stronger base in both S_N2 and S_N1 reactions.

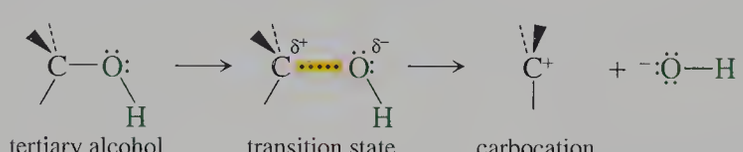
The alkyloxonium ions of tertiary alcohols react with hydrogen halides via an S_N1 mechanism in which a water molecule leaves in the rate-determining step. The positive charge is dispersed in the transition state between the carbon and oxygen atoms and eventually shifts to the carbon atom.



The carbocation formed in the rate-determining step then combines with the halide ion to give the observed product in a fast second step.



Now consider an alternative S_N1 mechanism in which a hydroxide ion leaves to give a carbocation. This process would require separating the charges of the hydroxide ion and the carbocation. The activation barrier for this process is higher than that for the separation of the carbocation from the neutral water molecule. That's why the reaction of a hydrogen halide with a tertiary alcohol occurs via the alkyloxonium ion.



Structural Contributions to S_N2 and S_N1 Mechanisms

Primary alcohols react via an S_N2 process in which water is displaced by the nucleophilic halide ion because the primary carbon atom is sterically accessible to the nucleophile. The alternate S_N1 mechanism would have a high activation energy because the transition state would resemble a highly unstable primary carbocation. We recall that a similar argument was outlined to explain the direction of electrophilic addition to double bonds. According to the Hammond postulate, the structure of a transition state most closely resembles the species that is most similar to it in energy. In the case of the S_N1 mechanism for the reaction of an alkyloxonium ion, a positive charge is developed at the carbon atom in the transition state. Because the intermediate carbocation forms in an endothermic process, the structure of the transition state resembles that intermediate (Figure 8.7). Thus, the activation energy for the S_N1 mechanism for alcohols increases in the order 3° < 2° < 1° < methyl. Only 3° and 2° alcohols react by this mechanism.

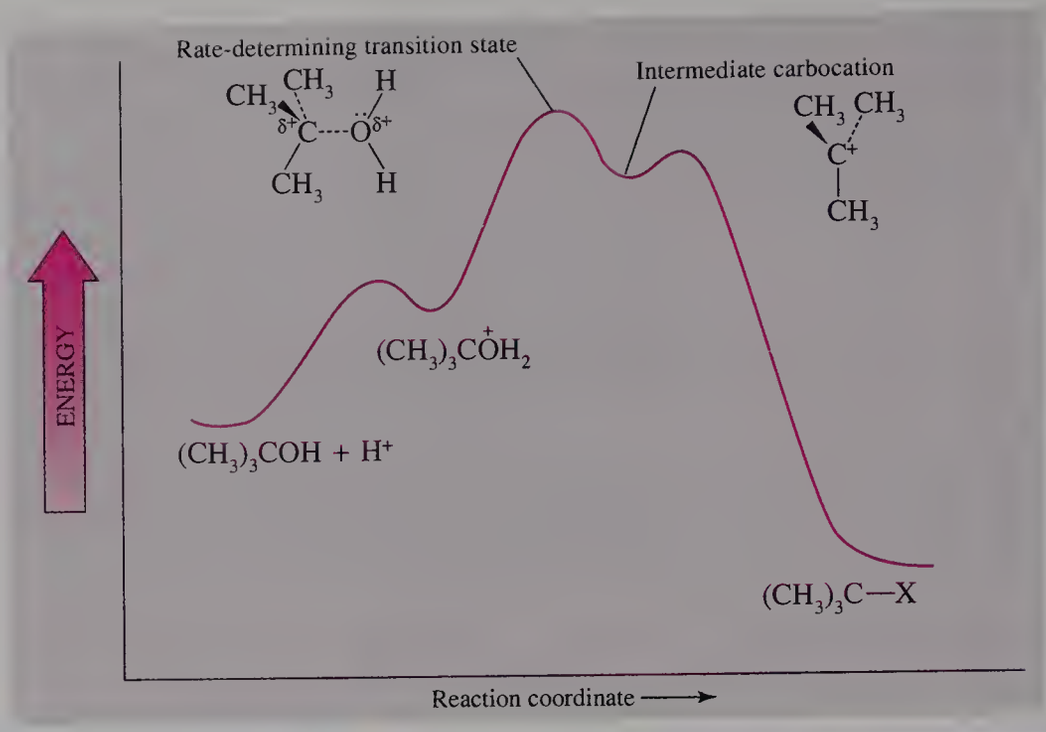
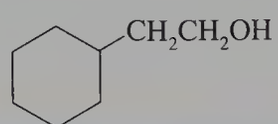


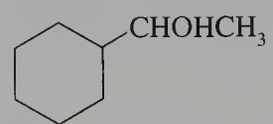
FIGURE 8.7 Reaction Coordinate Diagram for Substitution Reaction of an Alcolhol
The acid-catalyzed substitution reaction of 2-methyl-2-propanol occurs via a tertiary carbocation that is formed in a rate-determining step after a rapid reaction that forms an oxonium ion. Subsequent capture by a nucleophile yields the substitution.

Problem 8.15

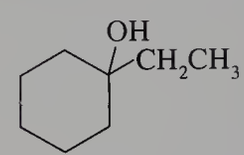
What is the most likely mechanism for the reaction of each of the following isomeric alcohols with HBr?



I



II



III

Problem 8.16

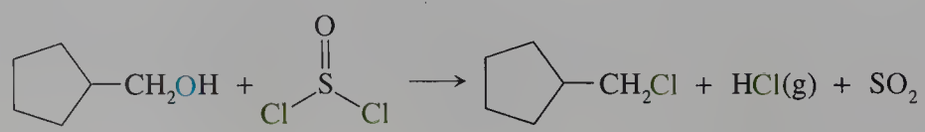
The reaction of *cis*-2-methylcyclohexanol with HBr yields 1-bromo-1-methylcyclohexane. Write a mechanism to explain the origin of this product.

8.15 Alternate Methods for the Synthesis of Alkyl Halides

Alkyl halides are starting materials for the synthesis of many functional groups. One method of preparing alkyl halides is a substitution reaction of an alcohol with a hydrogen halide. However, as we will see in Chapter 10, strong acids, such as hydrogen halides, catalyze elimination reactions that often compete with substitution reactions. The elimination reaction of alcohols—an acid-catalyzed dehydration reaction—will be discussed in Section 8.16. To avoid this competing reaction, alternate synthetic methods have been developed that do not use strongly acidic reagents.

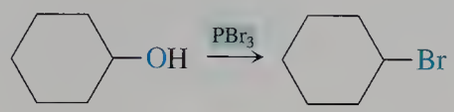
Primary and secondary alcohols, which react only slowly with HBr and HCl, react readily with thionyl chloride and phosphorus trihalides, such as phosphorus tribromide, to give the corresponding alkyl halides. The products of these reactions are easily separated from the inorganic by-products. Thionyl chloride produces hydrogen chloride and sulfur dioxide, which are released from the reaction as gases. The chloroalkane remains in solution.

$$R—OH + SOCl_2 \longrightarrow R—Cl + HCl(g) + SO_2(g)$$



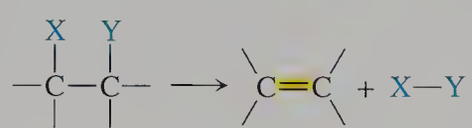
The reaction with phosphorus tribromide produces phosphorous acid, which has a high boiling point and is water soluble. Therefore, the bromoalkane can be separated from the reaction mixture by distillation or by adding water.

$$3\,R{-}OH + PBr_3 \longrightarrow 3\,R{-}Br + \underset{\text{phosphorous acid}}{H_3PO_3}$$



8.16 Elimination Reactions

A single reactant molecule splits into two products in an elimination reaction. One product molecule contains most of the atoms in the reactant, and the remaining atoms are found in a second, smaller molecule. The atoms eliminated to form the smaller molecule are usually initially located on adjacent carbon atoms in the reactant. For this reason, the most common elimination reactions are called **1,2-elimination reactions**. They are also called β **eliminations**.

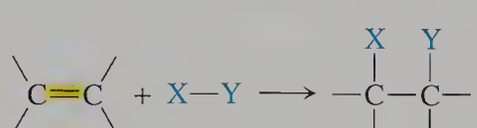


Elimination reactions are described by the name of the molecule undergoing elimination. The names are the same as those used for addition reactions, but the prefix *de-* is added. For example, the elimination of halogen atoms on two adjacent carbon atoms is **dehalogenation**; the elimination of water is **dehydration**; the elimination of a hydrogen halide is **dehydrohalogenation**, and in the case of a specific halogen halide such as hydrogen bromide, **dehydrobromination**.

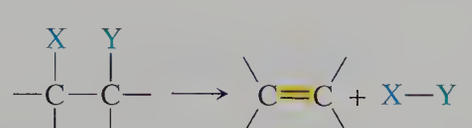
Thermodynamics of Elimination Reactions

Elimination reactions are the opposite of addition reactions, which we presented in Chapter 7. The general equations for addition and elimination reactions are

An addition reaction



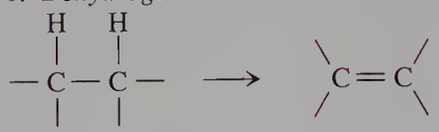
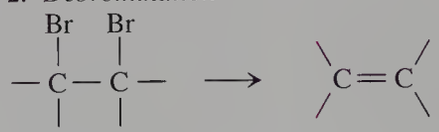
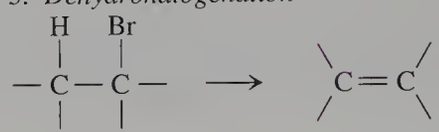
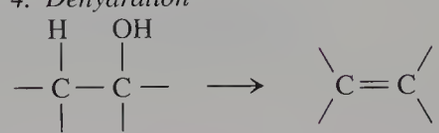
An elimination reaction



Because the general equations for addition and elimination, as shown, are simply the reverse of each other, the sign of the $\Delta H°$ for an elimination reaction is opposite that for the addition reaction. We learned in Chapter 7 that $\Delta H°_{rxn} < 0$ for an addition reaction. Therefore, the elimination reactions should all be endothermic. The $\Delta H°_{rxn}$ values for four types of elimination reactions are given in Table 8.4. We recall that

ΔH°_{rxn} equals the difference between the sum of the bond dissociation energies of all broken bonds and the sum of the bond dissociation energies of all bonds formed.

TABLE 8.4
Approximate Enthalpy Change for Elimination Reactions

1. Dehydrogenation		
		$\Delta H^\circ = +118$ kJ mole^{-1}
2. Debromination		
		$\Delta H^\circ = +105$ kJ mole^{-1}
3. Dehydrohalogenation		
		$\Delta H^\circ = +42$ kJ mole^{-1}
4. Dehydration		
		$\Delta H^\circ = +25$ kJ mole^{-1}

As Table 8.4 shows, all elimination reactions are endothermic. How can we make these reactions occur under such apparently unfavorable circumstances? The answer is surprisingly simple. We couple each endothermic reaction to an even more exothermic reaction so that the sum of the two reactions has a favorable negative ΔH°_{rxn}.

Another consideration is the effect of temperature on ΔG°_{rxn}. The ΔS°_{rxn} for elimination reactions is usually quite positive, and a sufficiently large positive ΔS°_{rxn} can act in opposition to an unfavorable enthalpy change in a reaction. Because the contribution of the entropy change to the free energy change depends on temperature, the $-T\Delta S^\circ_{rxn}$ term of the thermodynamic relation $\Delta G^\circ_{rxn} = \Delta H^\circ_{rxn} - T\Delta S^\circ_{rxn}$ becomes more important at higher temperatures.

8.17 Types of Elimination Reactions

In this section we begin our study of the four types of elimination reactions listed in Table 8.4. We will learn why only two of the four elimination reactions, dehydrohalogenation and dehydration, are useful for the synthesis of alkenes. The mechanisms of these two reactions are discussed in subsequent sections.

Dehydrogenation

The dehydrogenation reactions of alkanes are endothermic. The ΔH°_{rxn} values are 110–125 kJ mole^{-1} (26–30 kcal mole^{-1}). However, the reaction converts one reactant molecule into two product molecules, and the resulting entropy change, which is in the order of 125 J mole^{-1} deg^{-1} (30 cal mole^{-1} deg^{-1}), is strongly favorable. Still, at room temperature, the enthalpy term predominates. ΔG°_{rxn} is positive, and the equilibrium constant for dehydrogenation is much less than 1. We recall that the

reverse reaction, hydrogenation, is thermodynamically favorable, with $\Delta G^\circ_{rxn} < 0$ at room temperature.

At higher temperatures, the $-T\Delta S^\circ_{rxn}$ term becomes more negative, and thus more important than ΔH°_{rxn}. However, the temperatures required to make ΔG°_{rxn} for dehydrogenation favorable are in the 500–750 °C range for various alkanes. Therefore dehydrogenation reactions are of little use in laboratory syntheses. However, they are used industrially. Ethylene is produced by the dehydrogenation of ethane. This reaction provides the raw material for production of ethylene glycol, used in antifreeze, and polyethylene, used in a variety of plastics.

$$CH_3{-}CH_3 \xrightarrow[Pt]{750\ ^\circ C} CH_2{=}CH_2 + H_2$$

The amount of ethylene produced in the United States is 3×10^{10} lb per year, approximately 100 lb per person.

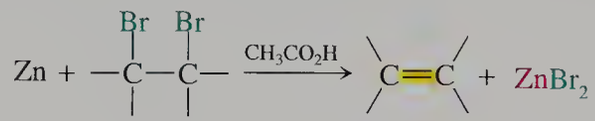
Besides the high temperature required for dehydrogenation, another factor limits this reaction as a method for the synthesis of alkenes. The reaction is not regioselective. Any of the many pairs of hydrogen atoms on adjacent carbon atoms can undergo a 1,2-elimination reaction. Therefore, the reaction is limited to a few types of symmetrical alkanes and cycloalkanes.

Debromination

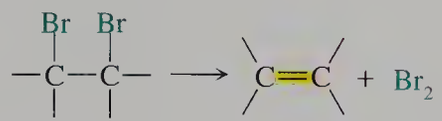
Although the debromination of a vicinal dihalide is endothermic, the reaction could in principle be carried out at a high temperature. However, the debromination reaction can be carried out at lower temperatures under laboratory conditions by an indirect method. The reaction is changed by adding another reagent. The objective is to "drive" the reaction to form the desired product by making the ΔH°_{rxn} negative for the modified reaction.

The debromination of vicinal dibromides occurs in the presence of zinc and acetic acid. The mechanism differs from that for a thermal debromination. A molecule of Br_2 is still removed from the alkene, but in an oxidation–reduction reaction that forms zinc bromide. Compare this reaction to the direct debromination of an alkene.

"Indirect" debromination

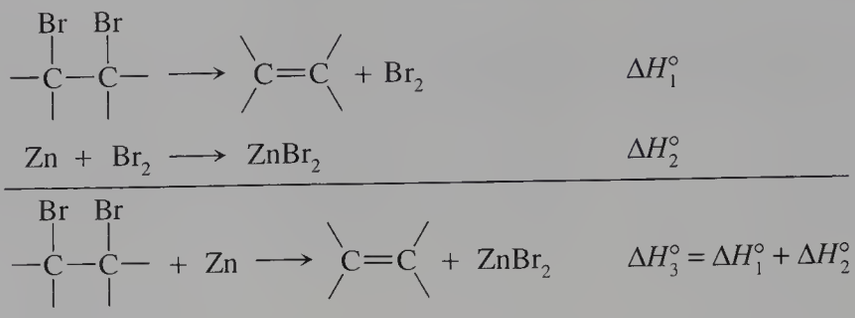


"Direct debromination"



Let's see how the ΔH°_{rxn} values differ for the two reactions. We recall that because ΔH° is a state function, we can add reactions and calculate ΔH°_{rxn} using Hess's law (Section 1.4). Adding the equation for the direct debromination reaction to the

equation for the reaction of bromine with zinc gives the equation for the reaction of a vicinal dibromide with zinc.

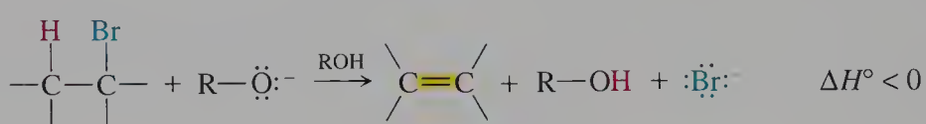


What is the consequence of adding the ΔH°_{rxn} values? We know that the direct combination of metals with nonmetals is strongly exothermic. Therefore the debromination reaction with zinc is much more favorable than the direct reaction. Note that the mechanism for the debromination with zinc does not occur by the above two-step mechanism. The two steps are given only for the purpose of showing why the debromination with zinc is exothermic.

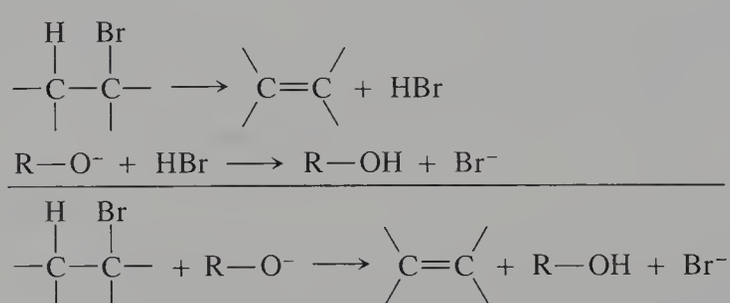
The debromination reaction with zinc is driven by an important experimental factor: The reaction is heterogeneous. It occurs on the surface of the zinc. Zinc bromide is not soluble in acetic acid, so it is also in a different phase than the product, which is dissolved in the acetic acid. Le Châtelier's principle applies because the zinc bromide product is removed from solution, and the equilibrium position shifts to the right.

Dehydrohalogenation

The dehydrohalogenation of an alkyl halide is a good laboratory method for the synthesis of alkenes because alkyl halides are readily available from reactions of several other starting materials. A thermal dehydrobromination reaction is extremely endothermic. A related dehydrobromination reaction using strong base is exothermic.



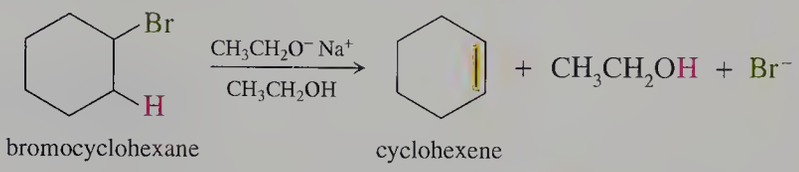
Why is the reaction with alkoxide ion exothermic? Let's add the equation for the direct dehydrobromination reaction to the equation for the reaction of the alkoxide ion with HBr to give the equation for the net dehydrobromination reaction.



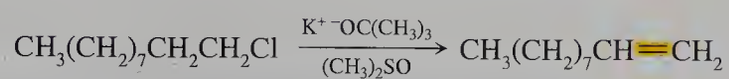
We know that the reaction of hydroxide ion with a strong acid is very exothermic, so we also expect the reaction of alkoxide ion with HBr to be strongly exothermic. Therefore, when the dehydrobromination reaction is carried out with an alkoxide ion, the reaction is exothermic. Again we should remind ourselves that the reaction does

not have to occur by the above two-step process. Indeed, it does not. The two equations are selected only to explain why ΔH°_{rxn} for the reaction of haloalkane with a base can be negative.

The dehydrohalogenation of alkyl halides is usually carried out with sodium methoxide in methanol, sodium ethoxide in ethanol, or potassium *tert*-butoxide in either *tert*-butyl alcohol or dimethyl sulfoxide, $(CH_3)_2SO$.



bromocyclohexane cyclohexene

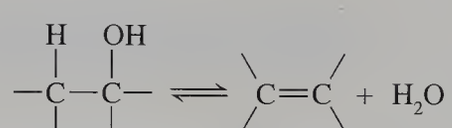


1-chlorodecane 1-decene

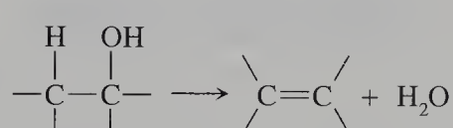
For the two reactions illustrated, only a single alkene can result from the dehydrohalogenation of the alkyl halide. In alkyl halides having two or three adjacent carbon atoms with hydrogen atoms that could lead to different elimination products, a regioselectivity is observed. This feature of dehydrohalogenation reactions is discussed in Section 8.18.

Dehydration

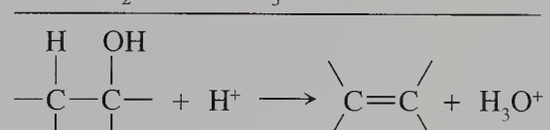
In Section 7.1 we noted that the ΔH°_{rxn} value for adding water to alkenes is less negative than that for the reactions of bromine and hydrogen bromide. This means that the addition reaction, hydration, can more easily be reversed to give an elimination reaction, dehydration.



The dehydration reaction is favored by using a concentrated acid such as sulfuric acid. The reaction produces the hydronium ion (H_3O^+) rather than water. The equation for the observed reaction can be obtained by combining the following two equations.



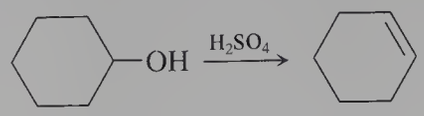
$$H^+ + H_2O \longrightarrow H_3O^+$$



We know that the formation of the hydronium ion is strongly exothermic. Thus, the overall dehydration reaction using a strong acid is also exothermic.

The dehydration reaction is also driven to completion in accord with Le Châtelier's principle because water, one of the products, is removed. We can also apply

Le Châtelier's principle to select reaction conditions that remove the alkene product from the reaction mixture. Because alcohols boil at higher temperatures than the related alkenes, the alkene can be distilled as it forms. For example, the boiling point of cyclohexanol is considerably higher than that of cyclohexene.



cyclohexanol
bp 161 °C

cyclohexene
bp 83 °C

As is the case for the dehydrohalogenation of alkyl halides, the reaction is regioselective. This feature of dehydration reactions will be presented in Section 8.20.

Problem 8.17

Propene, which is the second most abundant organic compound produced industrially, forms by the dehydrogenation of propane. Why is this reaction feasible? The reaction is carried out at a lower temperature than for the dehydrogenation of ethane. Explain why.

Sample Solution

Both carbon–carbon bonds are equivalent, and the elimination of hydrogen can give only one product. Propene is a more substituted compound than ethylene. Thus, the energy required to form this more stable alkene is smaller and a lower temperature can be used.

Problem 8.18

The industrial dehydrogenation of butane gives a mixture of three compounds with the molecular formula C_4H_8 and a compound with the molecular formula C_4H_6. What are the structures of these compounds?

Problem 8.19

Write the product of the reaction of 1,2-dibromooctane with zinc and acetic acid.

Problem 8.20

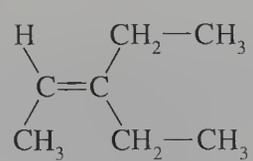
The dehalogenation of vicinal dihalides is not often used as a method to produce alkenes. Consider the source of vicinal dihalides and explain why.

Problem 8.21

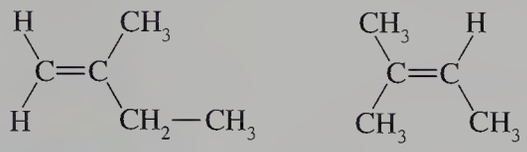
The dehydrobromination of 3-bromo-3-ethylpentane gives a single product, but the dehydrobromination of 2-bromo-2-methylbutane gives two products. What are the structures of the products for both reactions?

Sample Solution

In 3-bromo-3-ethylpentane there are three equivalent methylene groups adjacent to the carbon atom bearing the bromine atom. Elimination of HBr can only give a single product. The product is 3-ethyl-2-pentene.



In 2-bromo-2-methylbutane the carbon atoms adjacent to the carbon atom bearing the bromine atom are two methyl groups and a methylene group. The products are 2-methyl-1-butene and 2-methyl-2-butene.



Problem 8.22

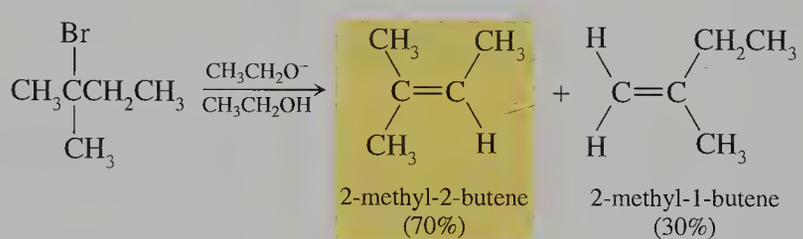
The C-2 and C-4 methylene units of 3-bromopentane are equivalent. However, the dehydrobromination of 3-bromopentane gives two products. Write their structures.

Problem 8.23

Two alkenes are produced in the dehydration of 2-methyl-2-butanol, but three are produced in the dehydration of 2-pentanol. Write the structures of the products of both reactions.

8.18 Regioselectivity in Dehydrohalogenation

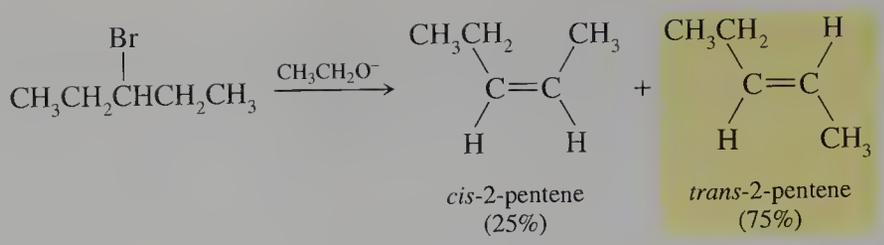
When two or more products can form in the dehydrohalogenation of an alkyl halide, it turns out that they are not formed in equal amounts. The more highly substituted alkene (more stable) predominates, as shown by the dehydrobromination of 2-bromo-2-methylbutane.



Although at first glance the reaction may not appear to be very regioselective, it is in fact quite regioselective, when we consider the number of hydrogen atoms that could be eliminated to lead to each product. The more substituted alkene is the major product even though the less substituted alkene would be expected to be favored on statistical grounds. The reactant has six equivalent hydrogen atoms that could be lost to give 2-methyl-1-butene, but only two can be lost to give 2-methyl-2-butene. The mechanism for the reaction has to explain why there is not three times as much of the less substituted product as the more substituted product.

The regioselectivity observed for 1,2-elimination reactions was summarized by Alexander Zaitsev in 1875. Zaitsev's rule states that the more substituted alkene is favored in 1,2-elimination reactions. We know that alkenes are stabilized by alkyl groups bonded to sp^2-hybridized carbon atoms, so Zaitsev simply observed that the major product of an elimination reaction is the more stable isomer.

As a corollary of Zaitsev's rule concerning the formation of the more stable isomer, we can account for the composition of mixtures of geometric isomers. For example, dehydrobromination of 3-bromopentane yields a mixture of *cis*- and *trans*-2-pentenes. The trans isomer is the major product.



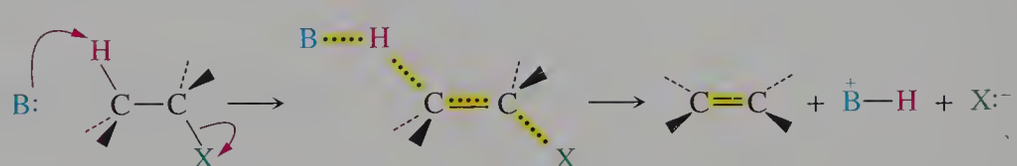
In the trans isomer, the alkyl groups are well separated, whereas in the cis isomer the alkyl groups are near each other. The proximity of the alkyl groups in the cis isomer causes steric hindrance. The trans isomer is more stable, so it predominates.

8.19 Mechanisms of Dehydrohalogenation Reactions

Elimination reactions can occur by two mechanisms proposed by Sir Christopher Ingold in the 1920s. These are designated E2 and E1, where E refers to elimination and the integers designate the molecularity of the rate-determining step of the reaction. The molecularity is reflected in the kinetics of the reaction. Reactions that are first order in alkyl halide and first order in base are overall second order and occur by an E2 mechanism. This behavior is observed for primary and secondary alkyl halides. Reactions that are first order in alkyl halide and are independent of the base concentration occur by an E1 mechanism. This behavior is observed for tertiary alkyl halides. The reaction rate increases in the order RF < RCl < RBr < RI regardless of the class of alkyl halide. Although alkyl chlorides and alkyl bromides are most commonly used in synthesis, the iodide ion formed from the alkyl iodides is the best leaving group. Alkyl fluorides are not used for the synthesis of alkenes.

The E2 Mechanism

Like the S_N2 reaction mechanism, the E2 mechanism is a one-step, concerted process. In an E2 dehydrohalogenation reaction, the base (nucleophile) removes a proton on the carbon atom adjacent to the carbon atom containing the leaving group. As the proton is removed, the leaving group departs, and a double bond forms. The transition state is shown for the general base represented by B: (X represents the halide).



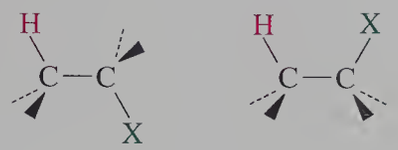
transition state
for E2 elimination

The carbon–hydrogen and carbon–halogen bonds are partially broken in the transition state, so the strength of the carbon–halogen bond affects the rate of the reaction. Alkyl iodides have the weakest carbon–halogen bond, and hence react at the fastest rate.

A partial double bond develops in the transition state for the E2 elimination. The partially formed double bond in the transition state is stabilized by alkyl groups just as the double bond of alkenes is stabilized by alkyl groups. Therefore, the transition state for the formation of the more substituted alkene has the lower energy barrier.

Stereoelectronic Effects in the E2 Reaction

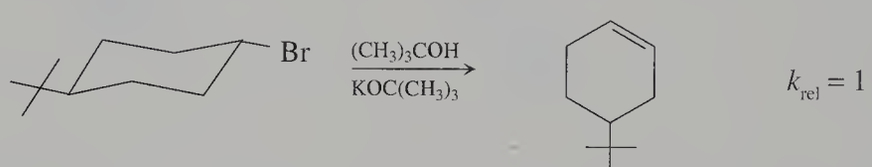
When a special arrangement of orbitals in forming or breaking bonds controls the direction of a reaction, the effect is called **stereoelectronic**. An E2 reaction is called **periplanar** when all reacting atoms—the two carbon atoms and the two atoms to be eliminated—lie in the same plane. An E2 reaction is **anti periplanar** if the hydrogen and halide atoms are on the opposite sides of the molecule and **syn periplanar** when they are on the same side of the molecule.



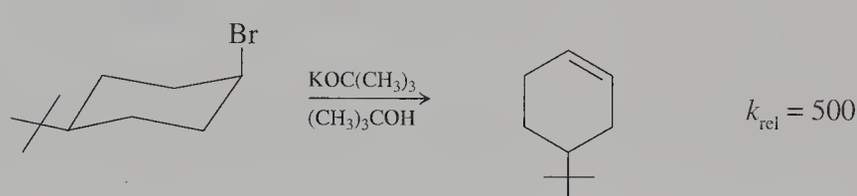
anti periplanar syn periplanar

Both arrangements allow π overlap of incipient parallel *p* orbitals as the σ bonds are broken. The more common anti periplanar geometry corresponds to the staggered anti conformation, which is easily achieved in conformationally flexible molecules. The syn periplanar geometry corresponds to an eclipsed conformation, which is important only in some rigid, cyclic compounds.

The effect of conformation on E2 reactions is demonstrated by the difference in the rates of the dehydrobromination of *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexane. The axial bromine atom of the *cis* isomer is eliminated about 500 times faster than the equatorial bromine atom of the *trans* isomer. Both isomers yield 4-*tert*-butylcyclohexene.



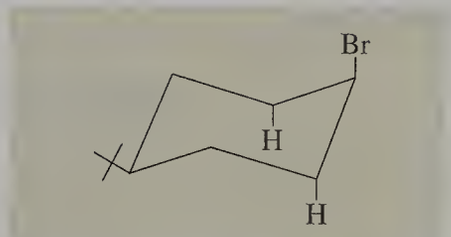
trans-1-bromo-4-*tert*-butylcyclohexane 4-*tert*-butylcyclohexene



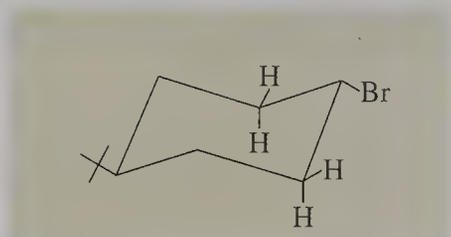
cis-1-bromo-4-*tert*-butylcyclohexane 4-*tert*-butylcyclohexene

As shown in Figure 8.8, the axial bromine atom of the cis isomer is anti periplanar with respect to the axial hydrogen atoms at C-2 and C-6. Therefore, the most favorable geometry for elimination is "built into" the molecule, and no conformational

FIGURE 8.8 Stereochemistry of E2 Elimination Reactions
The preferred relationship between a proton and a leaving group is anti periplanar as exists between the axial bromine and axial hydrogen atoms in the *cis* isomer. The equatorial bromine and either the equatorial or axial hydrogen atoms in the *trans* isomer are at 60° dihedral angles and cannot easily undergo an E2 elimination reaction.



cis-1-bromo-4-*tert*-butylcyclohexane



trans-1-bromo-4-*tert*-butylcyclohexane

equilibria are required to achieve it. In the trans isomer, however, no hydrogen atoms are anti periplanar to the equatorial bromine atom. To eliminate HBr in the trans isomer, a hydrogen atom that lies at a 60° dihedral angle with respect to the bromine atom must be removed. This process or any other reaction of a distorted ring that moves the two atoms into a better geometry for elimination requires more energy. Hence, the reaction rate is slower.

Now that we know the experimental facts, let's see why the stereoelectronic effect occurs. Consider the developing $2p$ π orbitals that must be generated to form the alkene. The anti periplanar arrangement is favored because it aligns the σ orbitals of the sp^3-hybridized C—H and C—X bonds so they can partially overlap as they become the $2p$ π orbitals in the product (Figure 8.9). A similar argument holds for the syn periplanar transition state.

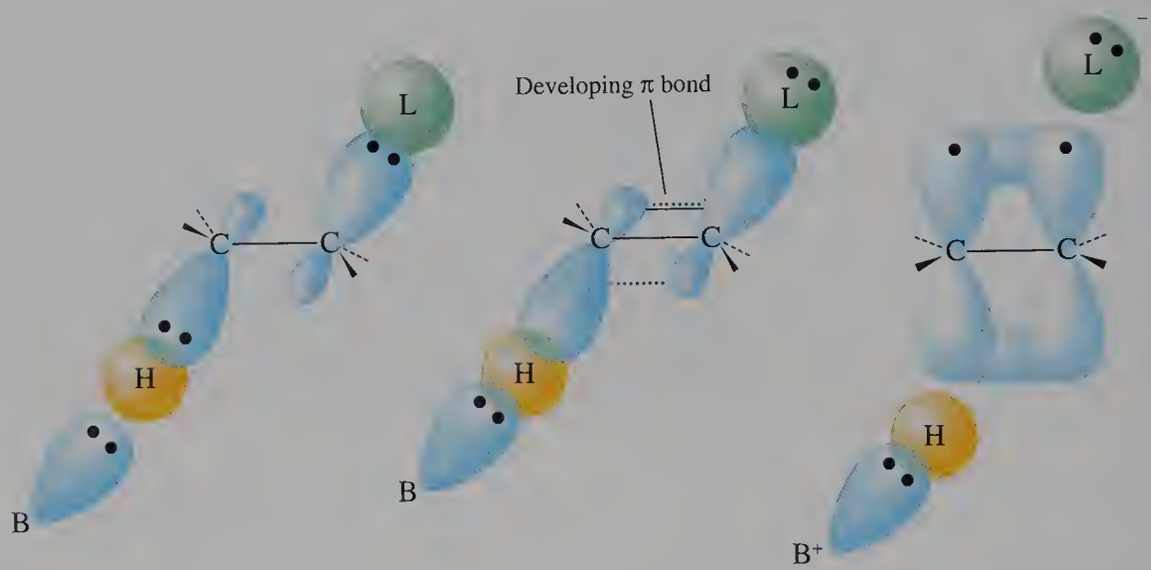


FIGURE 8.9 Orbital Representation of E2 Elimination Reactions
Partial overlap of the developing π orbitals occurs in the transition state for an E2 elimination reaction when the molecule can assume an anti periplanar geometry. The leaving group is represented by L, the base by B.

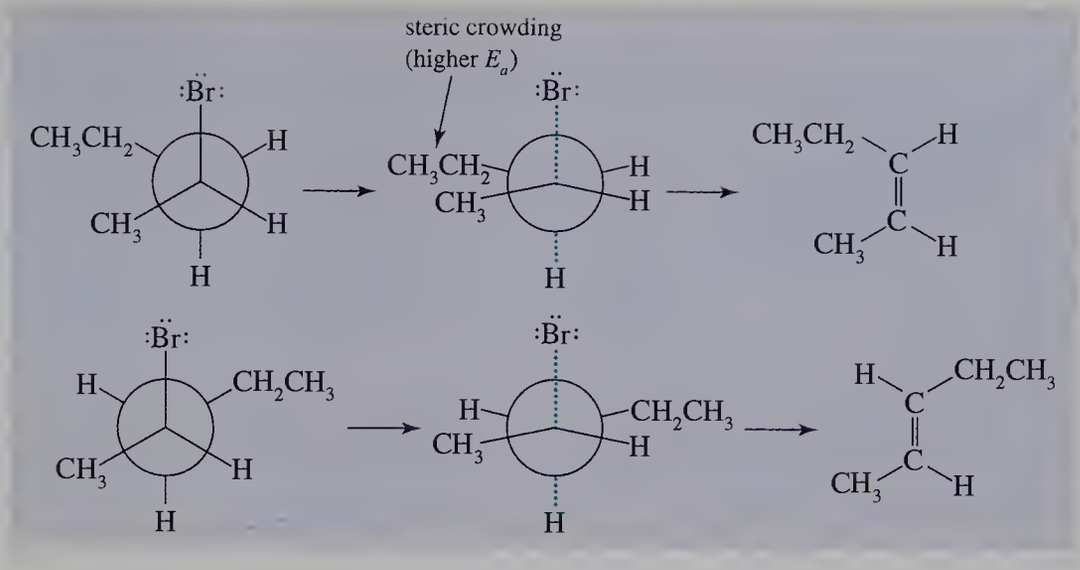
Stereoselectivity in E2 Reactions

We learned earlier that elimination reactions of alkyl halides are stereoselective, and yield the more stable trans alkene as the major product. Based on the geometry for the anti periplanar transition state of the E2 mechanism, we can now understand why. As the hydrogen and halogen atoms are eliminated, the groups bonded to the developing sp^2-hybridized carbon atoms must move closer together in the transition state. In the final product, they must all be in the same plane. Consider the two conformations required to form *cis*- and *trans*-2-pentenes from 2-bromopentane (Figure 8.10). The transition state leading to the cis isomer has more steric strain because the two alkyl groups are moved closer together. As a consequence, the energy of this transition state is higher than that for formation of the trans isomer. The rate of formation of the cis isomer is therefore slower than the rate of formation of the trans isomer.

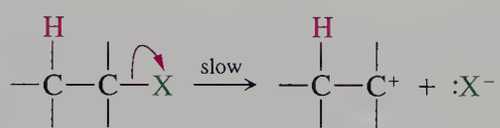
The E1 Mechanism

An E1 mechanism, which occurs in the dehydrohalogenation of tertiary alkyl halides, is a two-step process. The first step is formation of a carbocation by a heterolytic cleavage of the C—X bond. This step is rate determining.

FIGURE 8.10 Steric Effects in E2 Elimination Reactions
The stability of the respective alkenes is reflected in the transition state of the E2 elimination reaction. Steric crowding in the transition state leading to the *cis* isomer raises the activation energy relative to the transition state leading to the *trans* isomer.



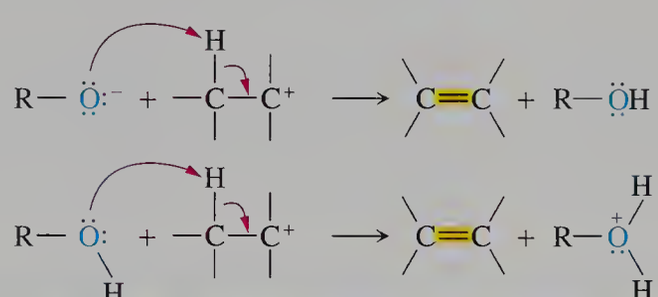
Step 1 (ionization)



As is the case for the E2 reaction, the strength of the carbon–halogen bond affects the rate of the reaction. In fact, the differences in reactivity are larger in the E1 reactions because only the carbon–halogen bond breaks in the rate-determining step. Alkyl iodides have the weakest carbon–halogen bond and hence react at the fastest rate. (The ionization step is also the first step for the S_N1 reaction. We will learn in Chapter 10 that the E1 mechanism competes with an S_N1 mechanism.)

Because the rate-determining step of an E1 reaction involves only the substrate, the formation of the carbocation is a unimolecular reaction. In the second, more rapid deprotonation step, a base such as an alkoxide ion or a solvent such as an alcohol removes a proton from the carbon atom adjacent to the cationic center. The overall result is loss of HX and formation of a π bond. These possibilities are outlined below.

Step 2 (deprotonation)



Problem 8.24

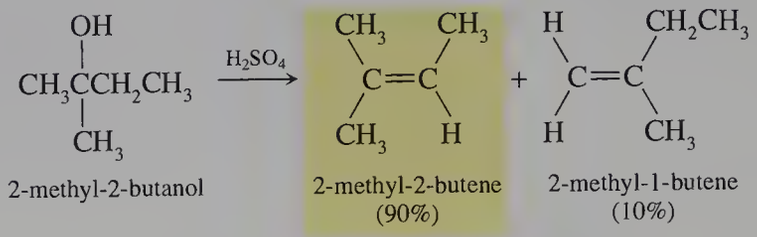
How many products can result from the dehydrobromination of 3-bromo-2,3-dimethylpentane? Predict the major alkene product formed. Predict the alkene formed in the smallest amount.

Problem 8.25

The product of the dehydrobromination of *trans*-1-bromo-2-methylcyclohexane is not 1-methylcyclohexene, the Zaitsev product, but rather 3-methylcyclohexene. Explain why. (Hint: Remember that the ring-flipping process gives a mixture of two conformations.)

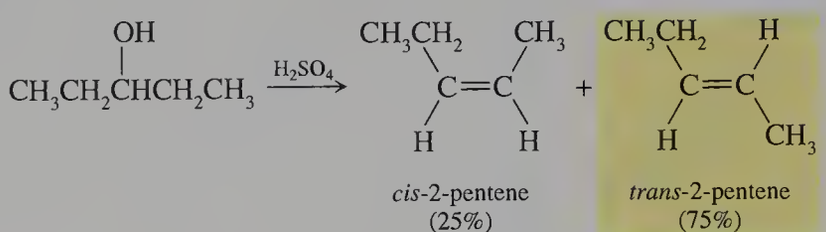
8.20 Regioselectivity in Dehydration of Alcohols

Dehydration of an alcohol is an elimination reaction that requires breaking the carbon–oxygen bond and a carbon–hydrogen bond on an adjacent carbon atom. Thus, dehydration of alcohols having two nonequivalent carbon atoms adjacent to the OH-bearing carbon atom can form a mixture of products. In such cases, the more substituted alkene is the major product. For example, the dehydration of 2-methyl-2-butanol yields 2-methyl-2-butene as the major product. The isomeric 2-methyl-1-butene forms in a substantially smaller quantity.



2-methyl-2-butanol → 2-methyl-2-butene (90%) + 2-methyl-1-butene (10%)

This product distribution is another example of Zaitsev's rule. Zaitsev's rule can be extended to mixtures of geometric isomers. That is, the major product is the more stable trans alkene. For example, 3-pentanol yields a mixture of *cis*- and *trans*-2-pentenes. The trans isomer is the major product. Thus, the dehydration of an alcohol is stereoselective.

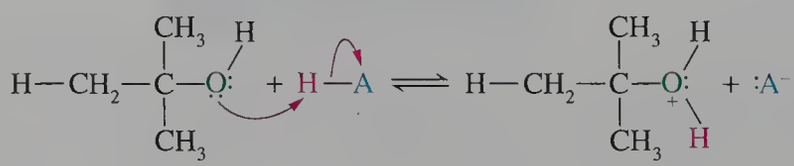


cis-2-pentene (25%) + *trans*-2-pentene (75%)

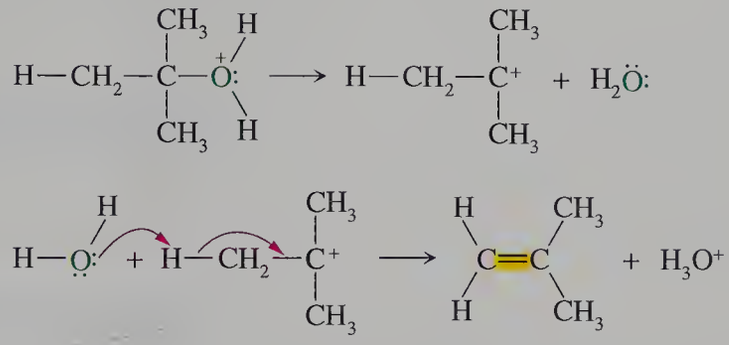
Mechanism of Dehydration of Alcohols

The mechanism for the dehydration of an alcohol must account for two experimental observations. First, the dehydration reaction requires an acid catalyst. Second, the order of reactivity of alcohols decreases in the order 3° > 2° > 1°. These facts remind us of the substitution reaction of tertiary and secondary alcohols using hydrogen halides, which occurs by an S_N1 process. Only primary alcohols react by an S_N2 mechanism.

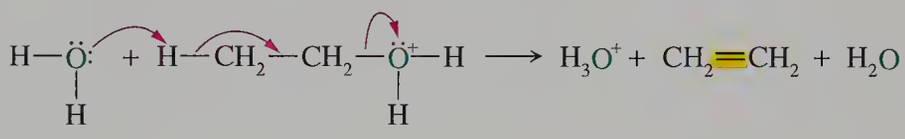
Tertiary and secondary alcohols undergo acid-catalyzed dehydration by an E1 mechanism; primary alcohols are dehydrated by an E2 mechanism. In either mechanism, the first step is the rapid protonation of the lone pair electrons of the oxygen atom to produce an alkyloxonium ion. The acid may be represented as HA in the reaction mechanism for the dehydration of *tert*-butyl alcohol shown below.



An E1 mechanism occurs in two steps. First, a tertiary alcohol loses water in a first-order process to produce a tertiary carbocation. Second, a proton is then rapidly transferred to a Lewis base from the carbon atom adjacent to the carbon atom bearing the positive charge in the tertiary carbocation.



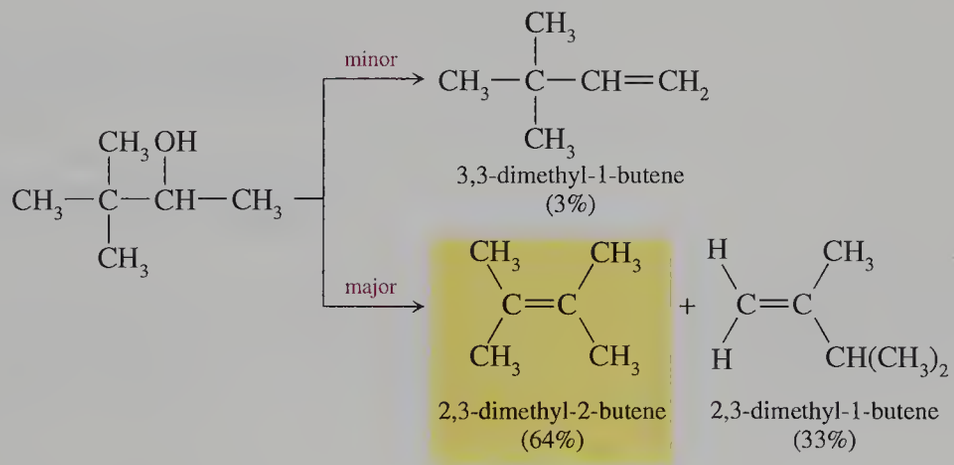
After protonation of the OH group of a primary alcohol to give a primary alkyloxonium ion, water is lost by an E2 mechanism because primary carbocations are too high in energy to form in an E1 process. This concerted step resembles the reaction of primary alkyl halides with a base. The β proton of the alkyloxonium ion is deprotonated by a Lewis base, which is water in the dehydration of alcohols. The electron pair in the C—H bond "moves" to form a carbon–carbon double bond, and the electron pair of the C—O bond is retained by the oxygen atom. The reaction with ethanol illustrates the process.



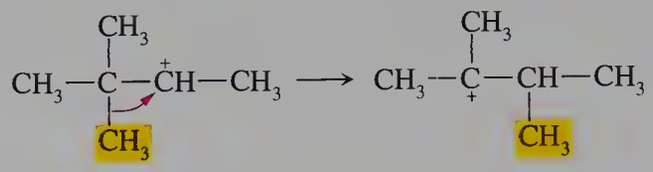
Note that in both the E1 process and the E2 process, the acid serves only as a catalyst. It is regenerated in the last step of the reaction.

Rearrangement in Dehydration Reactions

Because dehydration of secondary and tertiary alcohols occurs via carbocation intermediates, rearrangement reactions are common. Only 3% of the dehydration product from 3,3-dimethyl-2-butanol maintains the original carbon skeleton. The remaining 97% is a mixture of two isomeric alkenes with a rearranged carbon skeleton.



Rearrangement reactions in the dehydration of alcohols were studied by Professor F. C. Whitmore at Pennsylvania State University in the 1930s. He proposed that the product having the same carbon skeleton as the starting alcohol forms by loss of a proton from the C-1 atom of a secondary carbocation. The two alkenes that constitute the bulk of the product are derived from a rearranged tertiary carbocation.



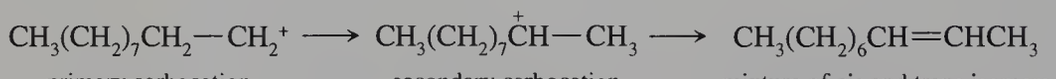
secondary carbocation tertiary carbocation

The rearrangement reaction is thermodynamically favored because tertiary carbocations are more stable than secondary carbocations. We recall that the same rearrangement occurs in the addition reaction of HCl with 3,3-dimethyl-1-butene, which gives not only the expected product, 2-chloro-3,3-dimethylbutane, but 2-chloro-2,3-methylbutane as well (Section 7.4).

The more substituted 2,3-dimethyl-2-butene forms from loss of a proton from C-3 of the tertiary carbocation. The less substituted 2,3-dimethyl-1-butene forms from the loss of any of the six hydrogen atoms located at the two methyl groups bonded to the carbocation center. Although the reaction of the rearranged carbocation may not appear to be very regioselective, it actually is. The more substituted alkene is favored even though the least substituted alkene would be expected on statistical grounds. Any of six equivalent hydrogen atoms could be lost to give 2,3-dimethyl-1-butene, but only one can be lost to give 2,3-dimethyl-2-butene. Thus, the regioselectivity of the reaction reflects the relative stability of the two possible alkenes.

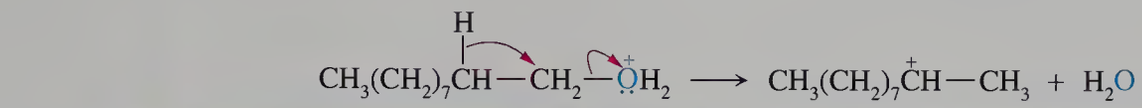
Alkyl groups other than the methyl group may also migrate from one carbon atom to an adjacent carbon atom if the resulting carbocation is more stable. Therefore, mixtures of alkenes result, and the dehydration of alcohols is somewhat limited as a synthetic method to form specific alkenes. We recall that the dehydrohalogenation of primary and secondary alkyl halides occurs via an E2 mechanism and rearranged products are not obtained. Thus, dehydrohalogenation of an alkyl halide using a strong base is a better synthetic method to form alkenes than the dehydration of an alcohol.

We recall that 1,2-hydride shifts occur in the carbocations formed in addition reactions (Section 7.4). Thus, 1,2-hydride shifts can also occur via the carbocations that are generated in dehydration reactions. The hydride ion moves from the carbon atom adjacent to the positive carbon atom if a more stable carbocation results. Such 1,2-hydride shifts occur even in the dehydration of primary alcohols. For example, the dehydration of 1-decanol gives 1-decene as a minor product, which may result from an E2 mechanism. However, the major product is largely a mixture of *cis*- and *trans*-2-decenes. This product could result from loss of a proton by an E1 mechanism from a secondary carbocation formed by a hydride shift of a primary carbocation.



primary carbocation secondary carbocation mixture of cis and trans isomers

However, primary carbocations are difficult to form directly. Thus, it is likely that a shift of the hydride ion from the C-2 atom to the C-1 atom to form the secondary carbocation occurs in a concerted process as water leaves the C-1 atom.



Problem 8.26

Predict the major product formed in the dehydration of each of the following alcohols.

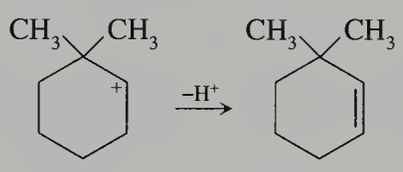
(a) 1-methylcyclohexanol (b) 3-ethyl-2-pentanol (c) 1-isopropylcyclohexanol

Problem 8.27

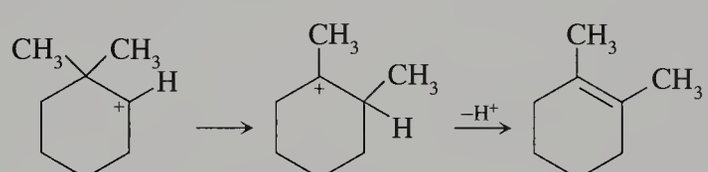
Draw the structures of the three isomeric cycloalkenes resulting from the dehydration of 2,2-dimethylcyclohexanol.

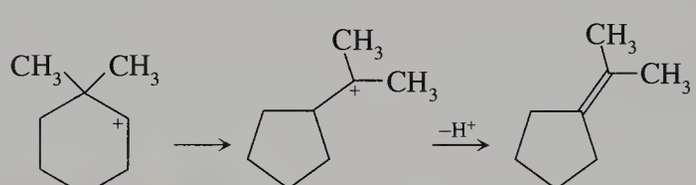
Sample Solution

Loss of a proton from the methylene group of the secondary carbocation gives 3,3-dimethylcyclohexene.



However, the secondary carbocation can rearrange to two possible tertiary carbocations, either of which can lose a proton, to give isomeric cycloalkenes.





Problem 8.28

Write structures of the products of the dehydration of 3-methyl-2-butanol.

Problem 8.29

Although there is no hydrogen atom on the carbon atom adjacent to the carbon atom bearing the hydroxyl group in 2,2-dimethyl-1-propanol, the alcohol is dehydrated in sulfuric acid. Write the structures of two resulting alkenes and predict which is the major isomer.

EXERCISES

Classification of Compounds

8.1 Classify each of the following haloalkanes.

(**a**) $CH_3-CH_2-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_2-CH_3$

(**b**) $CH_3-\underset{\displaystyle Cl}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2-CH_3$

(**c**) $CH_3-CH_2-\underset{\displaystyle F}{\overset{|}{CH}}-CH_3$

(**d**) $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-I$

8.2 Classify each of the following alcohols.

(**a**) $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2-OH$

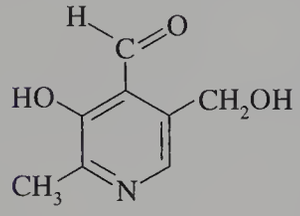
(**b**) $CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-CH_3$

(**c**) $CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-CH_2-CH_3$

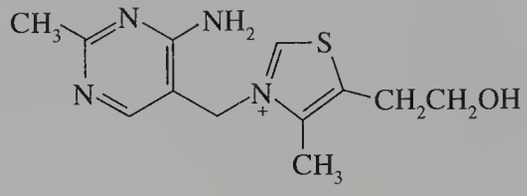
(**d**) $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2-CH_2-OH$

8.3 Classify each of the hydroxyl groups in the following vitamins.

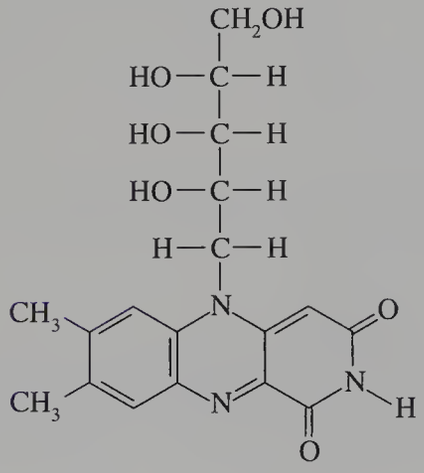
(**a**) pyridoxal (vitamin B_6)



(**b**) thiamine (vitamin B_1)

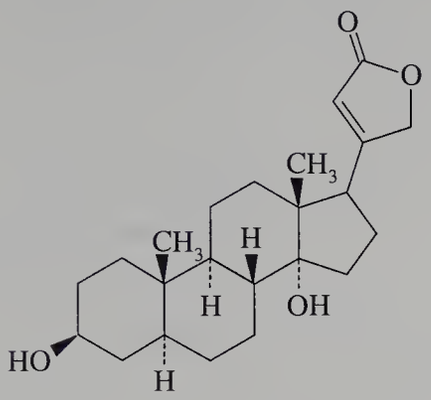


(**c**) riboflavin (vitamin B_2)

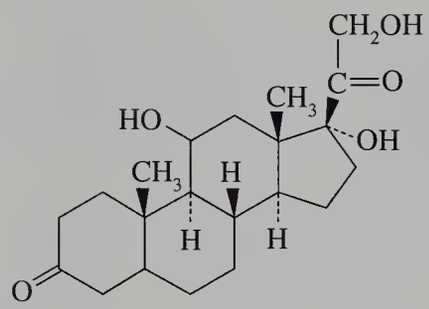


8.4 Classify each of the hydroxyl groups in the following steroids.

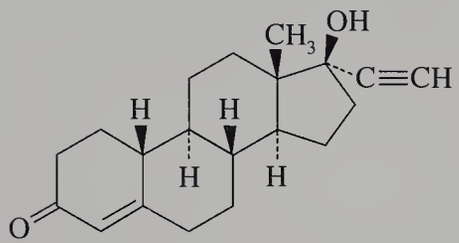
(**a**) digitoxigenin, a cardiac glycoside



(**b**) hydrocortisone, an anti-inflammatory drug



(**c**) norethindrone, an oral contraceptive



Nomenclature of Haloalkanes

8.5 What is the IUPAC name for each of the following compounds?

(**a**) vinyl fluoride
(**b**) allyl chloride
(**c**) benzyl bromide

8.6 What is the IUPAC name for each of the following compounds?

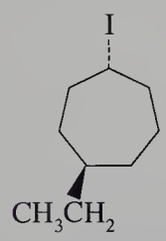
(**a**) $(CH_3)_3CCH_2Cl$ (neopentyl chloride)
(**b**) $(CH_3)_2CHCH_2CH_2Br$ (isoamyl bromide)
(**c**) $C_6H_5CH_2CH_2F$ (phenethyl fluoride)

8.7 Draw the structure of each of the following compounds.

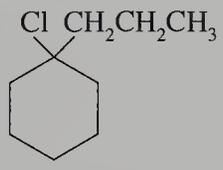
(**a**) *cis*-1-bromo-2-methylcyclopentane
(**b**) 3-chlorocyclobutene
(**c**) (*E*)-1-fluoro-2-butene
(**d**) (*Z*)-1-bromo-1-propene

8.8 What is the IUPAC name for each of the following compounds?

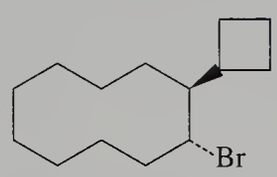
(**a**)



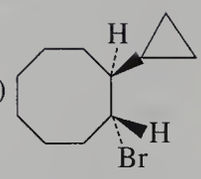
(**b**)



(**c**)



(**d**)



Nomenclature of Alcohols

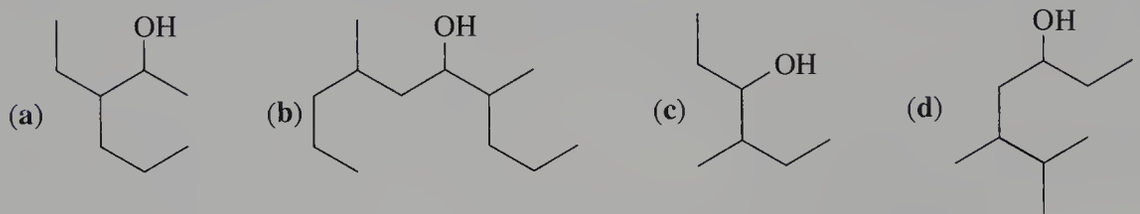
8.9 Write the structural formula of each of the following.

(a) 2-methyl-2-pentanol (b) 2-methyl-1-butanol (c) 2,3-dimethyl-1-butanol
(d) cyclopentanol (e) *trans*-2-methylcyclohexanol (f) 1,3-propanediol
(g) 1,2,4-butanetriol

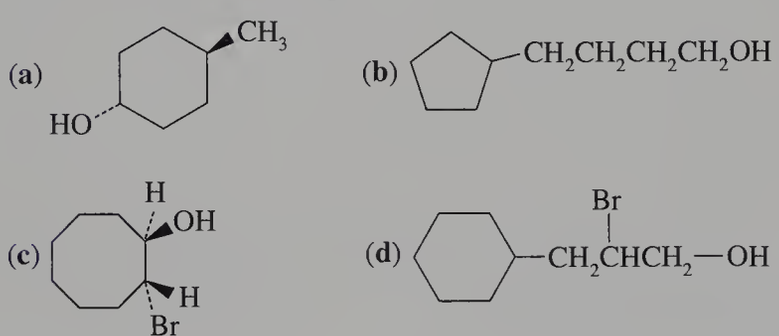
8.10 Write the structural formula of each of the following.

(a) 2-methyl-3-pentanol (b) 3-ethyl-3-pentanol (c) 4-methyl-2-pentanol
(d) 1-ethylcyclohexanol (e) *cis*-3-ethylcyclopentanol (f) 1,2-hexanediol
(g) 1,2,3,4,5,6-hexanehexol

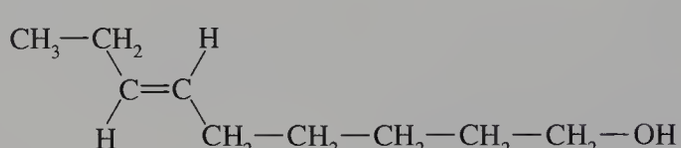
8.11 Name each of the following compounds.



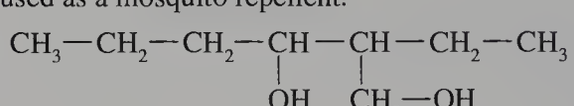
8.12 Name each of the following compounds.



8.13 Name the sex attractant of the Mediterranean fruit fly.



8.14 Name the following compound, used as a mosquito repellent.



Properties of Haloalkanes

8.15 Which compound is more polar, methylene chloride (CH_2Cl_2) or carbon tetrachloride (CCl_4)?

8.16 Tribromomethane is more polar than tetrabromomethane, but their boiling points are 150 and 189 °C, respectively. Explain why the more polar compound has the lower boiling point.

8.17 The densities of chloroiodomethane and dibromomethane are 2.42 and 2.49 g/mL respectively. Why are these values similar?

8.18 The density of 1,2-dichloroethane is 1.26 g/mL. Predict the density of 1,1-dichloroethane.

8.19 The dipole moment of (*Z*)-1,2-dichloroethene is 1.90 Debye. Predict the dipole moment of the *E* isomer.

8.20 The dipole moment of 1,2-dichloroethane is 1.19 Debye. What does this value indicate about the conformational equilibrium of this compound?

Physical Properties of Alcohols

8.21 1,2-Hexanediol is very soluble in water but 1-heptanol is not. Explain why these two compounds with similar molecular weights have different solubilities.

8.22 Ethylene glycol and 1-propanol boil at 198 and 97 °C, respectively. Explain why these two compounds with similar molecular weights have different boiling points.

8.23 Explain why 1-butanol is less soluble than 1-propanol in water.

8.24 Suggest a reason why 2-methyl-1-propanol is much more soluble than 1-butanol in water.

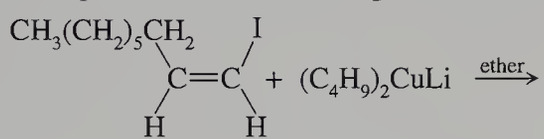
Organometallic Reagents

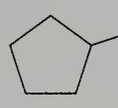
8.25 Devise a synthesis of 1-deutero-1-methylcyclohexane starting from 1-methylcyclohexene.

8.26 Devise a synthesis of 1,4-dideuterobutane starting from any organic compound that does not contain deuterium.

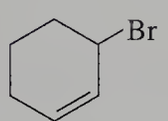
8.27 Devise two syntheses to prepare 2-methyloctane using reagents containing alkyl groups with five or fewer carbon atoms.

8.28 Write the products of the following reactions for Gilman reagents that contain primary alkyl groups.

(**a**) 

(**b**) 

$+ (C_3H_7)_2CuLi \longrightarrow$

(**c**) 

$+ (C_2H_5)_2CuLi \longrightarrow$

Nucleophilic Substitution Reactions

8.29 Write the structure of the product obtained for each of the following combinations of reactants.

(**a**) 1-chloropentane and sodium iodide
(**b**) 1,3-dibromopropane and excess sodium cyanide
(**c**) benzyl chloride and sodium acetylide
(**d**) 2-bromobutane and sodium hydrosulfide (NaSH)

8.30 What haloalkane and nucleophile are required to produce each of the following compounds?

(**a**) $CH_3CH_2CH_2C{\equiv}CH$ (**b**) $(CH_3)_2CHCH_2CN$ (**c**) $CH_3CH_2SCH_2CH_3$ (**d**) $C_6H_5CH_2OH$

Mechanism of Nucleophilic Substitution Reactions

8.31 Which compound in each of the following pairs reacts at the faster rate with sodium iodide in an S_N2 process to yield an alkyl iodide?

(**a**) 1-chlorohexane or 2-chlorohexane
(**b**) bromocyclohexane or 1-bromo-1-methylcyclohexane
(**c**) 2-bromo-4-methylpentane or 2-bromo-2-methylpentane

8.32 Rank the following compounds in order of increasing S_N2 reactivity with a common nucleophile.

I: 1-bromohexane II: 1-bromo-2-methylpentane III: 1-bromo-3-methylpentane

8.33 Which compound in each of the following pairs reacts at the faster rate in an S_N1 process under the same reaction conditions?

(**a**) bromocyclohexane or 1-bromo-1-methylcyclohexane
(**b**) 2-bromobutane or 1-bromo-2-methylpropane
(**c**) 2-bromobutane or 2-methyl-2-bromobutane

8.34 Rank the following compounds in order of increasing S_N1 reactivity under the same reaction conditions.

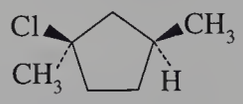
I: 2-bromohexane II: 2-bromo-2-methylpentane III: 1-bromo-2-methylpentane

8.35 Predict the product of the reaction of one molar equivalent of sodium iodide with 1,3-dichlorohexane.

8.36 Treatment of the following compound with sodium sulfide yields C_4H_8S. What is the structure of the product? How is it formed?

$$Cl{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Cl + Na_2S \longrightarrow C_4H_8S + 2\,NaCl$$

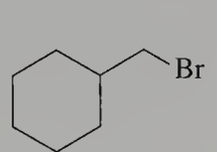
8.37 Reaction of the following compound with water under S_N1 conditions yields a mixture of two alcohols. Explain why.



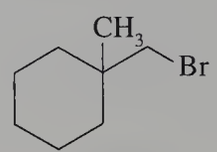
8.38 Reaction of either 3-bromo-1-butene or (*Z*)-1-bromo-2-butene with water under S_N1 conditions yields the same product. Explain why.

8.39 The rate of reaction of *cis*-1-bromo-4-*tert*-butylcyclohexane with methylthiolate (CH_3S^-) is faster than for the trans isomer. Suggest a reason for this difference.

8.40 Which of the following two compounds reacts at the faster rate with sodium cyanide?



I



II

Acid–Base Properties of Alcohols

8.41 1,1,1-Trichloro-2-methyl-2-propanol is used as a bacteriostatic agent. Compare its K_a to that of 2-methyl-2-propanol.

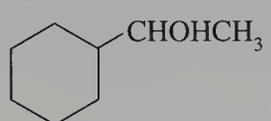
8.42 Based on the data in Table 8.3, estimate the K_a of 2-bromoethanol.

8.43 Based on the data in Table 8.3, estimate the K_a of cyclohexanol.

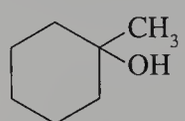
8.44 Which base is the stronger, methoxide ion or *tert*-butoxide ion?

Formation of Alkyl Halides from Alcohols

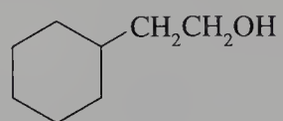
8.45 Rank the following isomeric compounds according to reactivity with HBr.



I

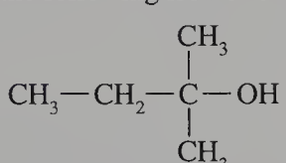


II

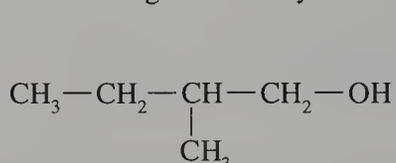


III

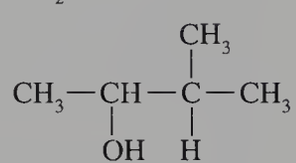
8.46 Rank the following isomeric compounds according to reactivity with HCl and $ZnCl_2$.



I

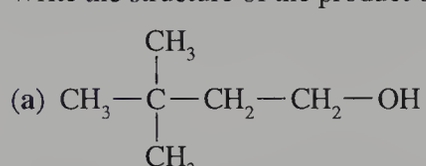


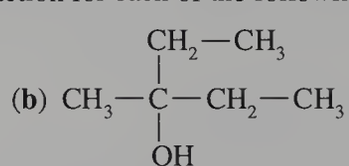
II

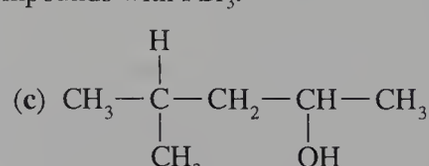


III

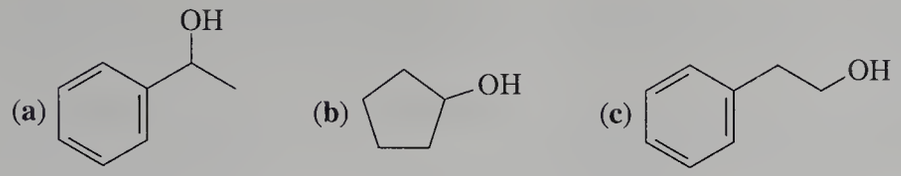
8.47 Write the structure of the product of reaction for each of the following compounds with PBr_3.





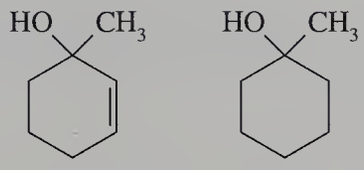


8.48 Write the structure of the product of reaction for each of the following compounds with $SOCl_2$.



8.49 Reaction of 3-buten-2-ol with HBr yields a mixture of two products: 3-bromo-1-butene and 1-bromo-2-butene. Explain why. (Hint: The reaction of this allyl alcohol occurs via an S_N1 process.)

8.50 The rate of reaction of the following unsaturated alcohol with HBr is faster than the rate of reaction of the saturated alcohol. Explain why.



8.51 Which of the compounds in Exercises 8.45 and 8.46 may yield rearranged products?

8.52 The reaction of 2-octanol with HBr gives 2-bromooctane and 3-bromooctane in a 13:1 ratio. Explain how 3-bromooctane forms in this reaction.

Thermodynamics of Elimination Reactions

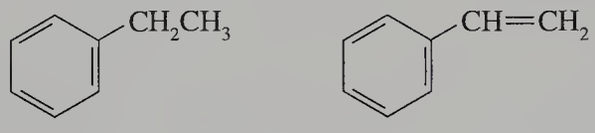
8.53 The heat of formation of $ZnBr_2$ is -326 kJ mole^{-1}. Calculate the heat of reaction of the debromination reaction of a dibromide using zinc.

8.54 The ΔH°_{rxn} for the reaction of H^+ and OH^- is -55 kJ mole^{-1}. Calculate the heat of reaction of the dehydrohalogenation reaction with OH^-.

Dehydrogenation Reactions

8.55 Would the dehydrogenation of 2-methylpropane require a higher or lower temperature than the dehydrogenation of ethane to make the reaction thermodynamically favorable?

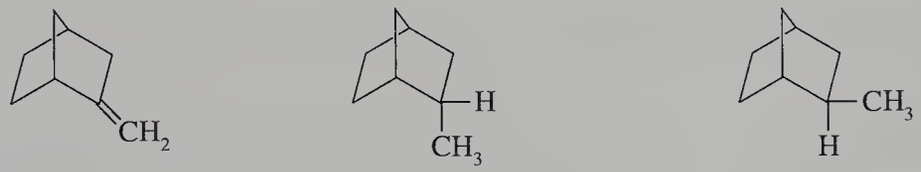
8.56 The dehydrogenation of ethylbenzene to give styrene occurs at 630 °C. Why is the temperature lower than that required for the dehydrogenation of ethane?



ethylbenzene styrene

8.57 Certain isomeric hydrocarbons can be thermodynamically equilibrated at temperatures near 300 °C in the presence of platinum provided that the contents of the mixture are sealed in a container. One such pair of isomeric hydrocarbons is *cis*- and *trans*-1,2-dimethylcyclohexane. Write a mechanism for the equilibrium process. Which of the two isomers is the major component at equilibrium?

8.58 Catalytic hydrogenation of 2-methylenenorbornane at room temperature yields a mixture of *endo*- and *exo*-2-methylnorbornane in a 4:1 ratio. Equilibration of the two isomers over a platinum catalyst at 300 °C in a sealed container yields a 1:4 ratio of *endo*- and *exo*-2-methylnorbornane. Explain why each ratio occurs.

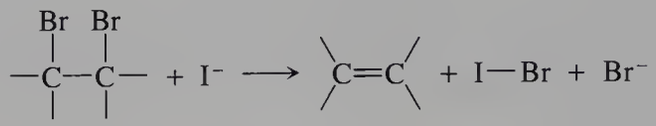


2-methylenenorbornane *endo*-2-methylnorbornane *exo*-2-methylnorbornane

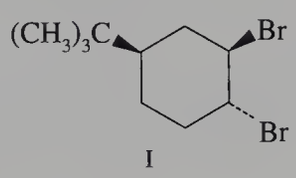
Dehalogenation of Vicinal Dibromides

8.59 Based on bond energies, would a vicinal dichloroalkane require a lower or higher temperature to dehalogenate than a vicinal dibromoalkane?

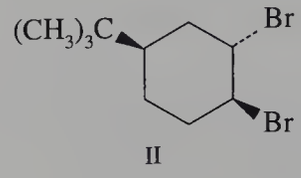
8.60 Dibromo compounds can be debrominated by iodide ion at relatively low temperatures as described by the following general equation. Explain why the reaction occurs.



8.61 The stereoelectronic features of debromination reactions are the same as for dehydrohalogenation. Based on this information, explain why one of the following isomeric compounds is easily debrominated whereas the other does not react at all.

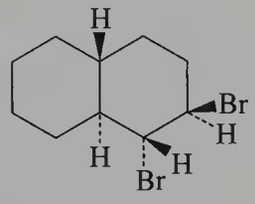


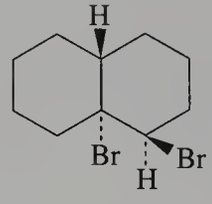
I



II

8.62 Explain why one of the following isomeric bicyclic compounds is easily debrominated whereas the other does not react at all.



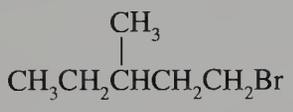


Regioselectivity in Dehydrohalogenation

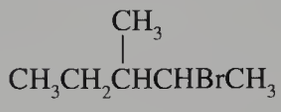
8.63 Consider each of the following isomeric compounds with the molecular formula $C_6H_{13}Br$. Which ones will give only a terminal monosubstituted alkene when dehydrobrominated via an E2 process?

I: $CH_3CH_2CH_2CH_2CH_2CH_2Br$ II: $CH_3CHBrCH_2CH_2CH_2CH_3$ III: $CH_3CH_2CHBrCH_2CH_2CH_3$

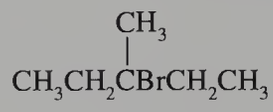
IV: $(CH_3)_2CHCH_2CH_2CH_2Br$ V: $(CH_3)_2CHCH_2CHBrCH_3$ VI: $(CH_3)_2CHCHBrCH_2CH_3$



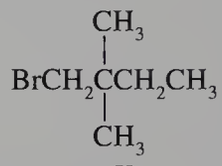
VII



VIII



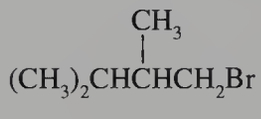
IX



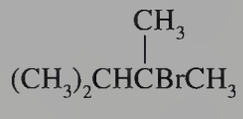
X

XI

XII



XIII



XIV

8.64 Consider each of the compounds in Exercise 8.63. Which ones can be dehydrobrominated via an E2 process to give only a terminal disubstituted alkene?

8.65 Consider each of the compounds in Exercise 8.63. Which ones can be dehydrobrominated via an E1 process?

8.66 Consider each of the compounds in Exercise 8.63. Which ones cannot be dehydrobrominated?

8.67 Consider each of the compounds in Exercise 8.63. Which ones can be dehydrobrominated to give at least one set of *E,Z* stereoisomers among the products?

8.68 Consider each of the compounds in Exercise 8.63. Which ones can be dehydrobrominated to give a trisubstituted alkene among the products? Which ones can be dehydrobrominated to give a tetrasubstituted alkene among the products?

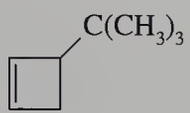
8.69 How many alkenes can form from each of the following compounds via an E2 elimination process? Write the structure of each alkene.

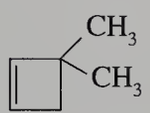
(**a**) 1-bromopentane (**b**) 2-chlorohexane
(**c**) 3-iodoheptane (**d**) 5-bromononane

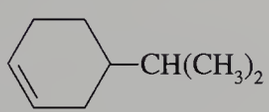
8.70 How many alkenes can form from each of the following compounds via an E2 elimination process? Write the structure of each alkene.

(**a**) 3-bromo-2-methylhexane (**b**) 2-chloro-3-methylhexane
(**c**) 3-iodo-4-ethylhexane (**d**) 4-bromo-4-methylheptane

8.71 What bromo compound can give each of the following unsaturated compounds in the best yield via an E2 elimination process?

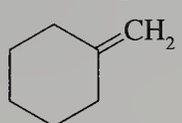
(**a**) 

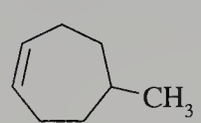
(**b**) 

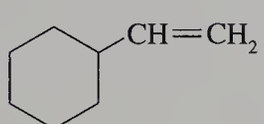
(**c**) 

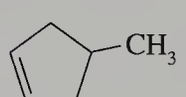
(**d**) 

8.72 Which of the following unsaturated compounds can be obtained in good yield via an E2 elimination process from a bromo compound?

(**a**) 

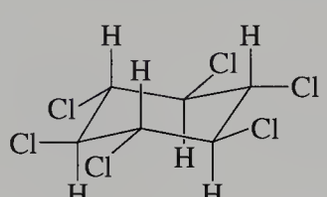
(**b**) 

(**c**) 

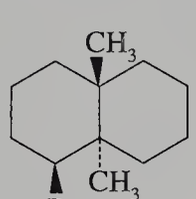
(**d**) 

Stereoelectronic Effects in Dehydrohalogenation

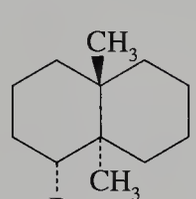
8.73 The following isomer undergoes an E2 reaction about 1000 times slower than any of the other stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane. Why?



8.74 One of the following two isomeric bicyclic compounds undergoes an E2 elimination much faster than the other. Identify the compound that reacts at the faster rate and explain why.

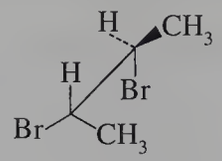


I

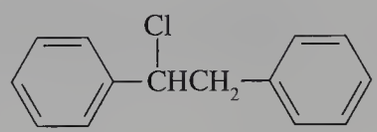


II

8.75 What is the configuration of the alkene formed by the elimination of one molar equivalent of HBr from the following compound?

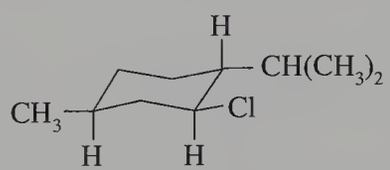


8.76 An E2 elimination of 1-chloro-1,2-diphenylethane can yield a mixture of (*E*)- and (*Z*)-1,2-diphenylethene. How would the *E*/*Z* ratio of isomers for this reaction compare to the *E*/*Z* ratio for the E2 elimination of 2-bromopentane?

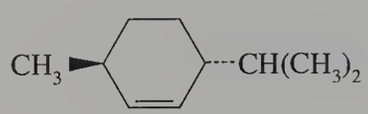


1-chloro-1,2-diphenylethane

8.77 When menthyl chloride reacts with sodium ethoxide in ethanol, the only alkene product is 2-menthene. Explain why.

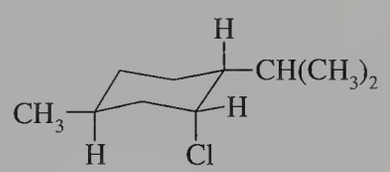


menthyl chloride

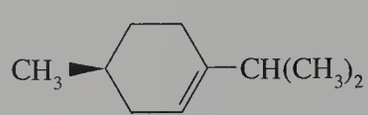


2-menthene

8.78 When neomenthyl chloride reacts with sodium ethoxide in ethanol, 3-menthene and 2-menthene are obtained in approximately a 3:1 ratio. Explain why 3-menthene is the predominant product.

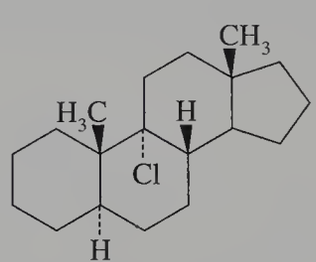


neomenthyl chloride

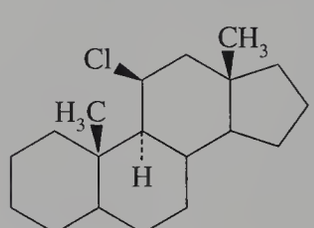


3-menthene

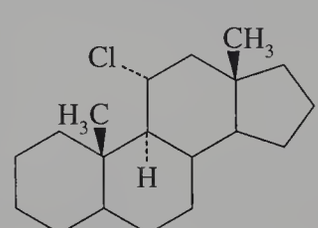
8.79 Draw the structure of the alkene formed in an E2 elimination of the following compound.



8.80 Which of the following compounds reacts at the faster rate in an E2 elimination reaction?

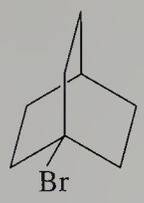


I



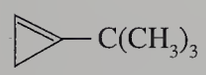
II

8.81 The following compound can't be dehydrobrominated under either E1 or E2 conditions. Explain why.



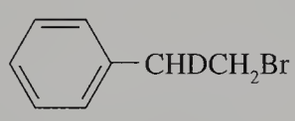
1-bromobicyclo[2.2.2]octane

8.82 Explain why 1-*tert*-butylcyclopropene is difficult to synthesize by a dehydrohalogenation reaction.

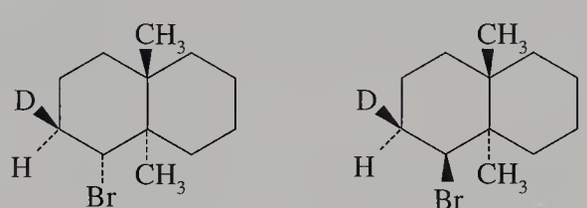


1-*tert*-butylcyclopropene

8.83 Reaction of 1-bromo-2-deutero-2-phenylethane with *tert*-butoxide in *tert*-butyl alcohol gives a 7:1 ratio of deuterated and nondeuterated phenylethenes. Write the structures of the products. What does the data suggest about the ease of abstraction of deuterium versus hydrogen?

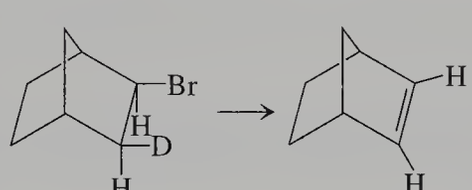


8.84 Dehydrobromination of each of the following compounds gives a single product. One compound yields a cycloalkene containing deuterium, the other yields a cycloalkene that does not contain deuterium. Which compound is which?

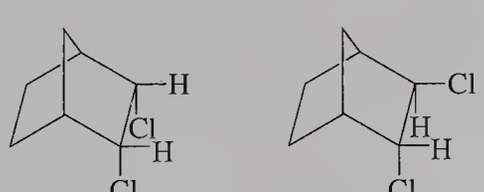


I II

8.85 Although the following reaction of the deuterated bicyclic compound with a strong base occurs at a somewhat slow rate, it gives the indicated product by an E2 mechanism. Explain why the product forms.

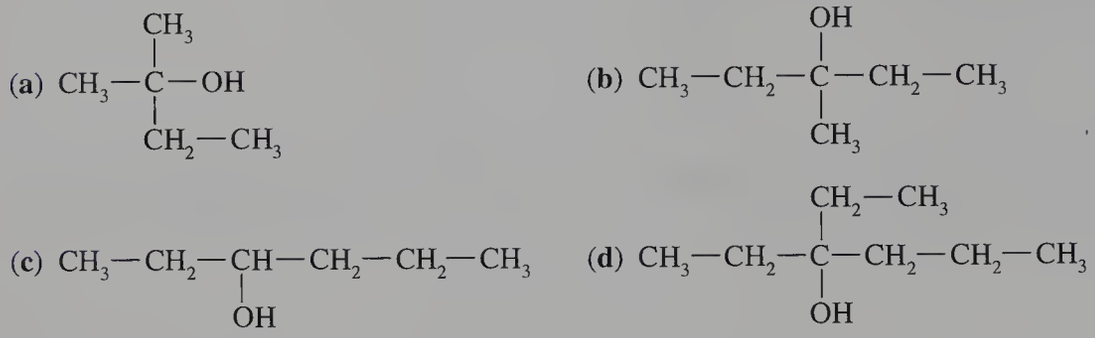


8.86 One of the following 2,3-dichlorobicyclo[2.2.1]heptanes undergoes an E2 elimination using potassium *tert*-butoxide in *tert*-butyl alcohol about 100 times as fast as the other. Which compound reacts at the faster rate? The same product, 2-chlorobicyclo[2.2.1]hept-1-ene, forms in both reactions.

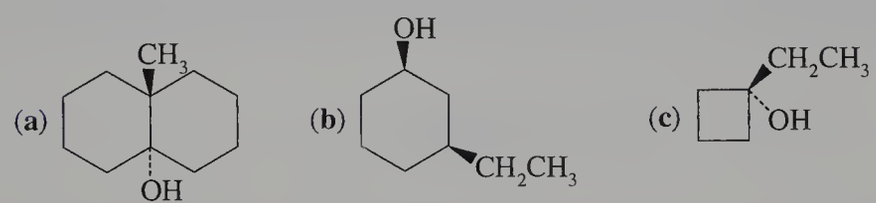


Dehydration of Alcohols

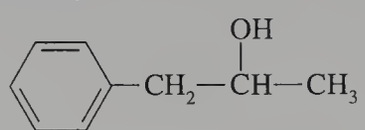
8.87 Draw the structure of the dehydration product(s) when each of the following compounds reacts with sulfuric acid. If more than one product forms, predict the major isomer assuming that no rearrangement reactions occur.



8.88 Draw the structure of the dehydration product(s) when each of the following compounds reacts with sulfuric acid. If more than one product forms, predict the major isomer assuming that no rearrangement reactions occur.

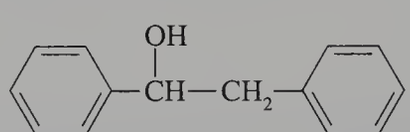


8.89 Write the expected product of the acid-catalyzed dehydration of 1-phenyl-2-propanol. The reaction is more rapid than the dehydration of 2-propanol. Explain why.



1-phenyl-2-propanol

8.90 1,2-Diphenylethanol dehydrates extremely easily. Explain why.



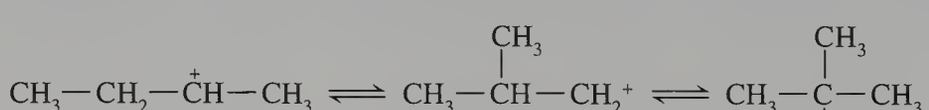
1,2-diphenylethanol

8.91 Dehydration of *cis*-2-methylcyclohexanol yields two products in a 5:1 ratio. What are the structures of the two products?

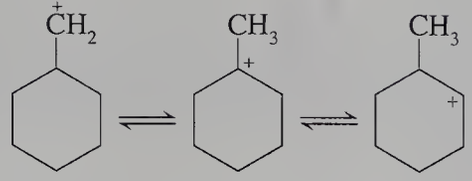
8.92 Dehydration of cyclododecanol yields two isomeric products in approximately equal amounts. Catalytic hydrogenation of either compound yields cyclododecane. What are the structures of the two products?

Carbocation Rearrangement

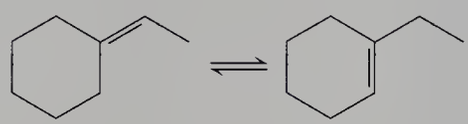
8.93 The following isomerization reactions occur in some industrial processes. Write a mechanism that accounts for each step. Indicate whether each reaction is endothermic or exothermic.



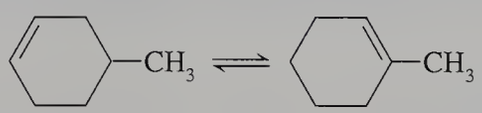
8.94 Consider the following isomerization reactions. Write a mechanism that accounts for each step. Indicate whether each reaction is endothermic or exothermic.



8.95 Ethylidenecyclohexane and 1-ethylcyclohexene can be equilibrated using an acid catalyst. Write a mechanism that accounts for this conversion.



8.96 4-Methylcyclohexene is isomerized to 1-methylcyclohexene over alumina (an acidic substance). Write a mechanism that accounts for this conversion.

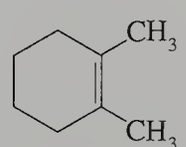


Rearrangement in Dehydration Reactions

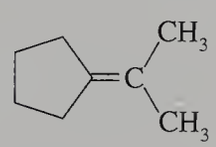
8.97 Dehydration of 2,2,4-trimethyl-3-pentanol with acid gives a complex mixture of the alkenes in the indicated percentages. Write a mechanism that accounts for each product.

I: 2,3,4-trimethyl-1-pentene	29%	II: 2,4,4-trimethyl-1-pentene	24%
III: 3,3,4-trimethyl-1-pentene	2%	IV: 2,4,4-trimethyl-2-pentene	24%
V: 2,3,4-trimethyl-2-pentene	18%	VI: 2-isopropyl-3-methyl-1-butene	3%

8.98 Dehydration of 2,2-dimethylcyclohexanol with acid gives both of the following isomeric alkenes. Write a mechanism that accounts for each product.



1,2-dimethylcyclohexene



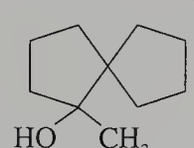
isopropylidenecyclopentane

8.99 1-Methylcyclopentene is one of the dehydration products obtained from 1-cyclobutyl-1-ethanol. Write a mechanism accounting for this reaction.

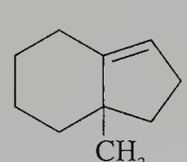
8.100 3,3-Dimethylcyclopentene is one of the dehydration products obtained from 2-cyclobutyl-2-propanol. Write a mechanism accounting for this reaction.

8.101 1-*tert*-Butylcyclohexene is one of several dehydration products obtained from 1,2,2-trimethylcycloheptanol. Two rearrangements are required for this transformation. Write a mechanism accounting for these reactions.

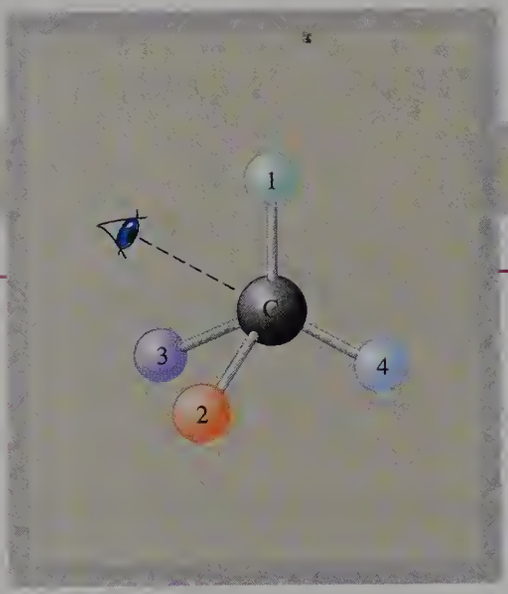
8.102 Dehydration of 2-methyl-2-spiro[4.4]nonanol gives a mixture containing 1-methyl-6-bicyclo[4.3.0]nonene. Write a mechanism accounting for formation of this product.



2-methyl-2-spiro[4.4]nonanol



1-methyl-6-bicyclo[4.3.0]nonene



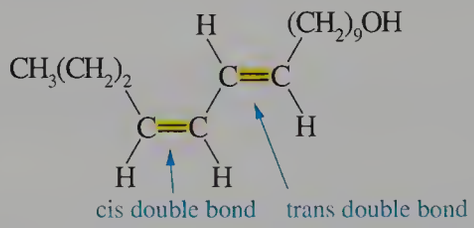
9

Stereochemistry

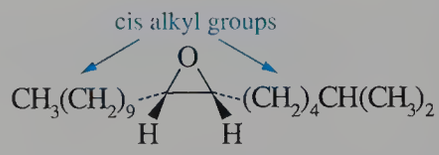
9.1 Configuration of Molecules

In Chapters 4 and 7, we considered the structures of geometric isomers, one type in the general class **stereoisomers**. Stereoisomers have the same connectivity—the same sequence of bonded atoms—but different configurations. The three-dimensional arrangement of the atoms in a molecule in space, as in geometric isomers, determines its **configuration**.

The configuration of a molecule plays a major role in its biological function. Two isomeric molecules that differ in configuration often have entirely different biological properties. For example, bombykol, the sex attractant of the male silkworm moth (Chapter 6), has a trans-cis arrangement around the double bonds at the C-10 and C-12 positions. This geometric isomer is 10^9 to 10^{13} times as potent in attracting male moths as the other three possible geometric isomers. Disparlure, the sex attractant of the female gypsy moth (Chapter 4), is active only if the large alkyl groups bonded to the three-membered ring are cis.



bombykol



disparlure

Geometric isomers are only one type of stereoisomer. Another type, which is based on mirror image relationships between molecules, is the subject of this chapter. This second type of stereoisomerism is not as easily visualized as geometric isomerism, but its consequences are even more vital to life processes. In this chapter we will see that the configuration around a tetrahedral carbon atom bearing four different groups of atoms affects a molecule's reactions, especially those occurring in living organisms.

9.2 Mirror Images and Chirality

The fact that we live in a three-dimensional world has important personal consequences. When you look into a mirror, you see someone who does not actually exist, your mirror image. Every object has a mirror image, but this reflected image need not be identical to the actual object. One such example is lettering in two-dimensional space, such as the reverse lettering on the front of an ambulance. The letters are painted as their mirror image, so that the lettering we see in the rearview mirror of our automobile identifies the ambulance.

Now let's think about the mirror images of a few common three-dimensional objects. A simple wooden chair looks exactly like its mirror image (Figure 9.1). Similarly, the mirror images of items such as a teacup or a hammer are identical to the objects themselves. When an object and its mirror image exactly match, we say that they are **superimposable**. Superimposable objects can be "placed" on each other so that each feature of one object precisely coincides in space with an equivalent feature in the mirror image.

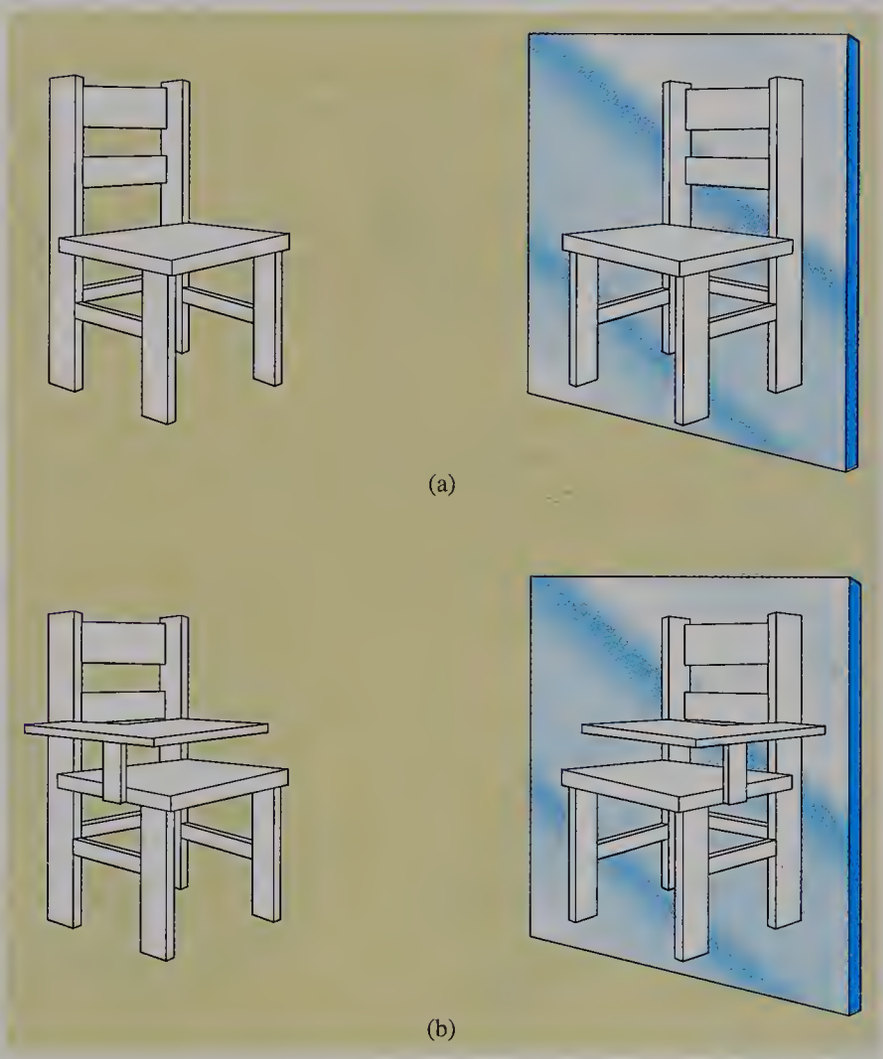


FIGURE 9.1 Objects and Their Mirror Images
In (a) the simple chair and its mirror image are identical. The mirror image can be superimposed on the original chair. In (b) the sidearm chair has a mirror image that is different. The chair is a right-handed object; the mirror image is a left-handed object. The mirror image cannot be superimposed on the original chair.

Now let's consider some objects that cannot be superimposed upon their mirror images. These are called **nonsuperimposable** objects. One example is the sidearm chair found in many classrooms. When a chair with a "right-handed arm" is reflected in a mirror, it becomes a chair with a "left-handed arm" (Figure 9.1). We can convince ourselves of this by imagining sitting in the chair or its mirror image.

Now consider the nonsuperimposability of hands, which are also related as mirror images. The mirror image of a left hand looks like a right hand. But, when we try to superimpose our hands, we find that it can't be done (Figure 9.2). Therefore, our hands are related as nonsuperimposable mirror images.

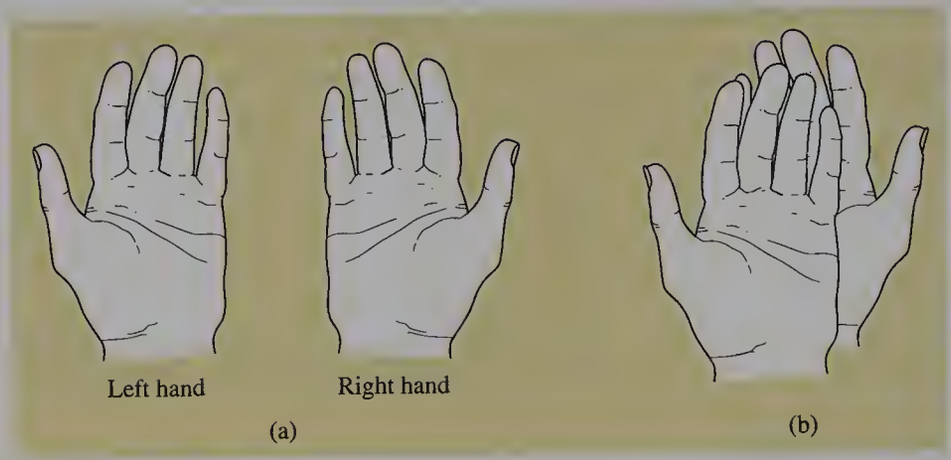


FIGURE 9.2 Chiral Objects Are Nonsuperimposable
The hands in (a) are mirror images and resemble each other. However, as shown in (b), the hands cannot be superimposed. Hands are nonsuperimposable mirror images; they are chiral.

An object that is not superimposable on its mirror image is called **chiral** (Greek *chiron*, hand). Objects such as gloves and shoes that have a "handedness" are chiral. An object that can be superimposed on its mirror image, such as a cup or hammer, is **achiral**. We can determine whether an object is chiral or achiral without trying to superimpose its mirror image. One way is to determine if it has a plane of symmetry. A **plane of symmetry** bisects an object so that one half is the mirror image of the other half. For example, because a cup has a plane of symmetry that divides it so that one half of it is the mirror image of the other half (Figure 9.3), it is achiral.

Any object that has a plane of symmetry is superimposable on its mirror image and is achiral. However, if an object, such as your hand, has no such plane of symmetry, it is chiral. The presence or absence of a plane of symmetry is one way to tell whether an object is achiral or chiral.

FIGURE 9.3 Plane of Symmetry
Any object with a plane of symmetry is achiral. The material on one side of the plane is the mirror image of the material on the other side of the plane. The cup shown can be divided into two equal halves that are mirror images of each other. It is achiral. The plane shown does not split a hand into two equal halves. A hand is chiral.

Molecules Can Be Chiral

The concept of chirality can be extended from macroscopic objects to molecules. Most molecules produced in living organisms are chiral. We do not have to find a plane of symmetry to tell if a molecule is chiral. A molecule is chiral if it contains

a single tetrahedral carbon atom attached to four different atoms or groups of atoms. Such a carbon atom is a **stereogenic center**. A stereogenic center is often also called a **chiral center**, and the carbon atom is called a **chiral carbon atom**.

The four atoms or groups of atoms at a stereogenic center can be arranged in two ways to correspond to two stereoisomers. Let's consider the stereoisomers of bromochlorofluoromethane. One stereoisomer of this molecule and its mirror image are illustrated in Figure 9.4. The two structures cannot be superimposed. Therefore, bromochlorofluoromethane is chiral.

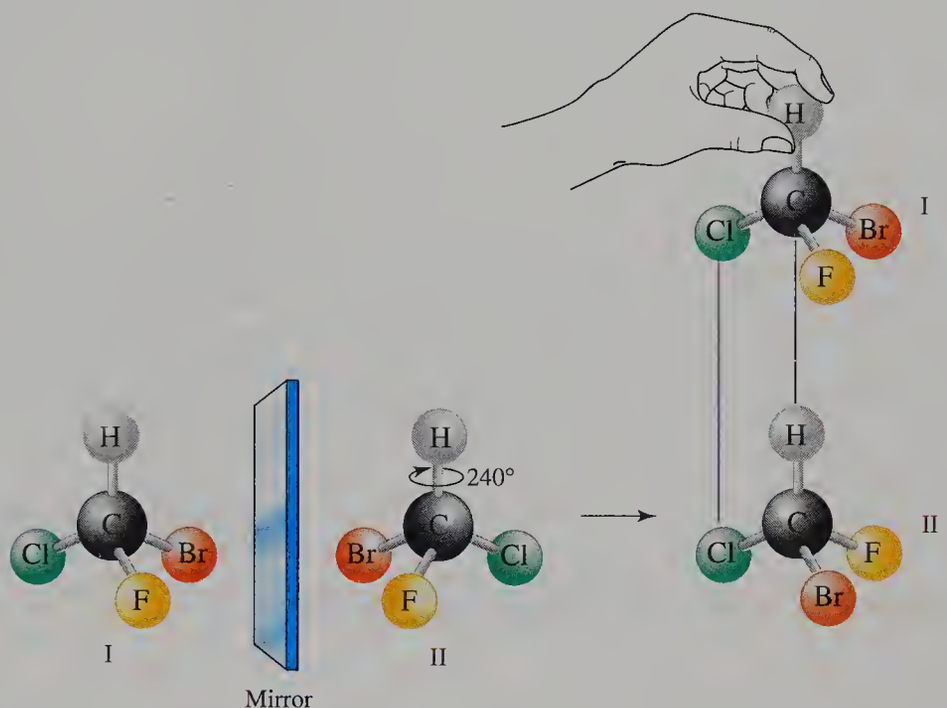


FIGURE 9.4 Criteria for Chirality in Molecules
The two molecular models representing the chiral molecule bromochlorofluoromethane cannot be superimposed. The spheres of structure I held in the hand do not line up with those of structure II, which has been rotated 240° to line up the chlorine atoms. The mirror image cannot be superimposed on the original structure.

Macroscopic achiral objects contain a plane of symmetry. This generalization also applies equally to molecules. Dichloromethane has two planes of symmetry, while bromochloromethane has one plane of symmetry (Figure 9.5). Each molecule can be superimposed on its mirror image and is therefore achiral. In contrast, bromochlorofluoromethane does not have a plane of symmetry, and it is chiral (Figure 9.5).

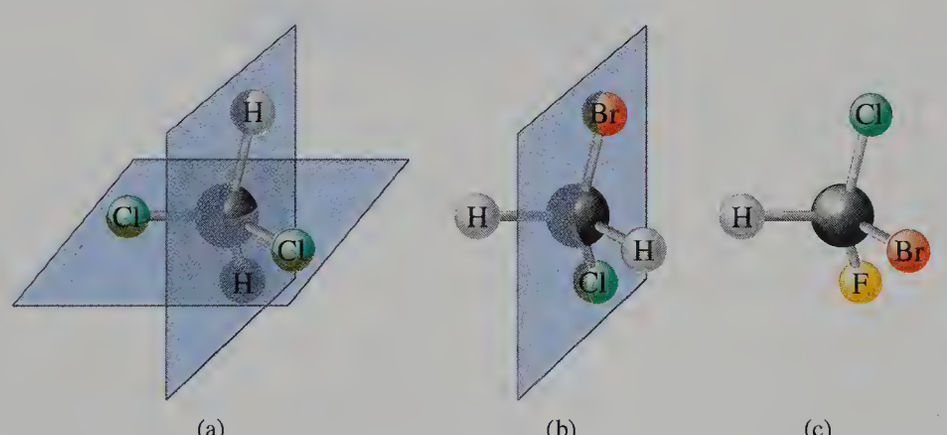
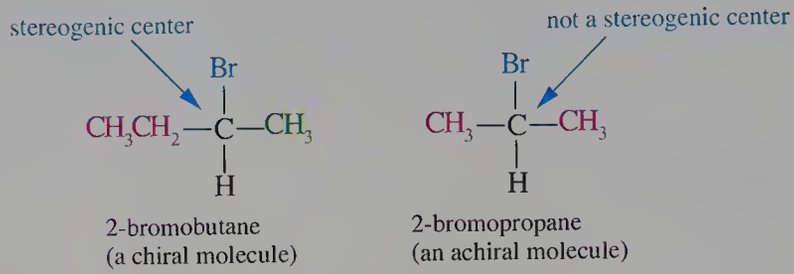


FIGURE 9.5 Planes of Symmetry for Molecules
(a) Dichloromethane is bisected by two planes of symmetry. (b) Bromochloromethane has one plane of symmetry. (c) Bromochlorofluoromethane has no plane of symmetry.

Enantiomers Are Mirror Image Isomers

Two stereoisomers related as nonsuperimposable mirror images are called **enantiomers** (Greek *enantios*, opposite + *meros*, part). We can tell that a substance is chiral and predict that two enantiomers exist by identifying the substituents on each carbon atom. A carbon atom with four different substituents is stereogenic, and a

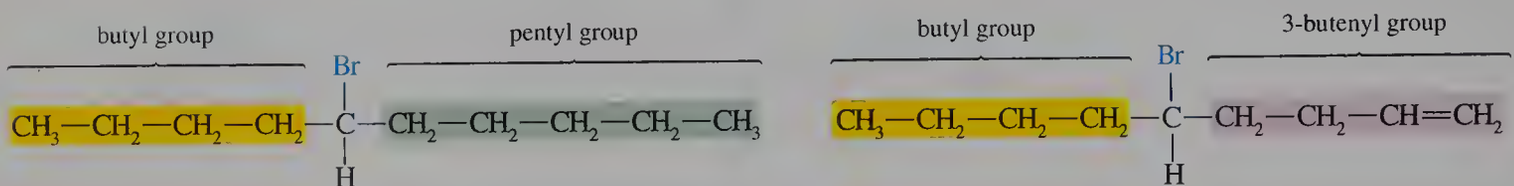
molecule with a stereogenic center is chiral. This molecule can exist as either of a pair of enantiomers. For example, 2-bromobutane is chiral because the C-2 atom is attached to four different groups (CH_3, CH_3CH_2, H, and Br). In contrast, 2-bromopropane does not contain any carbon atom attached to four different groups. The C-2 atom has two methyl groups attached to it.



2-bromobutane (a chiral molecule)

2-bromopropane (an achiral molecule)

A stereogenic center may not be immediately apparent. This situation occurs when the groups bonded to a chiral carbon atom differ at sites not immediately adjacent to the stereogenic center. The difference between a methyl group and an ethyl group is readily apparent in 2-bromobutane. However, in some molecules, the difference may be found many atoms away from the stereogenic center. For example, let's examine 5-bromodecane and 5-bromo-1-nonene, each of which has a stereogenic center.



In the case of 5-bromodecane, the butyl and pentyl groups are similar. However, there is a difference in the additional carbon atom of the pentyl group, four carbon atoms away from the stereogenic center. In the case of 5-bromo-1-nonene, both carbon groups bonded to the stereogenic center contain four carbon atoms. However, only one of the groups has a multiple bond.

Problem 9.1

Which of the following structures can represent a chiral molecule? Why?

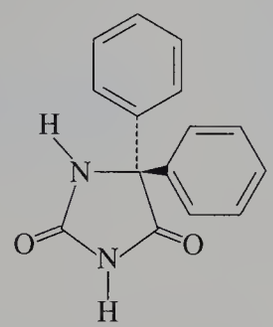
(a) $CH_3—CH_2—CH_2—CH_2—C(OH)(CH_3)—CH_2—CH_2—CH_2—CH_3$

(b) $CH_2=CH—CH_2—CH_2—C(Br)—CH_2—CH_2—C\equiv CH$
Br

(c) $CH_3—CH_2—CH_2—CH_2—C(Br)(Cl)—CH_2—CH_2—CH(CH_3)—CH_3$

Problem 9.2

Consider phenytoin, a compound with anticonvulsant activity. Is the molecule chiral or achiral? Determine your answer by identifying the number of different groups bonded to tetrahedral carbon atoms and by determining whether or not the molecule has a plane of symmetry.



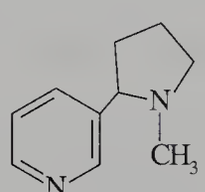
Sample Solution

Phenytoin has only one tetrahedral carbon atom in the entire molecule! That carbon atom is bonded to a nitrogen atom, a carbonyl group, and two benzene rings. Because the tetrahedral carbon atom is attached to two identical benzene rings, the molecule is achiral.

Phenytoin has a plane of symmetry that lies in the plane of the page. One of the benzene rings of phenytoin is above and the other below the symmetry plane. Note that the other atoms of phenytoin are bisected by the plane.

Problem 9.3

Consider the following structural formula for nicotine. Is the molecule chiral?

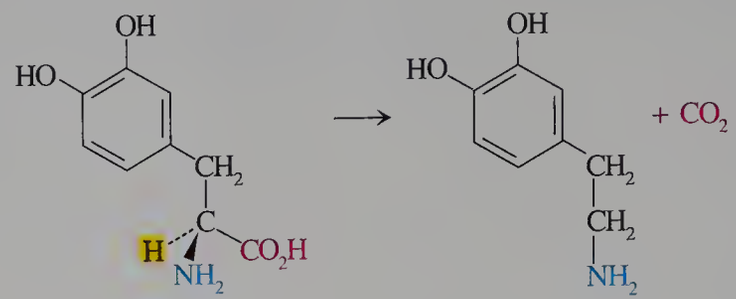


Properties of Enantiomers

We can regard hands as analogous to the enantiomers of a chiral molecule. Let's consider the interaction of hands with a symmetrical object such as a pair of tweezers. The tweezers are symmetrical. They can be used equally well with either hand because there is no preferred way to pick up or manipulate a pair of tweezers. However, even if blindfolded, you could easily use your hands to distinguish right- and left-handed gloves. Your hands are "a chiral environment", and in this environment, mirror image gloves do not interact with hands in the same way. The right glove will fit only the right hand. We can distinguish chiral objects only because we are chiral.

Pairs of enantiomers have the same heats of formation, density, melting point, and boiling point. They also have the same chemical properties in an achiral environment. However, enantiomers can be distinguished in a chiral environment. This difference is important in many processes in living cells. Only one of a pair of enantiomers fits into a specific site in a biological molecule such as an enzyme catalyst because the site on the enzyme that binds the enantiomer is chiral. The binding of this enantiomer is called **stereospecific**. An example of a stereospecific process is the conversion of the drug levodopa to dopamine, a neurotransmitter in the brain. Levodopa (or L-dopa),

the precursor of dopamine, is administered to treat Parkinson's disease. Levodopa has one chiral carbon atom. It can thus exist as either of two enantiomers. Only the enantiomer with the configuration shown below is transformed into dopamine.



levodopa dopamine

The transformation occurs because of the loss of a carboxyl group by formation of carbon dioxide (decarboxylation). The biological catalyst responsible is a stereospecific decarboxylase. This enzyme has a chiral binding site for levodopa, but does not bind the enantiomer of levodopa.

9.3 Optical Activity

Although enantiomers have identical chemical properties in achiral environments, they differ in one physical property: Enantiomers behave differently toward plane-polarized light. This difference is used to distinguish a chiral molecule from its enantiomer in the laboratory.

Plane-Polarized Light

Light consists of waves oscillating in an infinite number of planes at right angles to the direction of propagation of the light. When a beam of "ordinary" light passes through a **polarizing filter**, it is converted to **plane-polarized light** vibrating in a single plane. We are familiar with this phenomenon in everyday life: Plane-polarized light can be produced by Polaroid sunglasses, which reduce glare by acting as a polarizing filter. They partly block horizontally oscillating light reflecting off the surfaces of various objects.

The Polarimeter

Plane-polarized light interacts with chiral molecules, and this interaction can be measured by an instrument called a **polarimeter** (Figure 9.6). In a polarimeter, light with a single frequency of vibration—that is, monochromatic light—passes through a polarizing filter. The polarized light then traverses a tube containing a solution of the compound to be examined. While passing through the solution, the polarized light is unaffected by achiral molecules. But the plane of polarized light rotates because of an interaction with chiral molecules. After the plane-polarized light leaves the sample tube, it passes through a second polarizing filter called an analyzer. The analyzer must be rotated either clockwise or counterclockwise to match the plane of polarization of the light and allow it to pass. An angle, α, can be read off the analyzer and is called the observed rotation. It equals the angle by which the light has been rotated by the chiral compound. Because chiral molecules rotate plane-polarized light, they are **optically active**. Achiral molecules do not rotate plane-polarized light, so they are **optically inactive**.

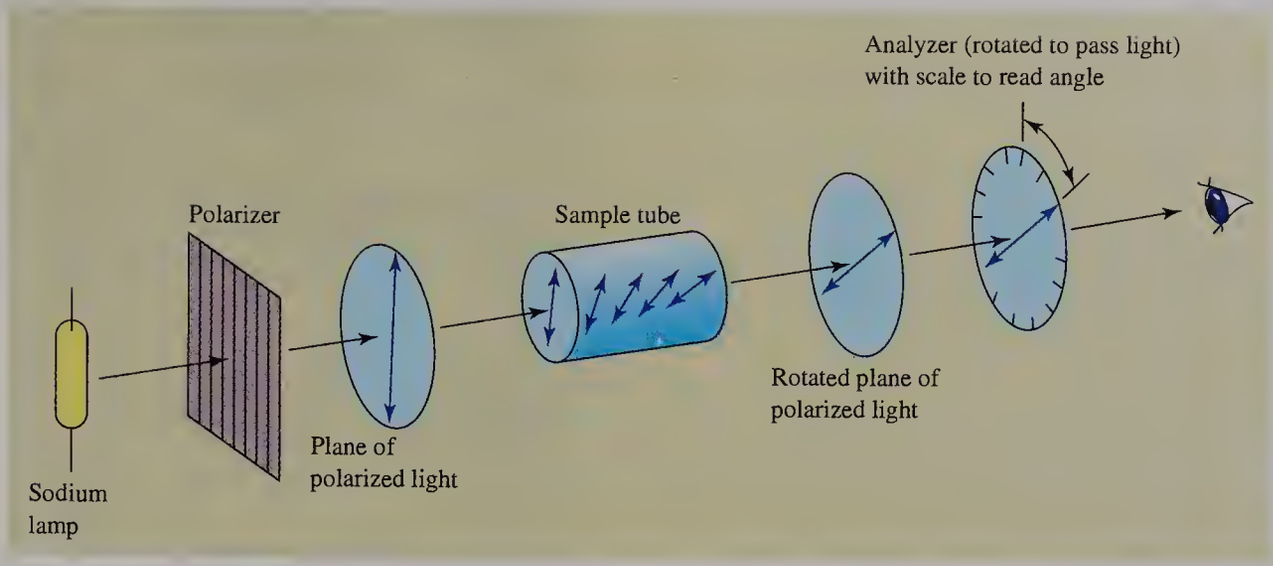


FIGURE 9.6
Representation of a Polarimeter
Plane-polarized light is obtained by the passage of light through the polarizer. Any chiral compound contained in the sample tube rotates the plane of light. The direction and magnitude of the rotation are determined by rotating the analyzer to allow the light to emerge.

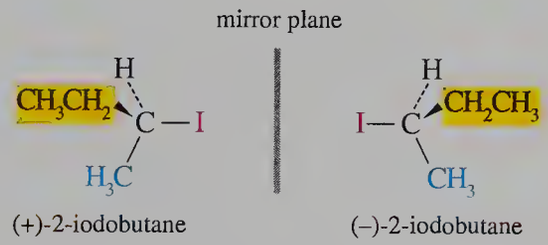
Specific Rotation

The amount of rotation observed in a polarimeter depends on the structure of the substance and the number of molecules encountered by the light. The optical activity of a pure chiral substance is reported as its **specific rotation**, symbolized by $[\alpha]_D$. It is the number of degrees of rotation of a solution at a concentration of 1 g mL^{-1} in a tube 1 dm long. The standard conditions selected for these experiments are 25 °C and the yellow light (D line, 589 nm) of the sodium vapor lamp.

$$[\alpha]_D = \frac{\alpha}{l \times c}$$

If a chiral substance rotates plane-polarized light to the right—that is, in a positive (+) or clockwise direction—the substance is **dextrorotatory** (Latin *dextro*, right). If a chiral substance rotates plane-polarized light to the left—in a negative (–) or counterclockwise direction—the substance is **levorotatory** (Latin *laevus*, left). The two enantiomers of a chiral substance—called dextrorotatory and levorotatory isomers—rotate polarized light the same number of degrees but in opposite directions. Therefore, they are sometimes called **optical isomers**.

We often refer to an enantiomer by prefixing the sign of the optical rotation at 589 nm to the name of the compound. For example, one of the enantiomers of 2-iodobutane has $[\alpha]_D = -15.15$. It is called (–)-2-iodobutane. The other enantiomer is (+)-2-iodobutane, $[\alpha]_D = +15.15$.



The (+) isomer is sometimes called the **D form**, and the (–) isomer is called the **L form**. Earlier, we encountered levodopa, so named because it is levorotatory. It is also called L-dopa and (–)-dopa. The specific rotation of L-dopa is –13.1. The specific rotations of some common substances are listed in Table 9.1.

TABLE 9.1
Specific Rotations of Common Compounds

Compound	$[\alpha]_D$
azidothymidine (AZT)	+99
cefotaxine (a cephalosporin)	+55
cholesterol	−31.5
cocaine	−16
codeine	−136
epinephrine (adrenaline)	−5.0
heroin	−107
levodopa	−13.1
monosodium glutamate (MSG)	+25.5
morphine	−132
oxacillin (a penicillin)	+201
progesterone (female sex hormone)	+172
sucrose (table sugar)	+66.5
testosterone (male sex hormone)	+109

Optical Purity

Most naturally occurring molecules with stereogenic centers exist as one enantiomer. Samples that contain only one enantiomeric form are **optically pure**. Naturally occurring cholesterol, for example, exists only as the L form. It rotates light in a counterclockwise direction. However, compounds synthesized in the laboratory may not all have the same handedness. What is the optical rotation of a mixture of enantiomers, and how is it related to the percentage of each enantiomer in the mixture?

When plane-polarized light interacts with a single enantiomer of a chiral molecule, the plane is rotated in one direction. If the light wave interacts with the other enantiomer, the plane is rotated in the opposite direction an equal number of degrees. If a solution contains equal amounts of two enantiomers, the clockwise and counterclockwise rotations resulting from all molecules cancel and there is no net rotation. Mixtures containing equal amounts of enantiomers are called **racemic mixtures**. A racemic mixture is represented with a (±) prefix, as in (±)-2-iodobutane.

Now consider a circumstance in which the percent ratio of a mixture of enantiomers is not 50:50. The percent enantiomeric excess of the enantiomer present in the larger amount is calculated as follows.

$$\%\ \text{enantiomeric excess} = \%\ \text{of one enantiomer} - \%\ \text{of other enantiomer} = \text{optical purity}$$

The percent enantiomeric excess is the optical purity of the sample. For example, a 60:40 ratio of (+)-2-iodobutane and (−)-2-iodobutane is 20% optically pure. This value indicates that the rotation of the levorotatory isomer (40% of the total) cancels the rotation of some of the dextrorotatory isomer (40% of the total). The remaining 20% of the sample, which is (+)-2-iodobutane, is responsible for the observed rotation, so the sample is called 20% optically pure.

The optical purity of a mixture of enantiomers is calculated by determining the specific rotation of the sample and comparing it to the specific rotation of the pure enantiomer.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\%$$

Problem 9.4

What is the $[\alpha]_D$ of the enantiomer of naturally occurring testosterone? (See Table 9.1.) What is the name of this enantiomer?

Problem 9.5

A sample of a solution of 1.5 g of cholic acid, a bile steroid, in 10 mL of alcohol is placed in a 10.0 cm tube. The observed rotation is +5.5. Calculate $[\alpha]_D$ for cholic acid.

Problem 9.6

A synthetic sample of epinephrine has $[\alpha]_D = -0.5$. What is the optical purity of the sample? What is the percentage of each enantiomer in the sample? (See Table 9.1.)

Sample Solution

The specific rotation of epinephrine is −5.0. We calculate the optical purity using the following equation.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\% = \frac{-0.5}{-5.0} \times 100\% = 10\%$$

The enantiomeric excess is equal to the optical purity. The sum of the two enantiomers is 100%. Let the percent of the enantiomer with the negative optical rotation be x. The percent of the other enantiomer is $100 - x$. Use the following equation and substitute the algebraic quantitites.

$$\%\ \text{enantiomeric excess} = \%\ \text{of one enantiomer} - \%\ \text{of other enantiomer} = \text{optical purity}$$

$$10\% = x - (100\% - x)$$

$$x = 55\%$$

Thus, the percentages of the two enantiomers are 55% and 45%.

9.4 Fischer Projection Formulas

Drawing molecules in three dimensions is time consuming. Furthermore, the resulting perspective structural formulas are difficult to use, especially for compounds that contain several chiral carbon atoms (Section 9.6). The structural formulas of chiral substances can be conveniently drawn, however, using a convention proposed by the German chemist Emil Fischer more than a century ago. The configurations of chiral substances are indicated by comparing them to the configuration of a reference compound called glyceraldehyde.

Glyceraldehyde contains a carbon atom bonded to four different groups, so it exists as two enantiomeric forms (Figure 9.7). The enantiomers of glyceraldehyde are written according to the projection method proposed by Fischer. The carbonyl group (—CHO), the hydroxymethyl group ($—CH_2OH$), and the chiral carbon atom are arranged vertically, with the most oxidized group (—CHO) at the "top". The chiral carbon atom is placed in the plane of the paper. Because this carbon atom is tetrahedral, the CHO group and the CH_2OH group extend behind the plane of the page, and the hydrogen atom and the hydroxyl group extend up and out of the plane. When these four groups are projected onto a plane, the projection is called the **Fischer projection formula**. The chiral carbon atom is usually not shown in this convention. It is located at the point where the bond lines cross. The vertical lines are assumed to project away from the viewer. The horizontal lines project out toward the viewer.

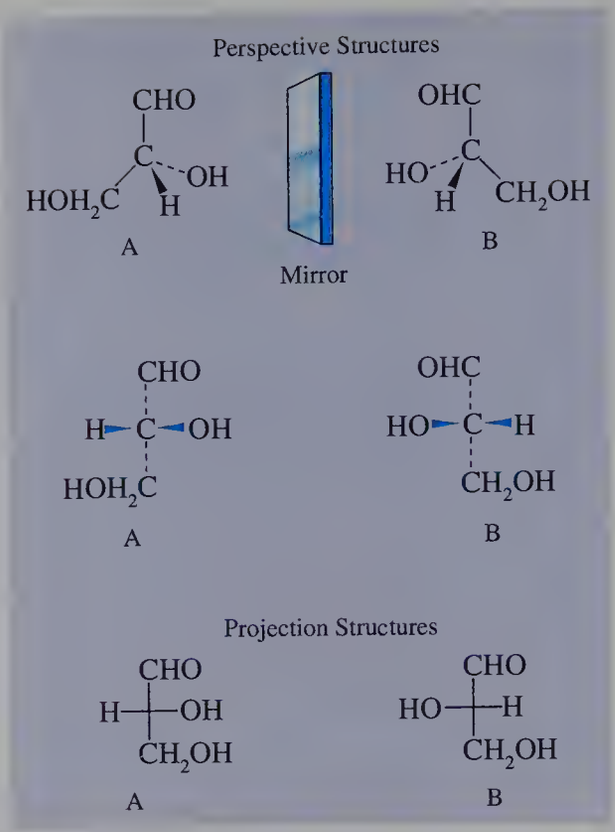
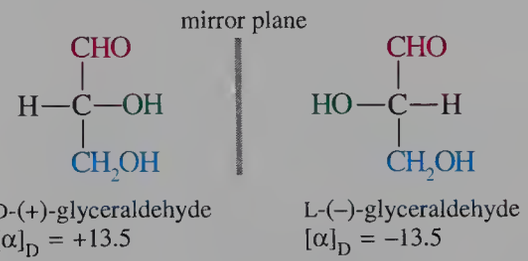


FIGURE 9.7 Projection Formulas of Enantiomers of Glyceraldehyde
The Fischer projections of the two enantiomers of glyceraldehyde have crossed lines at a point where the chiral carbon atom would be. The carbon atom is not usually shown. The vertical lines are assumed to project away from the viewer. The horizontal lines project out toward the viewer.

A Fischer projection formula is a two-dimensional representation. It might appear that if we lifted one formula out of the plane and rotated it 180° around the carbon backbone, we would obtain the formula of the enantiomer. However, if this were done for molecule A, the carbonyl group and the hydroxymethyl group, originally behind the plane, would be in front of the plane. These groups would not occupy identical positions with respect to the carbonyl group and hydroxymethyl group of molecule B, which are behind the plane. Therefore, to avoid the error of apparently achieving a two-dimensional equivalence of nonequivalent three-dimensional molecules, it is important not to mentally lift two-dimensional representations out of the plane of the paper.

Fischer projection formulas can be drawn to depict any pair of enantiomers. These formulas imply that we "know" the configuration at the chiral carbon atom. However, the true configuration could not be determined by early chemists because there was no way to "see" the arrangement of the atoms in space. Therefore, Fischer arbitrarily assigned a configuration to one member of the enantiomeric pair of glyceraldehydes. The dextrorotatory enantiomer of glyceraldehyde, which rotates plane-polarized light in a clockwise direction (+13.5), was assigned to the Fischer projection with the hydroxyl group on the right side. Fischer called the compound D-glyceraldehyde. The mirror image compound, (−)-glyceraldehyde, corresponds to the structure in which the hydroxyl group is on the left. It rotates plane-polarized light in a counterclockwise direction. Fischer called the compound L-glyceraldehyde.

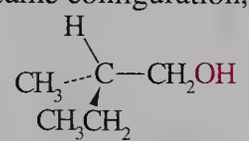


Problem 9.7

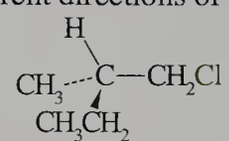
Write the Fischer projection formula of each of the following compounds.
(a) D-lactic acid, $CH_3CH(OH)CO_2H$
(b) L-serine, $HOCH_2CH(NH_2)CO_2H$
(c) D-valine, $(CH_3)_2CHCH(NH_2)CO_2H$

9.5 Absolute Configuration

We began this chapter by saying that the arrangement of atoms in space determines the configuration of a molecule. When we know the exact positions of these atoms in space, we know the molecule's **absolute configuration**. The absolute configuration of an enantiomer cannot be established by measuring the direction or magnitude of its optical rotation. Optical rotation depends on both the configuration and the identity of the four groups around the central carbon atom. One "left-handed" molecule could be levorotatory, whereas another "left-handed" molecule with different groups could be dextrorotatory. For example, in spite of the similarity of three of the groups (CH_3CH_2, CH_3, and H), the following structures of 2-methyl-1-butanol and 1-chloro-2-methylbutane, which have the same configuration, have different directions of optical rotation.



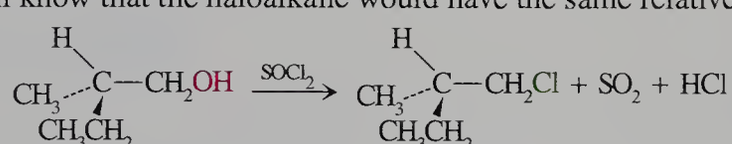
(–)-2-methyl-1-butanol
$[\alpha]_D = -5.8$



(+)-1-chloro-2-methylbutane
$[\alpha]_D = +1.7$

To determine the absolute configuration, we require a method that can specify the positions of all atoms in the molecule. The best way to do this is by X-ray crystallography. The absolute configuration of an optically active substance was first determined in 1950. The arrangement of its atoms in space corresponds to the arrangement of atoms in (+)-glyceraldehyde arbitrarily assigned by Fischer. His original choice was correct! As a result, all configurations that had been deduced by using (+)-glyceraldehyde as the reference compound are also correct.

The absolute configuration of a compound can be determined by comparing it to a reference compound of known absolute configuration. This structure proof sometimes requires an elaborate series of reactions. However, the principle is easily illustrated with the conversion of 2-methyl-1-butanol to 1-chloro-2-methylbutane. Alcohols can be converted into chloroalkanes by thionyl chloride ($SOCl_2$). The reaction does not affect any of the bonds at the stereogenic center of 2-methyl-1-butanol. Hence, the configuration is unchanged. If the absolute configuration of the alcohol is known, the groups bonded to the stereogenic center in the chloroalkane must be arranged in the same configuration. If the absolute configuration of the alcohol were not known, we would still know that the haloalkane would have the same relative configuration.



R,S Configurations

The configurations of some molecules, such as amino acids and carbohydrates, can easily be compared to reference compounds such as (+)-glyceraldehyde. But this procedure is not easily applied to molecules whose structures differ considerably from the reference compound. To circumvent this difficulty, three chemists, R. S. Cahn, K. C. Ingold, and V. Prelog, established a set of rules in 1964 describing the absolute

configuration of any chiral molecule. Once established, the configuration is designated by the symbol *R* or *S* within parentheses in front of the name of the compound.

The ***R,S* system** of configurational nomenclature for describing absolute configurations is related to the method previously described in Chapter 6 to assign the configuration of alkenes. In the *R,S* system, the four groups bonded to each chiral carbon atom are arranged from highest to lowest priority. The highest priority group is assigned the number 1, the lowest priority group the number 4. Then, the molecule is oriented so that the bond from the carbon atom to the group of lowest priority is arranged directly along our line of sight pointing downward (Figure 9.8). When this has been done, the three higher priority groups point up and lie on the circumference of a circle. (It may help to imagine holding the lowest priority group in your hand like the stem of a flower as you examine the petals.) Consider the path taken as we trace the groups ranked 1 to 3. In Figure 9.8 this direction is clockwise. Therefore, the configuration is designated *R* (Latin *rectus*, right). If we trace a counterclockwise path from groups ranked 1 to 3, the configuration is designated *S* (Latin *sinister*, left).

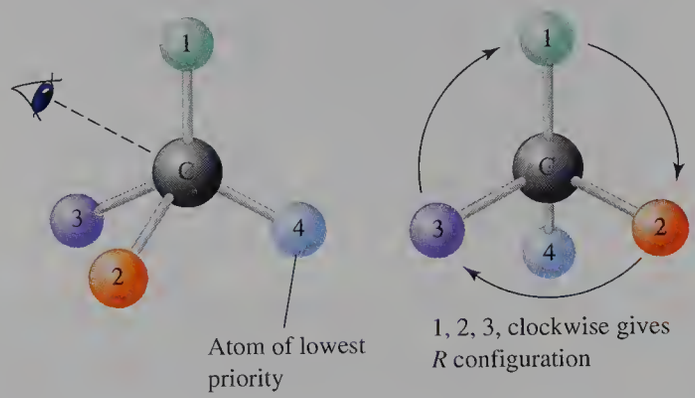


FIGURE 9.8 The Cahn–Ingold–Prelog System
Place the atom of lowest priority away from your eye and view the chiral site along the axis of the carbon-bond to the lowest priority group. Imagine holding the atom of lowest priority as you move the molecule into an alternate position for viewing.

Priority Rules

The priority rules we defined in Chapter 7 for describing the configuration of geometric isomers also apply to chiral compounds.

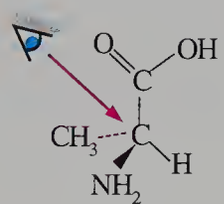
1. *Atoms*—We rank the four *atoms* bonded to a chiral carbon atom in order of decreasing atomic number; the lower the atomic number, the lower the priority.

   $$\underset{\text{highest priority}}{\text{I}} > \text{Br} > \text{Cl} > \text{F} > \text{O} > \text{N} > \text{C} > {}^{2}\text{H} > \underset{\text{lowest priority}}{{}^{1}\text{H}}$$

   As the priority order ^{2}H (deuterium) > ^{1}H indicates, isotopes are ranked in order of decreasing mass.
2. *Groups of atoms*—If a chiral atom is attached to two or more identical atoms, move down the chain until a difference is encountered. Then apply rule 1. Using this rule, we find that the priority of alkyl groups is $(CH_3)_3C— > (CH_3)_2CH— > CH_3CH_2— > CH_3—$.
3. *Multiple bonds*—If a group contains a double bond, both atoms are doubled. That is, a double bond is counted as two single bonds to each of the atoms of the double bond. The same principle is used for a triple bond. Thus the order $HC{\equiv}C— > CH_2{=}CH— > CH_3CH_2—$. The priority order for common functional groups containing oxygen is $—CO_2H$ (carboxylic acid) > —CHO (aldehyde) > $—CH_2OH$ (alcohol).

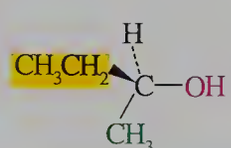
Let's use the *R,S* system to determine the configuration of one of the enantiomers of alanine, an amino acid isolated from proteins. Alanine has a chiral carbon atom bonded to a hydrogen atom, a methyl group, a carboxyl group (CO_2H), and an amino group (NH_2). A perspective drawing of this enantiomer of alanine is shown below.

First, we rank the four groups attached to the chiral carbon atom in order of their priority from lowest to highest. The lowest priority (4) is given to the atom with the lowest atomic number that is directly attached to the chiral carbon atom, hydrogen. The highest priority (1) is given to the atom with highest atomic number directly attached to the chiral carbon atom, nitrogen. The chiral carbon atom is attached to two other carbon atoms, one in a methyl group and the other in a carboxyl group. The carboxyl group has the higher priority (2) because the carbon atom is attached to two oxygen atoms, whereas the carbon atom in the methyl group is attached only to hydrogen atoms. This carbon atom has priority (3). Having assigned priorities, we next look into the molecule along the C—H bond and orient the molecule so that the hydrogen atom points away from us. When this is done, we trace a path from the group with priority 1 to the group with priority 2, to the group with priority 3. The highest priority amino group lies at "4 o'clock", the next highest group (COOH) is at the "12 o'clock" position, and the methyl is at the "8 o'clock" position Tracing a path from the amino group to the carboxyl group to the methyl group requires a counterclockwise motion. Therefore, the configuration of this enantiomer of alanine, the one found in proteins, is *S*.



alanine

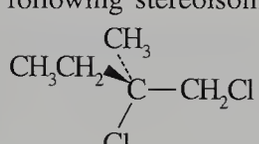
We need to recall that the absolute configuration of a molecule cannot be established by measuring the direction or magnitude of the optical rotation of an enantiomer. We noted earlier that optical rotation depends on both the configuration and the identity of the four groups around the central carbon atom. For example, the optical rotation of *S*-2-butanol is clockwise. This isomer is designated *S*-(+)-2-butanol.



(*S*)-(+)-2-butanol

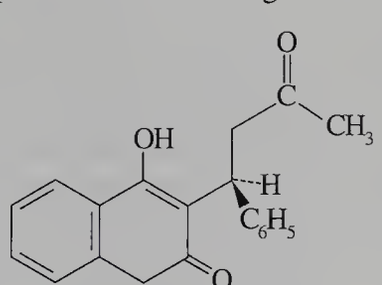
Problem 9.8

Assign the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane.



Problem 9.9

Warfarin is a drug that prevents blood clotting. That is, it is an anticoagulant drug. Warfarin is used both to treat thromboembolic disease and, in larger doses, as a rat poison. Assign its configuration. (The C_6H_5 represents a benzene ring bonded at the chiral center.)

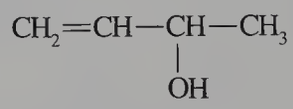


Sample Solution

Warfarin contains only one tetrahedral carbon atom that is attached to four different groups. That chiral carbon atom is attached to a hydrogen atom, a C_6H_5 group, and two other more complex groups. The lowest priority group is the hydrogen atom. The remaining three groups are linked through carbon atoms. One of them, the methylene group at the 12 o'clock position, has the next lowest priority (3) because it is attached to two hydrogen atoms. Next we assign the priorities of the benzene ring and the ring system to the left. Both groups are attached to the chiral carbon atom by a carbon atom that also has a carbon–carbon single and a carbon–carbon double bond. Therefore we must move to the next atom. When we do this in the complex ring, we find a carbon atom bonded to an oxygen atom, which has a higher priority than the carbon atom bonded to a hydrogen atom at a similar position in the benzene ring. Therefore, the complex ring has a higher priority (1) than the benzene ring (2). Looking into the carbon–hydrogen bond at the chiral carbon atom, so that the hydrogen atom points away from us, we trace a counterclockwise path from group 1 to group 2 to group 3: this enantiomer of warfarin has the *S* configuration.

Problem 9.10

Reduction of (–)-3-buten-2-ol with hydrogen over a palladium catalyst gives (–)-2-butanol. Does the same sign of rotation establish that the relative configurations of the two compounds are the same? Based on the mechanism of catalytic hydrogenation, can you establish the relative configuration of the two compounds? If (–)-3-buten-2-ol has the R configuration, what is the configuration of (–)-2-butanol?



3-buten-2-ol

9.6 Molecules with Two Stereogenic Centers

So far, we have considered only molecules with a single stereogenic center. However, many compounds contain several stereogenic centers. For example, the antibiotic erythromycin (Figure 9.9) contains 18 chiral centers! Erythromycin is effective against many bacterial infections.

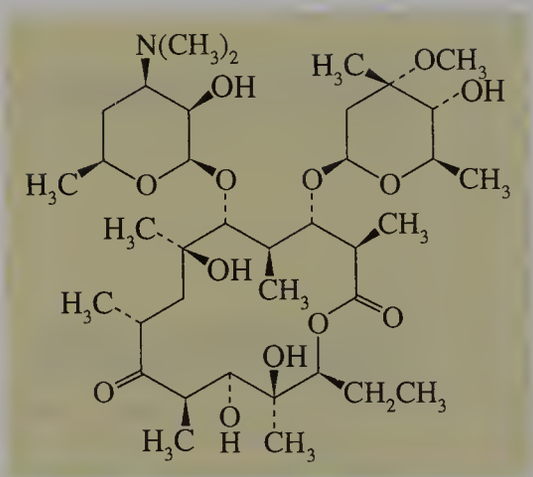
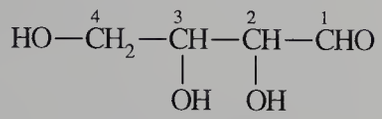


FIGURE 9.9
Erythromycin—a Chiral Antibiotic
Erythromycin has 18 chiral centers. Each center is designated with dashed or wedge-shaped lines.

A molecule with one stereogenic center can exist as either of two enantiomers with equal and opposite optical rotations. How is the number of stereoisomers of a molecule related to the number of stereogenic centers? What relationships exist between these isomers, and how are their optical rotations related? The answers to these questions depend on the relationship between the groups at each stereogenic center. Are the centers equivalent or nonequivalent? If the chiral carbon atoms are not bonded to identical sets of substituents, the stereogenic centers are **nonequivalent**. In contrast, if the stereogenic centers are bonded to identical sets of substituents, the centers are **equivalent**.

Nonequivalent Stereogenic Centers

If a molecule contains n nonequivalent chiral carbon atoms, the number of stereoisomers isomers is 2^n. Consider the following example.



2,3,4-trihydroxybutanal

The C-2 and C-3 atoms are chiral. They are also nonequivalent because they are not bonded to identical sets of substituents. Therefore, the absolute configuration at C-2 may be *R* or *S* and the same alternatives are possible for C-3. Without even drawing the structures, we predict that the four stereoisomers calculated from the 2^n rule can be identified as (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). These configurations are shown in Figure 9.10 in Fischer projection formulas.

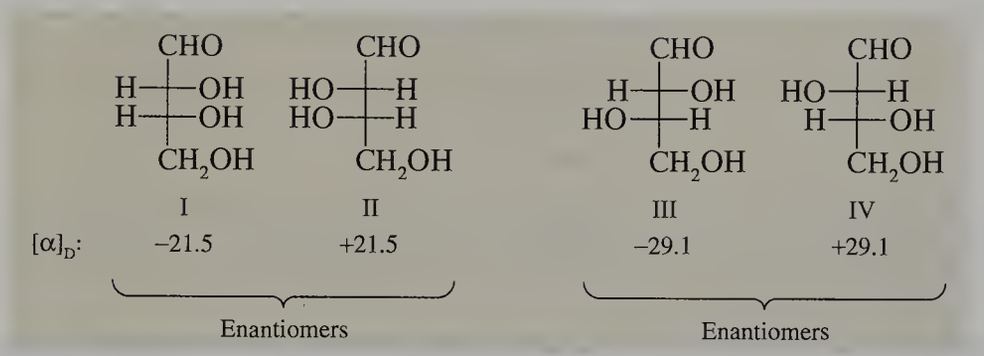


FIGURE 9.10
Enantiomers and Diastereomers
There are four stereoisomers of a compound containing two nonequivalent chiral centers. There are two sets of enantiomers. Any stereoisomers that are not enantiomers are diastereomers.

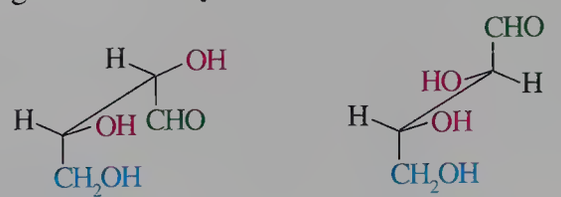
The relationships between the stereoisomeric 2,3,4-trihydroxybutanals are established by using mirror planes. Imagine a mirror placed between I and II. Structures I and II are nonsuperimposable mirror images and are enantiomers. Structures III and IV are also nonsuperimposable mirror images. Like all enantiomers, they rotate plane-polarized light in equal and opposite directions.

Now consider structures I and III. These stereoisomers are not related as mirror images. Stereoisomers that are not enantiomers are called **diastereomers**. The pairs II and III, I and IV, and II and IV are diastereomeric pairs. In contrast to enantiomers, which have the same chemical and physical properties, diastereomers have different chemical and physical properties, even in achiral environments. For example, the enantiomers I and II both are liquids at room temperature and are very soluble in ethanol. The enantiomers III and IV both melt at 130 °C and are only slightly soluble in ethanol.

Nomenclature of Diastereomers

The name of a compound with two or more chiral centers must indicate the configuration of every chiral center. The configuration of each chiral carbon atom is indicated by a number that corresponds to its position in the carbon chain and the letter *R* or *S*. Commas separate the configurations. This designation immediately tells us about the relationship between stereoisomers without reference to three-dimensional structures or assignment of the priorities of the groups at the stereogenic centers. Let's consider the four stereoisomers labeled (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). The enantiomer of the 2*R*,3*R* compound must be the 2*S*,3*S* isomer, which has the opposite configuration at each chiral center. Compounds whose configurations differ at only one of the two chiral centers are diastereomers. For example, the 2*R*,3*R* compound is a diastereomer of the 2*S*,3*R* isomer.

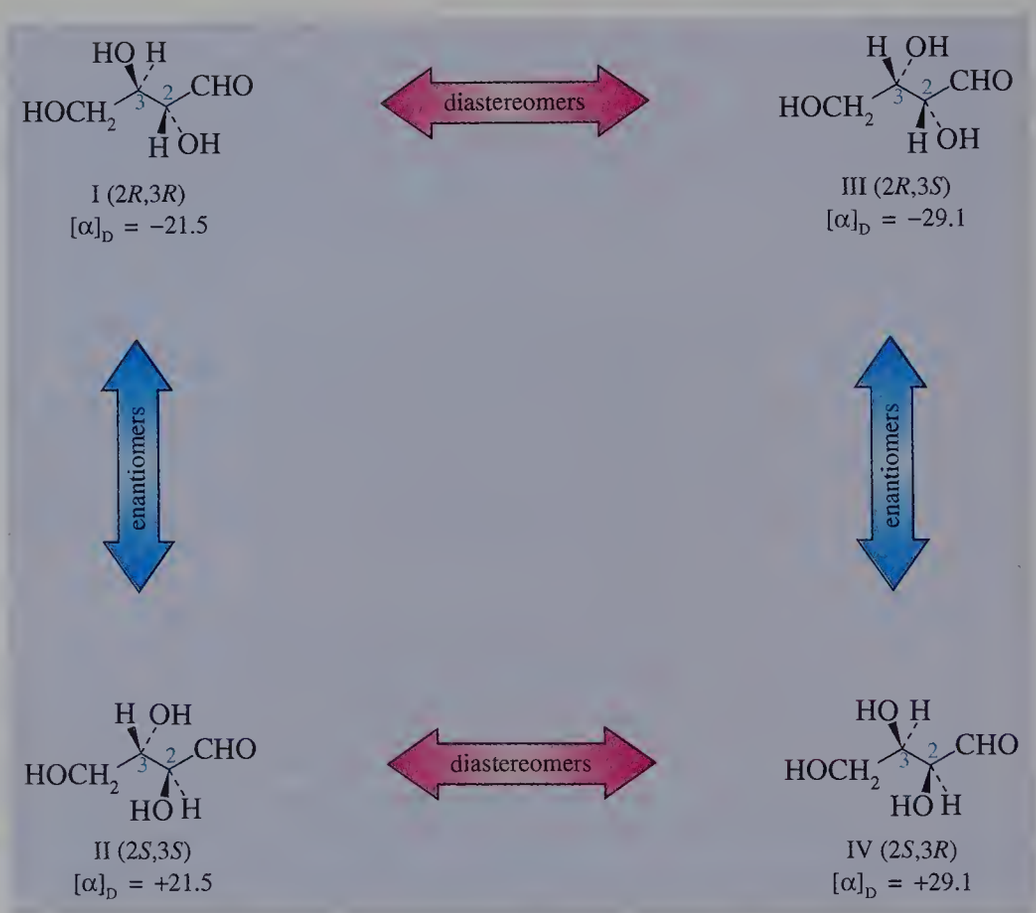
To assign the configurations of the 2,3,4-trihydroxybutanals shown in the Fischer projections in Figure 9.10, we restore the three dimensionality of the molecules. Consider structure I. The CHO and CH_2OH groups are behind the plane of the page. The H and OH groups are in front of the plane of the page. Note that the Fischer projection formula places the carbon chain in an eclipsed conformation. The configuration of each center can be established from this conformation. The configurations can be also assigned from the more stable staggered conformation resulting from rotation around the C-2 to C-3 bond. Bond rotation does not change the configuration at any chiral center.



eclipsed conformation staggered conformation

Converting the stereoisomeric 2,3,4-trihydroxybutanals into three-dimensional, staggered conformations gives the structures shown in Figure 9.11. You should confirm the assigned absolute configurations of each structure. Structure I is the 2*R*,3*R* stereoisomer. Structure II is the mirror image of structure I. If a mirror were placed behind the plane of the page you would see structure II. Because structure II is the enantiomer of structure I, we know that its configuration must be 2*S*,3*S*. The observed specific rotation of structure I is −21.5, of structure II, +21.5. The common names of structures I and II are (−)-erythrose and (+)-erythrose, respectively.

FIGURE 9.11
Configuration of Enantiomers and Diastereomers



Now consider the absolute configuration of structure III in Figure 9.11. Is the designation 2*R*,3*S* reasonable? Compare this structure to structure I. The configuration at C-2 is the same, the configuration at C-3 opposite. If structure I is 2*R*,3*R*, then structure

III must be 2*R*,3*S*. The observed specific rotation of structure III is −29.1. Because structure IV is the enantiomer of structure III, its specific rotation is +29.1. The common names of compounds III and IV are (−)-threose and (+)-threose, respectively.

Equivalent Stereogenic Centers

We began our discussion of molecules with two or more stereogenic centers by noting that these chiral centers could be either equivalent or nonequivalent. Now let's consider compounds with equivalently substituted chiral centers. Examples of equivalent substituted chiral centers are shown in the eclipsed conformations of the tartaric acids (Figure 9.12). In each structure, the C-2 and C-3 atoms are connected to four different groups. How do the number of these stereoisomers and their optical properties differ from those of the stereoisomers of the 2,3,4-trihydroxybutanals? Only three stereoisomers exist. Of these, one is optically inactive! The structures labeled (2*S*,3*S*) and (2*R*,3*R*) are enantiomers; therefore, they are optically active. But look at the structures labeled (2*R*,3*S*) and (2*S*,3*R*). Although the structures are drawn as "mirror images", they are superimposable and, in fact, are identical. To show that this is so, rotate one structure 180° in the plane of the paper; the resulting structure superimposes on the original structure. Thus, the two structures represent the same molecule. It is achiral and cannot be optically active.

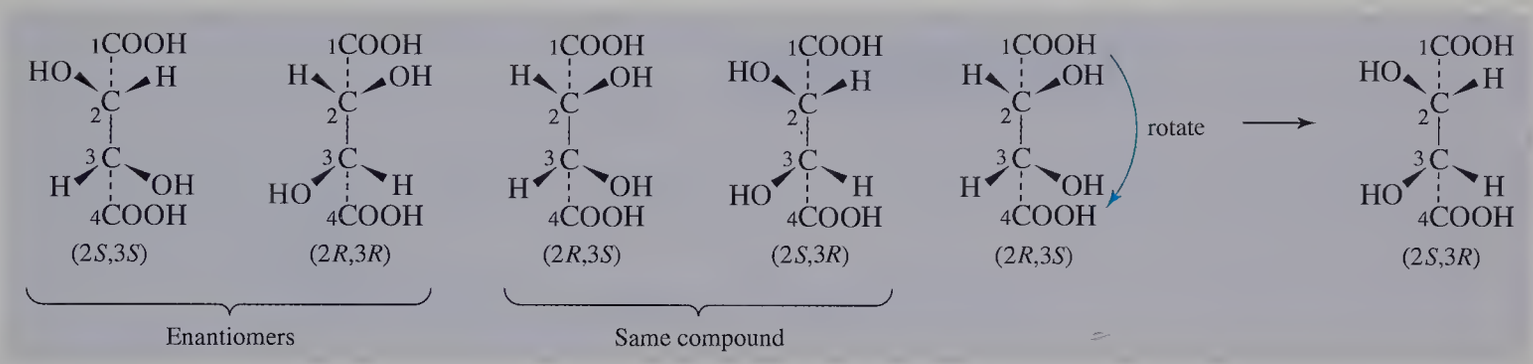
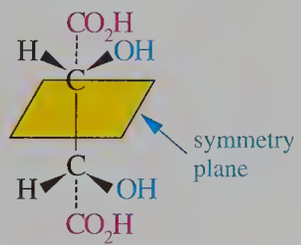


FIGURE 9.12 Tartaric Acids—Optically Active and Meso Compounds
There are only three stereoisomers of a compound with two equivalent chiral centers. Two compounds are enantiomers. The third compound has a plane of symmetry. It is optically inactive and is called a meso compound.

Why is one of the stereoisomeric tartaric acids optically inactive? The structures labeled (2*R*,3*S*) and (2*S*,3*R*) have two *equivalent* chiral carbon atoms, and each structure has a plane of symmetry. We recall from Section 9.2 that a structure with a plane of symmetry is achiral, and that it is superimposable on its mirror image. In the case of the tartaric acid, the plane of symmetry is between the C-2 and C-3 atoms, so that the top half of the molecule is the mirror image of the bottom half.



Compounds, such as tartaric acid, which have two or more chiral centers but are nevertheless achiral, are called **meso compounds** (Greek *meso*, middle). Meso compounds are not optically active.

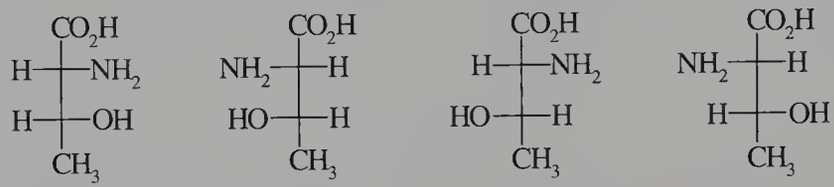
Problem 9.11

Threonine, an amino acid isolated from proteins, has the following condensed molecular formula. Write the Fischer projections of the possible stereoisomers.

$$\underset{4}{CH_3}\underset{3}{CH(OH)}\underset{2}{CH(NH_2)}\underset{1}{CO_2H}$$

Sample Solution

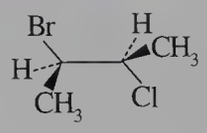
The C-2 and C-3 atoms are each attached to four different substituents. Therefore, the compound has two chiral centers. Because the chiral centers are nonequivalent, four diastereomers are possible. The Fischer projections are written by placing the carboxyl group at the top of the vertical chain. The amino and hydroxyl groups may be on the right or left sides of the projection formula.



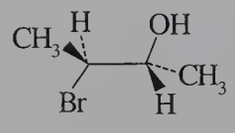
The structure of threonine isolated from proteins is given by the Fischer projection at the right.

Problem 9.12

Assign the configuration at the stereogenic centers of each of the following structures.



2-bromo-3-chlorobutane



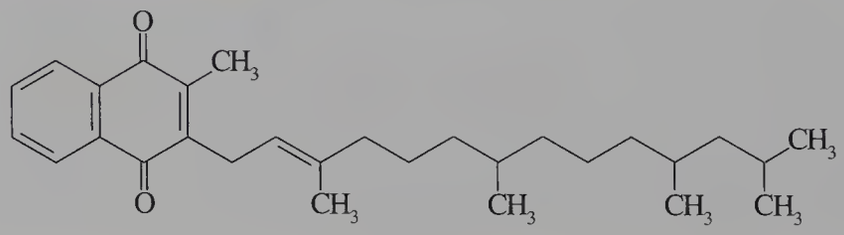
3-bromo-2-butanol

Problem 9.13

Write the Fischer projection formulas of the stereoisomeric 2,3-dibromobutanes. What relationship should exist between the optical activities of these isomers?

Problem 9.14

Determine the number of chiral centers in vitamin K_1. How many stereoisomers are possible?



vitamin K_1

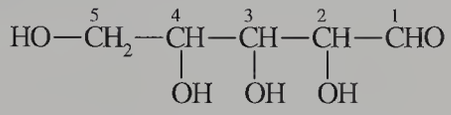
Sample Solution

The carbon atoms in the two rings are not chiral because they are not tetrahedral. The long alkyl chain contains eight methylene units, none of which is chiral because a carbon atom in a methylene group is bonded to two hydrogen atoms. The tertiary carbon atom near the end of the alkyl chain, which has two methyl groups, also is not chiral.

Next, consider the positions in the middle of the alkyl chain that have methyl group branches. The methyl group on the left is bonded to a double-bonded carbon atom, which does not have four groups bonded to it and therefore is not chiral. The next two methyl groups are located on chiral centers. Because there are two chiral carbon atoms, $2^2 = 4$ stereoisomers are possible.

Problem 9.15

D-Ribose is a component of ribonucleic acids. Its name is 2,3,4,5-tetrahydroxypentanal. Using numbers and the symbols *R* and *S*, write the prefix designations of all of the possible stereoisomeric compounds.



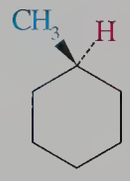
2,3,4,5-tetrahydroxypentanal

9.7 Cyclic Compounds with Stereogenic Centers

The definition of a stereogenic center is not restricted to acyclic compounds (Section 9.2). One or more stereogenic centers may be part of one ring or several rings in a polycyclic compound. When a cyclic compound has one or more stereogenic centers, we assign their configurations in the same manner outlined for acyclic compounds.

Structures with One Stereogenic Center

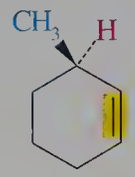
When a stereogenic center is in a ring, we assign the priorities of the groups bonded to it by treating two "parts" of the ring as groups. First, we examine the atoms in the path around the ring in one direction. Then, we look at the atoms in the path around the ring in the opposite direction. Next, we apply priority rules 1 through 3 (Section 9.5). For example, consider the following structure for methylcyclohexane.



methylcyclohexane

The methyl group and the hydrogen atom at the C-1 atom are two of the required four groups for a stereogenic center. What about the other two groups? The C-2 and C-6 atoms are equivalent methylene units by priority rule 1. We apply rule 2 and proceed to the next atom in each path and find that C-3 and C-5 are also equivalent methylene units. Finally, we encounter C-4 from either direction. Thus, the C-1 atom is bonded to two equivalent "groups" that are part of the ring itself. The same conclusion could be reached if we had determined that the molecule has a plane of symmetry containing the C-1 and C-4 atoms.

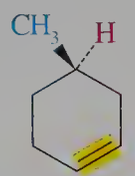
Now consider a compound in which the two paths around the ring are not equivalent. In 3-methylcyclohexene a methyl group and a hydrogen atom are bonded to the C-3 atom. The C-2 and C-4 carbon atoms are not equivalent by rule 3. As a result, the C-3 atom of 3-methylcyclohexene is a stereogenic center.



3-methylcyclohexene

What is the absolute configuration of this enantiomer of 3-methylcyclohexene? The lowest priority group is the hydrogen atom located behind the plane of the page. Thus, the arrangement of the other three higher priority groups is ideal to assign the configuration. The highest priority group, the sp^2-hybridized carbon atom, is located at the "4 o'clock" position. Priority group 2 is the methylene group of the C-4 atom because it is bonded to another carbon atom. It is located at the "8 o'clock" position. The methyl group is priority group 3 and is located at the "12 o'clock" position. The path traced by the three highest priority groups is clockwise, so the configuration of the compound is *R*.

As in acyclic compounds, differences in the groups may be at a distance from the stereogenic center. The difference in 4-methylcyclohexene is two carbon atoms away from the stereogenic center.



(R)-4-methylcyclohexene

Structures with Two Stereogenic Centers

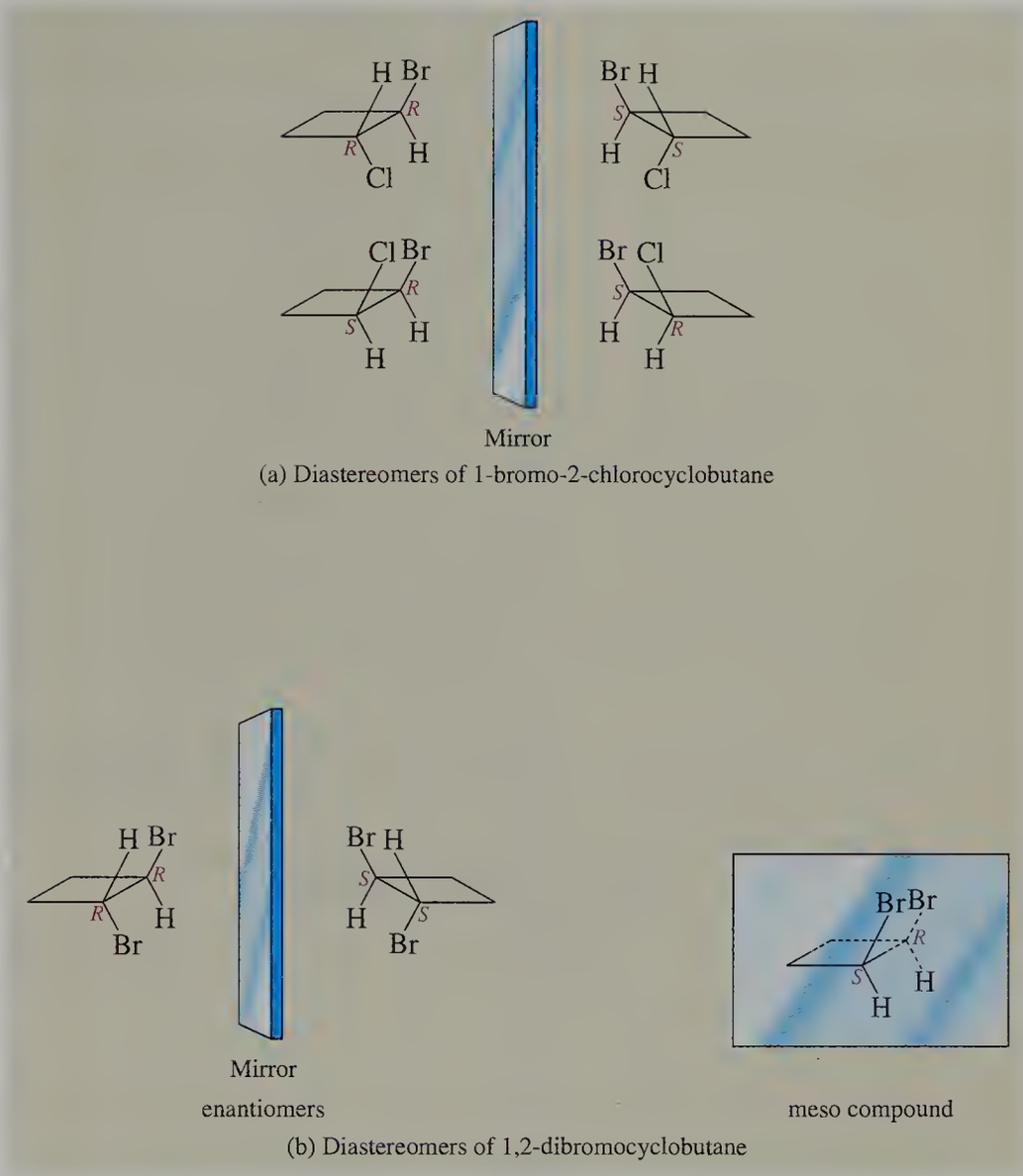
As was established for acyclic compounds containing two stereogenic centers, the number of stereoisomers of cyclic compounds depends on whether the centers are equivalent. First let's consider the isomeric *cis*- and *trans*-1-bromo-2-chlorocyclobutanes (Figure 9.13a). These compounds, we now recognize, are in fact diastereomers. The compounds in Figure 9.13 are arranged to demonstrate the mirror image relationship of the two enantiomeric trans compounds, whose configurations are 1*R*,2*R* and 1*S*,2*S*. There are also two enantiomeric cis compounds.

Now consider the consequences of the two equivalent stereogenic centers of 1,2-dibromocyclobutane (Figure 9.13b). There are still two enantiomeric trans compounds. However, the cis compound has a plane of symmetry passing through the C-1 to C-2 bond, perpendicular to the plane of the ring. The 1*R*,2*S* and 1*S*,2*R* structures are identical and represent a single meso compound.

Disubstituted Cyclohexanes

The relationship between the chiral cyclohexane compounds that we originally called geometric isomers follows from the above discussion of the disubstituted cyclobutanes. Cyclohexane exists in a chair conformation. However, for the purposes of determining stereochemical relationship, a planar structure gives the "right" answers.

FIGURE 9.13
Stereoisomerism in 1,2-Disubstituted Cyclobutanes
(a) There are four stereoisomers of a 1,2-disubstituted cyclobutane with nonequivalent chiral centers. (b) However, there are only three stereoisomers of a 1,2-disubstituted cyclobutane with equivalent chiral centers.

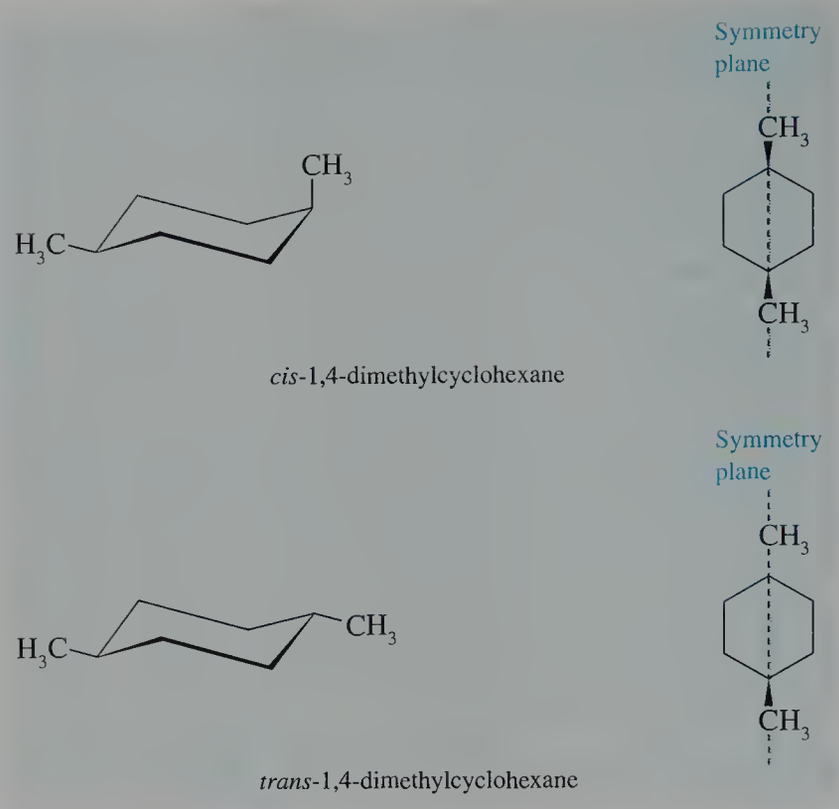


In this section we will examine only dimethyl compounds. First, let's examine the isomeric 1,4-dimethylcyclohexanes (Figure 9.14). These compounds have no stereogenic centers. A symmetry plane passes through the C-1 and C-4 atoms and cuts through both methyl groups. This plane is more easily seen in the planar projection of the compounds.

The 1,3-dimethylcyclohexanes have two stereogenic centers. Because the centers are equivalent, only three stereoisomers occur (Figure 9.15). *cis*-1,3-Dimethylcyclohexane, a meso compound, has a symmetry plane that passes through the C-2 and C-5 atoms. The symmetry plane is easily seen in the planar projection structure. *trans*-1,3-Dimethylcyclohexane has two stereogenic centers and no plane of symmetry. Thus, there are two enantiomers of this molecule.

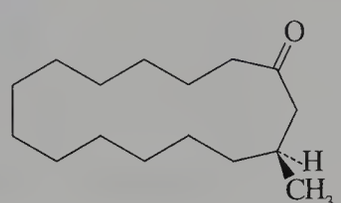
The 1,2-dimethylcyclohexanes have two stereogenic centers. The trans isomer has no plane of symmetry. Thus, there are two enantiomers of this structure (Figure 9.16). The cis isomer is meso, but for reasons that are not straightforward. As a consequence of the ring-flipping process, two conformations of equal energy exist. One is the mirror image of the other. Hence, there is no net optical rotation (Figure 9.17). (If the ring-flipping process were slow—which it is not—then two enantiomers could in principle be separated.)

FIGURE 9.14
Diastereomers of 1,4-Dimethylcyclohexane
The geometric isomers of 1,4-dimethylcyclohexane are achiral because each has a plane of symmetry.



Problem 9.16

What is the absolute configuration of muscone, a compound used in perfumes to provide a musk odor?



Sample Solution

The stereogenic center is at the branch containing the methyl group. The lowest priority group is a hydrogen atom that points below the plane of the page at the branching carbon atom. The methylene carbon atoms of the ring attached to the branching point both have higher priorities than the methyl group, which is priority (3). The methylene portion of the ring containing the carbonyl carbon atom has a higher priority than the other methylene portion of the ring. Looking down on the plane of the page and down the C—H bond and tracing the other three groups we go in a counterclockwise direction. The compound has the *S* configuration.

Problem 9.17

Write the structures of (1*R*,2*S*)- and (1*S*,2*S*)-1-bromo-2-chlorocyclopropane. Which is a cis and which is a trans isomer? Are the structures enantiomers or diastereomers?

Problem 9.18

Assign the configuration of each stereogenic center in the following *trans*-2,3-dimethyloxirane. Write a structure of its enantiomer.

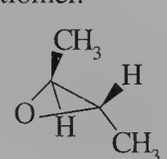


FIGURE 9.15
Diastereomers of 1,3-Dimethylcyclohexane
There are three stereoisomers of 1,3-dimethylcyclohexane, a meso compound that has a plane of symmetry and a set of enantiomers.

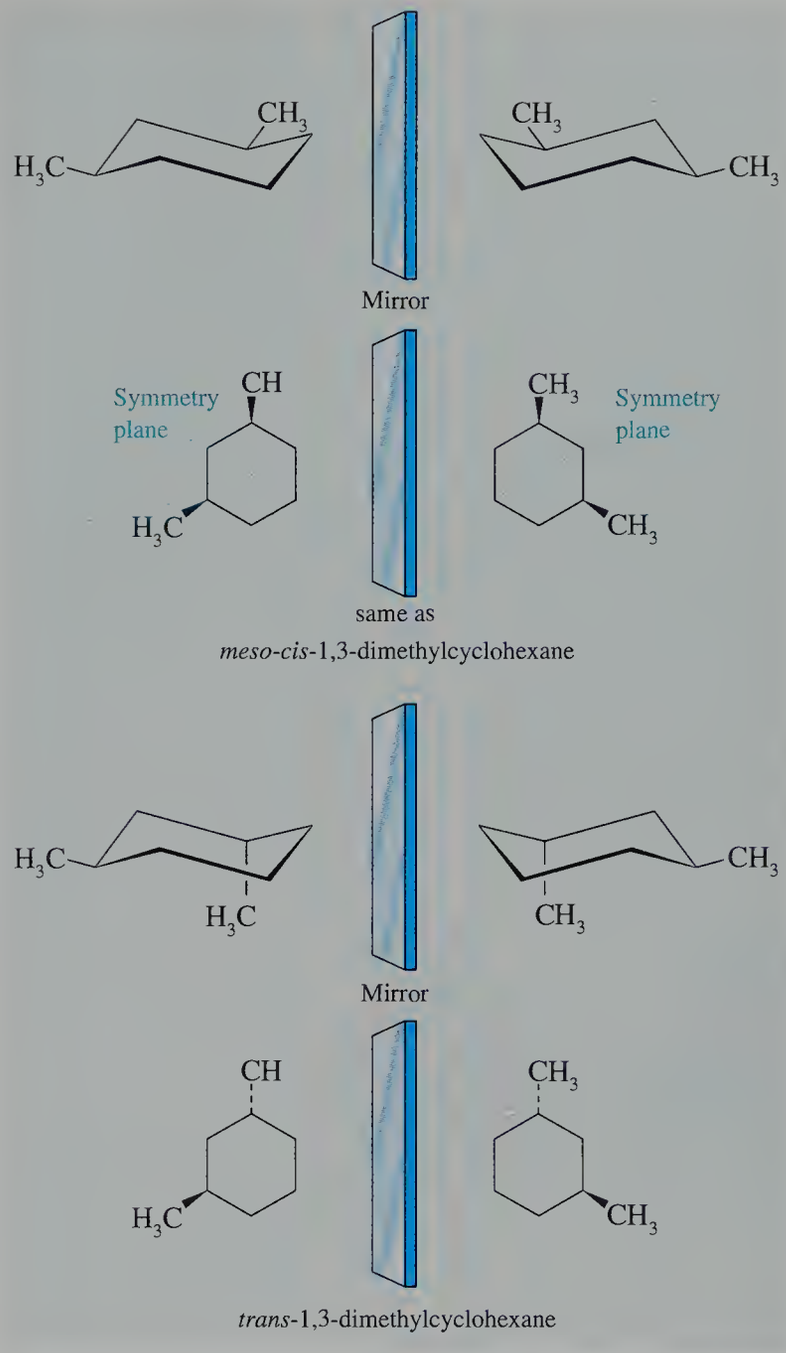
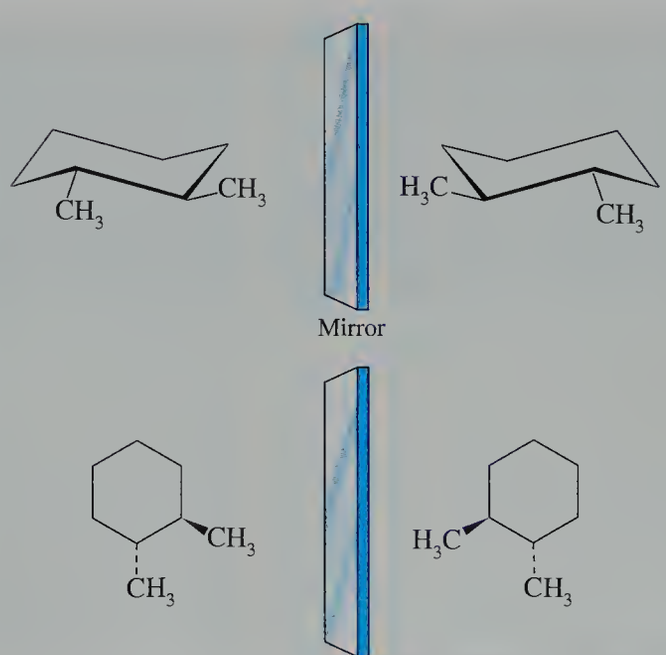
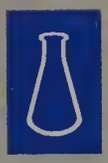


FIGURE 9.16
Enantiomers of *trans*-1,2-Dimethylcyclohexane
trans-1,2-Dimethylcyclohexane exists as two enantiomers. There is no plane of symmetry.

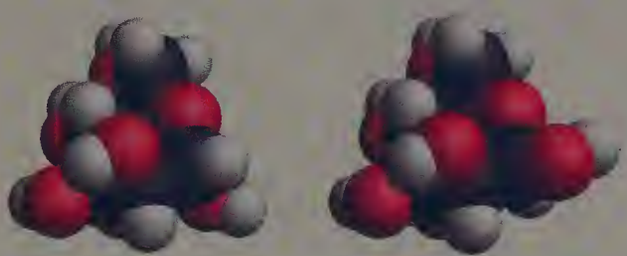


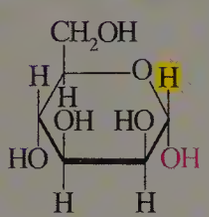


Chirality and the Senses

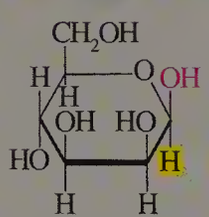
Senses are sensitive to the configuration of molecules. Both the sense of taste and the sense of smell result from changes induced in each sensory receptor when it binds a specific molecule. The binding causes a conformational change that triggers a sequence of events culminating in transmission of a nerve impulse to the brain by sensory neurons. The brain interprets the input from sensory neurons as the "odor" of, say, spearmint.

Enantiomeric and diastereomeric molecules interact differently with sensory receptors in living systems. Differences in biological response to diastereomeric compounds is perhaps the easier to understand. After all, diastereomeric compounds have different physical properties. For example, mannose, a carbohydrate, exists in two diastereomeric forms that differ in configuration at one center. The α form tastes sweet, but the β form tastes bitter.



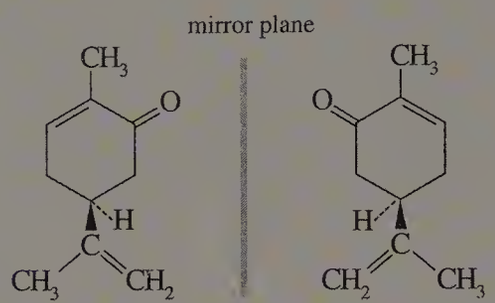


α-D-mannose
(sweet)



β-D-mannose
(bitter)

Sensory receptors also readily distinguish enantiomers. The specificity of response is similar to the relationship between our hands and how they fit into gloves. Because sensory receptors are chiral, they interact stereospecifically with only one of a pair of enantiomers. The two enantiomeric forms of carvone have very different odors. (+)-Carvone is present in spearmint oil, imparting the familiar smell. In contrast, its enantiomer, (–)-carvone is present in caraway seed. It has the odor associated with rye bread.



(+)-carvone
(spearmint)

(–)-carvone
(caraway)

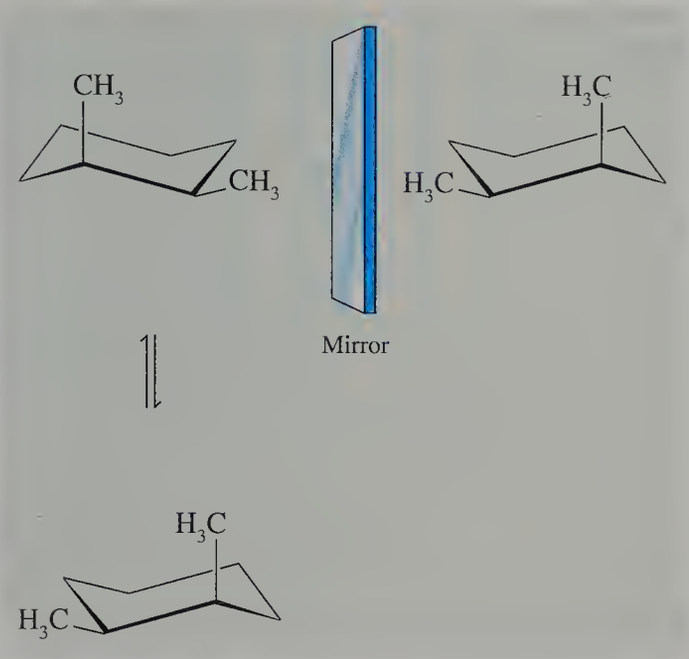


FIGURE 9.17 *cis*-1,2-Dimethylcyclohexane
The mirror image of *cis*-1,2-dimethylcyclohexane is not superimposable on the original structure. However, a ring flip of the original structure gives the mirror image. Thus, the enantiomers are interconverted rapidly.

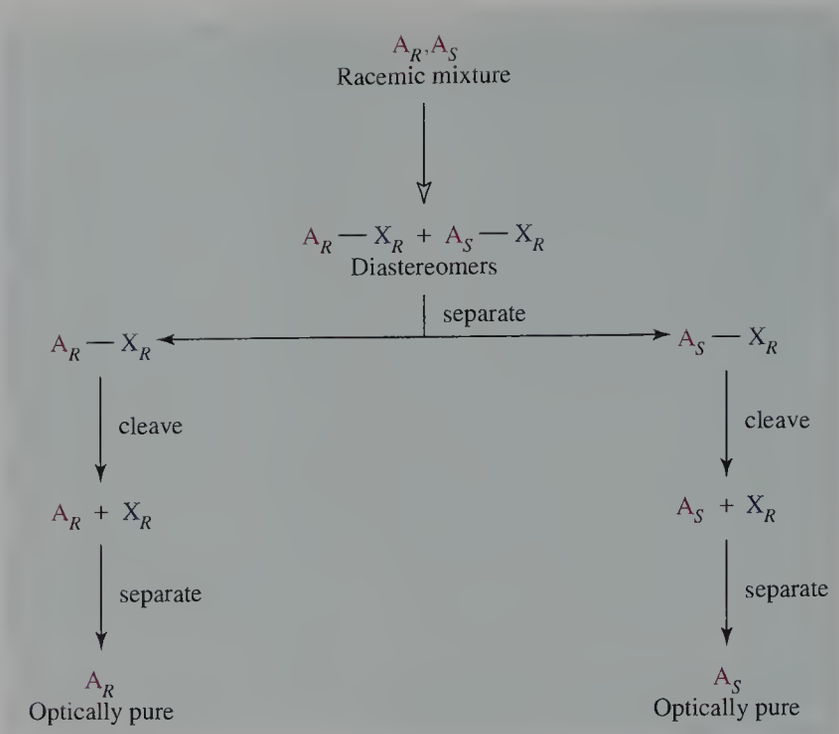
9.8 Separation of Enantiomers

Substances with stereogenic centers are invariably found in nature as a single enantiomer. However, as mentioned in Section 9.3, compounds with stereogenic centers prepared in the laboratory from achiral starting materials are racemic. Can we separate the racemic mixture into pure samples of each enantiomer? Because enantiomers have the same physical properties, such as boiling point or solubility, they cannot be separated by distillation or crystallization.

Enantiomers can be separated indirectly by reacting the racemic mixture with another optically pure compound to produce a mixture of diastereomers (Figure 9.18). Because diastereomers have different physical properties, they can often be separated on the basis of solubility differences. Then each enantiomer is recovered from its diastereomeric derivative by another chemical reaction. The entire process is called **resolution** of enantiomers. The optically pure compound used to form the diastereomeric mixture is called the **resolving agent**.

The racemic mixture to be resolved in Figure 9.18 is designated A_R,A_S. It consists of A_R and A_S. The optically active compound selected as the resolving agent is represented X_R. The choice of X_R over X_S is arbitrary in this discussion. The choice we make in the laboratory is based on the configuration of the available resolving agent. The derivative diastereomeric compounds are $A_R—X_R$ and $A_S—X_R$. After the diastereomers are separated, one or the other or both may be reacted to liberate the pure enantiomers. In practice, only one of the enantiomers is easily obtained. For example, the least soluble diastereomer may crystallize from solution and yield one of the enantiomers in the subsequent step. Because some of the less soluble diastereomer remains in solution with the more soluble diastereomer, it is difficult to obtain the second enantiomer in optically pure form.

FIGURE 9.18 Principle of the Resolution of Enantiomers

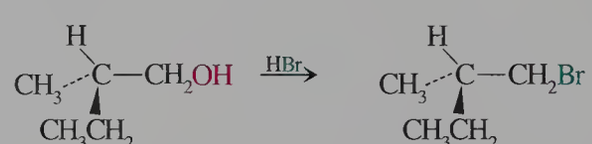


9.9 Reactions of Compounds with Stereogenic Centers

In this section we consider some reactions of molecules with stereogenic centers that form products with stereogenic centers. Whether or not the product is optically pure depends on the type of reaction that occurs. The results of such reactions are often used to postulate reaction mechanisms.

Reactions Not Involving the Stereogenic Center

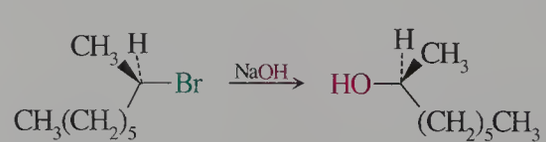
First let's consider the simplest case. If a reaction of a chiral compound does not form or cleave any bonds to the stereogenic center, then the optical purity of the product is the same as the optical purity of the reactant. This principle, discussed in Section 9.3, allows us to establish the absolute configuration of particular molecules using reference molecules of known absolute configuration. For example, 2-methyl-1-butanol is converted to 1-bromo-2-methylbutane by HBr in a nucleophilic substitution reaction. The reaction does not occur at the stereogenic center. The *S* alcohol yields the *S* bromo compound.



(*S*)-2-methyl-1-butanol (*S*)-1-bromo-2-methylbutane

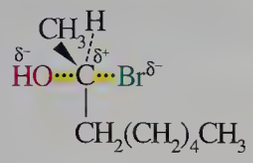
Stereochemistry of Nucleophilic Substitution

Now let's consider a reaction that occurs at the stereogenic center of a chiral compound and yields a chiral product. Treating (*R*)-2-bromooctane with sodium hydroxide yields (*S*)-2-octanol in a bimolecular nucleophilic substitution reaction (S_N2).



(*R*)-2-bromooctane (*S*)-2-octanol

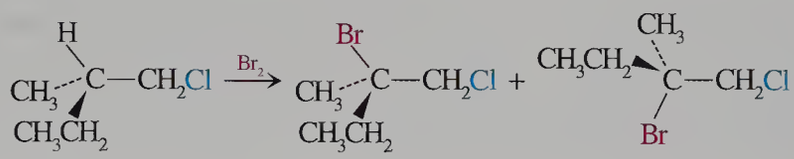
The nucleophilic hydroxide ion attacks (*R*)-2-bromooctane at the carbon atom from the side opposite the C—Br bond axis. This type of reaction occurs with **inversion of configuration**. The details of this reaction will be discussed in Chapter 10. Because the reaction occurs with inversion of configuration, it is reasonable to propose a transition state in which the stereogenic center has partial bonds to both the hydroxide and the bromide ions.



transition state for inversion of configuration

Stereochemistry of a Radical Reaction

Substitution of a group at a stereogenic center by another can lead to a racemic mixture of products. For example, the free radical bromination of (*S*)-1-chloro-2-methylbutane that replaces hydrogen at the tertiary stereogenic center with bromine gives a racemic mixture of (*R*)- and (*S*)-2-bromo-1-chloro-2-methylbutanes.



This experimental result indicates that the radical intermediate produced in the first step of the two chain-propagation steps (Section 5.4) is achiral. The radical is planar (Figure 9.19). Therefore, reaction of the radical with bromine in the second of the two chain-propagation steps can occur with equal ease from above or below the plane, and a 50:50 mixture of enantiomers results.

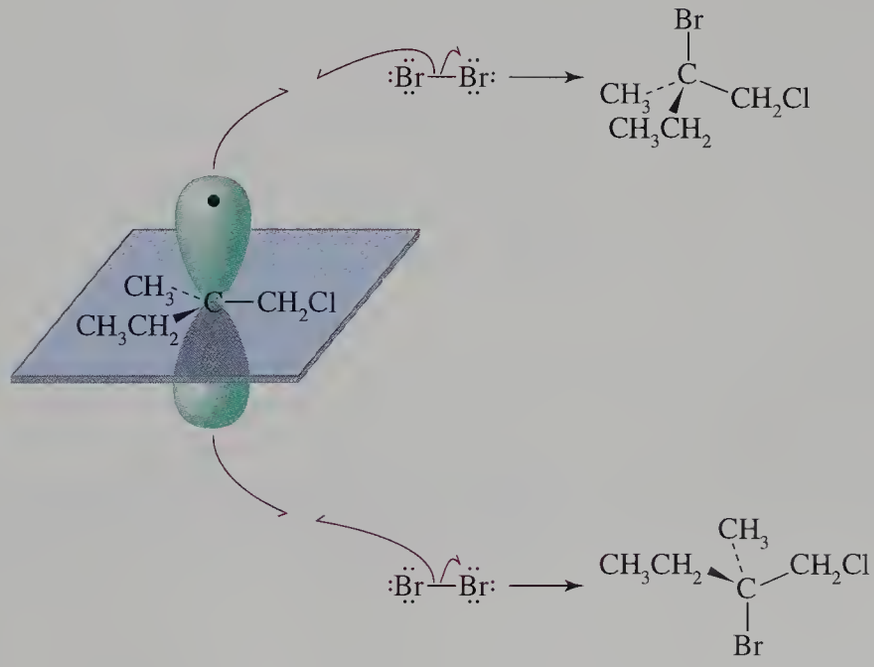


FIGURE 9.19 Free Radical Reaction at a Stereogenic Center
The free radical intermediate is achiral because it has a plane of symmetry. The subsequent attack of a halogen molecule can occur on either side of the plane and results in a 50:50 mixture of enantiomers.

Problem 9.19

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure of the 2-bromo-1-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Problem 9.20

Based on the data for the conversion of (*R*)-2-bromooctane into (*S*)-2-octanol using NaOH, predict the product of the reaction of (*S*)-2-bromooctane with NaOH.

Sample Solution

The nucleophilic attack at the side opposite the bond of the displaced leaving group from (*S*)-2-bromooctane gives a product with inversion of configuration. Thus the enantiomeric *R* compound should react likewise and give an inverted product, (*S*)-2-octanol.

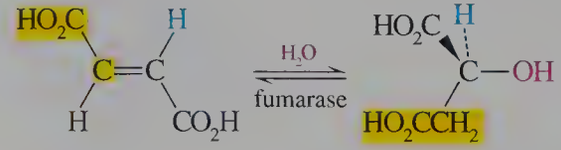
9.10 Formation of Compounds with Stereogenic Centers

We have studied several reactions yielding products with stereogenic centers from compounds with no stereogenic centers. What prediction can we make about the configuration of the product? The reaction of an achiral radical described above demonstrates that optically active products cannot form from the reaction of achiral reactants. Note that molecules with stereogenic centers can form. However, the enantiomers occur in equal amounts.

Stereochemistry and Markovnikov Addition

Let's consider the addition reaction of HBr with 1-butene to give 2-bromobutane, which we studied in Section 7.2. 1-Butene is protonated at the C-1 atom to give an intermediate secondary carbocation that is achiral because it has a plane of symmetry (Figure 9.20). The carbocation is attacked by the nucleophilic bromide ion with equal probability from the top or bottom. Attack at the top gives the *S* enantiomer, attack at the bottom gives the *R* enantiomer, and a racemic mixture results.

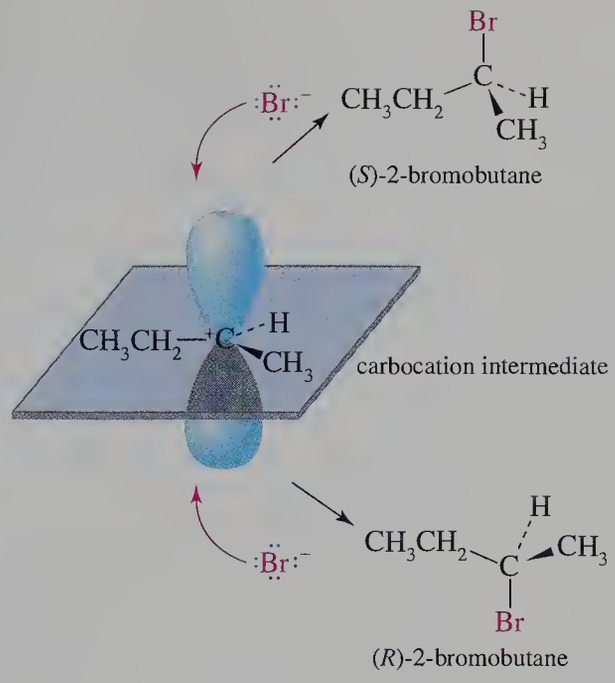
Biochemical processes are catalyzed by enzymes that have multiple stereogenic centers and are therefore chiral. Enzymes provide a chiral environment in which to form stereogenic centers. As a consequence, only one enantiomer forms from a reaction involving an enzyme, even if the reactant is achiral. For example, fumaric acid is hydrated in an addition reaction catalyzed by the enzyme fumarase in the citric acid cycle to give only (*S*)-malic acid. (Biochemists commonly represent carboxylic acids as their conjugate bases because they are ionized at pH 7, hence "fumarate" and "(*S*)-malate".) This reaction converts fumarate to (*S*)-malate.



fumaric acid (*S*)-malic acid

Not only does only one enantiomer form in the reversible reaction, but only the trans geometric isomer reacts. The cis unsaturated isomer is not converted to a hydrated product by fumarase.

FIGURE 9.20
Stereochemistry of Markovnikov Addition of HBr
The carbocation intermediate produced by electrophilic attack of a proton on an alkene is achiral because it has a plane of symmetry. Attack of bromide ion can occur from either side of the plane.



Stereochemistry of Addition of Bromine

We recall that the reaction of bromine with an alkene gives a product with bromine atoms on adjacent carbon atoms. For example, 2-butene reacts with bromine to give 2,3-dibromobutane.

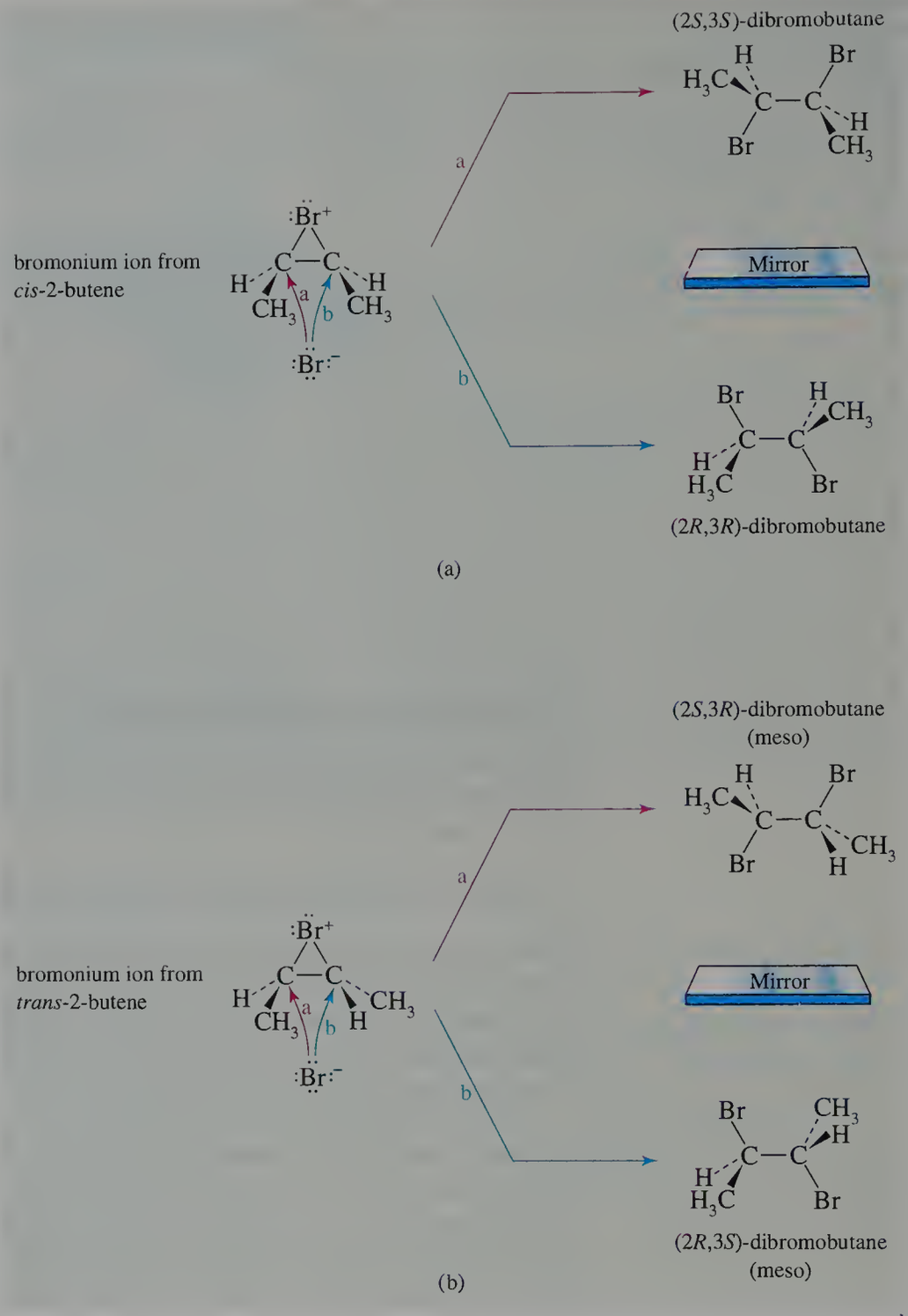
$$CH_3CH{=}CHCH_3 + Br_2 \longrightarrow CH_3CHBr{-}CHBrCH_3$$

Two equivalently substituted stereogenic centers form in this reaction. There are three stereoisomers for such compounds, an enantiomeric pair of compounds and a meso compound. Which compounds would you predict based on the reaction mechanism discussed in Section 7.6? Put another way, how do the observed products support the proposed mechanism of the reaction?

The configuration of the addition product depends on the configuration (*E* or *Z*) of the 2-butene and the stereochemistry of the anti addition process. Bromine adds to *cis*-2-butene to give a mixture of the enantiomeric (2*R*,3*R*)- and (2*S*,3*S*)-dibromobutanes (Figure 9.21a). Although the bromonium ion could form by attack equally well on the top or bottom, let's examine the intermediate obtained from attack on the top. (The intermediate obtained from attack on the bottom is the same because it is achiral.) Subsequent attack of bromide ion can occur at either the right or left carbon atom. Attack at the right carbon atom gives the 2*R*,3*R* isomer. Attack at the left carbon atom gives the 2*S*,3*S* isomer. Both paths of attack are equally probable, and a racemic mixture results.

Now let's consider the consequences of formation of the cyclic bromonium ion derived from *trans*-2-butene followed by nucleophilic attack by bromide ion (Figure 9.21b). The bromonium ion depicted results from attack on the top. Bromide ion attacks equally well at the right and left carbon atoms, giving the 2*S*,3*R* and 2*R*,3*S* structures, respectively. As we learned earlier, such designations for two equivalently substituted chiral carbon atoms correspond to a single meso compound.

FIGURE 9.21
Stereochemistry of Addition of Br_2
The bromonium ion intermediate produced by electrophilic attack of bromine on the isomeric 2-butenes can react with the nucleophilic bromide ion at either carbon atom. The stereochemical consequences are different for the two isomeric bromonium ions.



We now can confidently accept the mechanism for addition of bromine to alkenes because it agrees with the experimental facts. We have also again learned that achiral reactants—in this case either of the two isomeric 2-butenes and bromine—always form optically inactive products. Remember: the products have stereogenic centers; the reaction results in either a racemic mixture or a meso compound.

Drug Metabolism May Vary by Species and Within Species

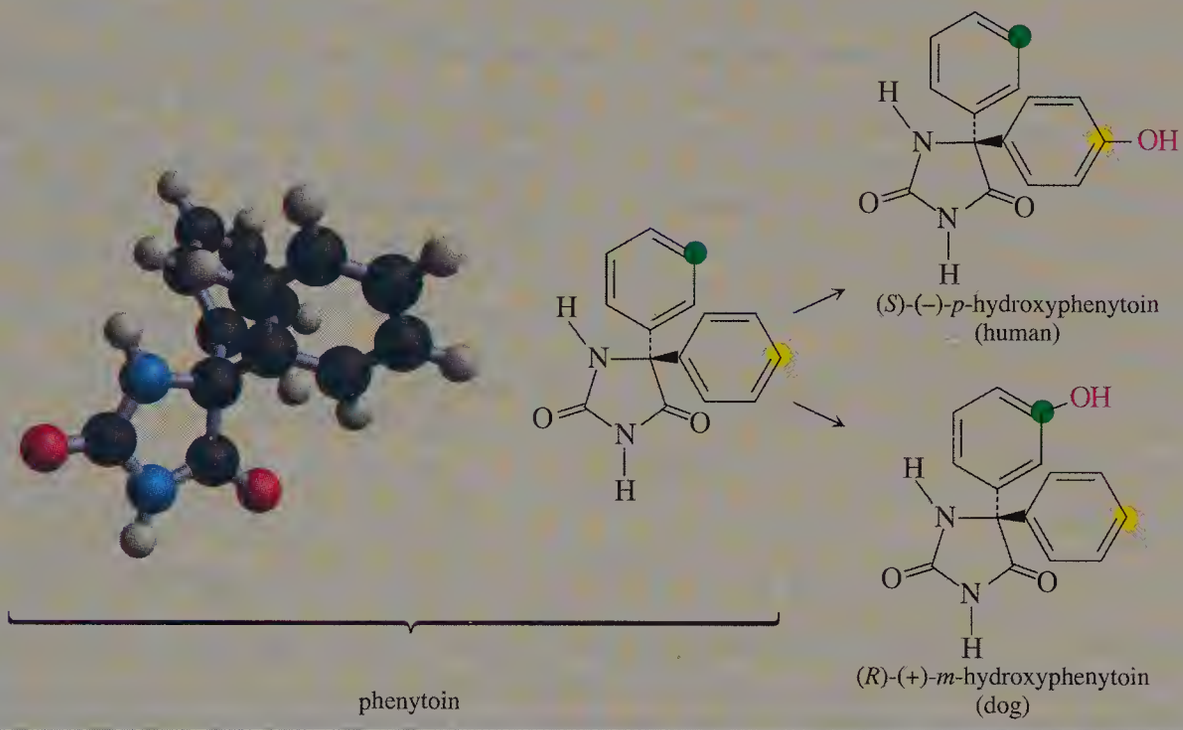
The metabolism of drugs is often species dependent, a fact that must be considered by medical researchers, who usually test drugs on animals prior to human trials. Even within the same species, differences in strains are common among inbred test animals such as mice and rabbits.

The anticonvulsant phenytoin shows a dramatic difference in metabolism depending on species. This achiral compound is oxidized to a chiral phenol.

In humans, the hydroxylation occurs at the para position of one ring, and the compound has the *S* configuration. In dogs, the hydroxylation occurs at the meta position of the other ring, and the compound has the *R* configuration.

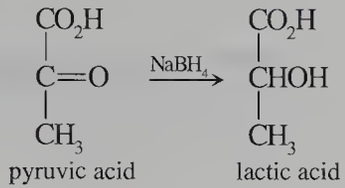
Genetic differences in drug metabolism have been clearly established in humans. Differences among northern Europeans, Eskimos, Mediterraneans, and Asians must be considered in prescribing certain drugs.

Drug metabolism also varies by sex. Some oxidative processes are controlled by sex hormones, particularly the androgens. This is important because it has been common practice to test drugs only on men. This practice resulted partly from concern about the possible effect of drugs on a very early fetus before a woman knows she's pregnant. In addition, metabolism of drugs in men is more easily studied because of smaller hormonal changes. However, recent protocols proposed by federal agencies stipulate that information about the metabolism of drugs in humans be determined on a more representative sample of the population that might use the drug.



Problem 9.21

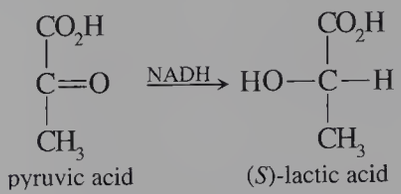
Consider the reduction of the C-2 carbonyl carbon atom of pyruvic acid with $NaBH_4$. The atoms directly bonded to the carbonyl carbon atom are arranged in a trigonal plane. What is the optical rotation of the product(s)?



pyruvic acid lactic acid

Problem 9.22

Reduction of pyruvic acid by NADH using the liver enzyme lactate dehydrogenase yields exclusively (*S*)-lactic acid. Write the Fischer projection of this product. Why does only a single product form?

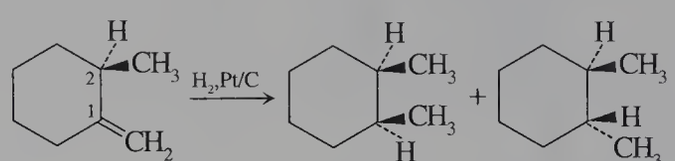


pyruvic acid (*S*)-lactic acid

9.11 Formation of Diastereomers

In the previous section, we examined the formation of compounds with one or two stereogenic centers from achiral reactants. Now we examine what happens when a second stereogenic center forms in a chiral molecule. Diastereomers could result. A molecule with one stereogenic site, designated A_R, that forms a second stereogenic site at B within the molecule could give A_RB_R and A_RB_S. We recall that a single enantiomer results when a stereogenic center forms in a molecule in a chiral environment, such as is provided by an enzyme. Similarly, a chiral site in a molecule should affect the stereochemistry of the second site when diastereomers form.

In the hydrogenation of an alkene using a transition metal catalyst, the planar molecule associates with the surface of the metal. If the alkene is achiral, the "side" presented to the surface of the metal is not important. The alkene can be hydrogenated from the "top" or "bottom" to give the same product. Consider the catalytic hydrogenation of (*R*)-2-methylmethylenecyclohexane. Two stereoisomers, 1*S*,2*R* and 1*R*,2*R*, form, but in unequal amounts. Approximately 70% of the product is the cis isomer (1*S*,2*R*).



(2*R*) (1*S*,2*R*) (70%) (1*R*,2*R*) (30%)

Because the alkene is chiral, there is a difference between the steric environment of the two faces of the double bond. The methyl group above the plane decreases the probability of hydrogenation from that face of the double bond. Hydrogenation from the less hindered bottom side "pushes" the newly formed methyl group up, and the cis isomer results. The two stereoisomeric products form in unequal amounts as a consequence of the chiral center. The reaction is called **stereoselective**.

Similar observations show that one enantiomer reacts with an achiral reagent to give unequal amounts of diastereomeric products. The relative yields of the diastereomers often depend on the structure of the existing stereogenic center and its proximity to the newly formed stereogenic center. Many stereogenic centers are present in an enzyme catalyst. They create a chiral environment, which leads to high stereoselectivity. Usually only one diastereomer forms in enzyme-catalyzed reactions.

Problem 9.23

Write the structure of the oxirane (epoxide) of (*Z*)-2-butene formed in the laboratory. Assign the configurations of the stereogenic centers.

Problem 9.24

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure(s) of the 2-bromo-3-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Problem 9.25

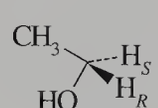
Based on the data for the hydrogenation of 2-methylmethylenecyclohexane, predict the product(s) of the hydrogenation of 2-*tert*-butylmethylenecyclohexane.

Sample Solution

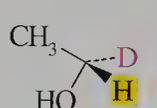
The 2-*tert*-butyl group on the "top" of the molecule decreases the probability of hydrogenation from that face. Hydrogenation tends to occur from the less hindered side and "pushes" the newly formed methyl group up. The methyl and *tert*-butyl groups are cis. The cis/trans ratio should be larger than the 70:30 obtained from 2-methylmethylenecyclohexane because the larger *tert*-butyl group should hinder attack by hydrogen more than does the smaller methyl group.

9.12 Prochiral Centers

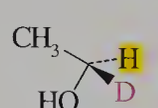
We have considered some examples of biochemical reactions in which an enzyme can stereospecifically distinguish between enantiomers. Enzymes can also distinguish between apparently equivalent groups in achiral substrates. Under such circumstances, the enzyme can generate a chiral center at an atom of an achiral reactant. An atomic center that can become chiral as a result of a stereospecific reaction is called **prochiral**. Let's consider the methylene group of ethanol. Because the methylene carbon atom is bonded to two hydrogen atoms, it is not chiral. Now assume that a reaction is possible that substitutes a deuterium atom for one hydrogen atom. Two enantiomers result. The original hydrogen atoms are called **enantiotopic** because enantiomeric compounds form by the replacement of one or the other hydrogen with another atom or group—in this case, a deuterium atom.



ethanol



(*S*)-ethanol-*1*-*d*

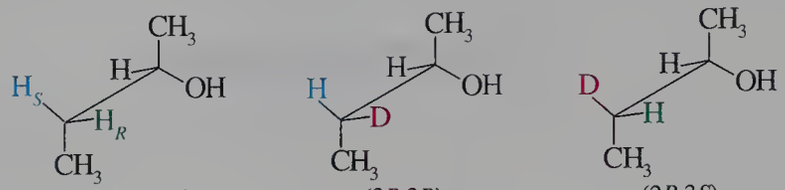


(*R*)-ethanol-*1*-*d*

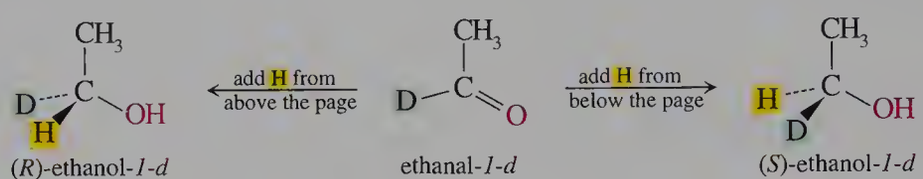
Enantiotopic atoms are designated *pro-R* and *pro-S*. The hydrogen atom behind the page, as shown above, is designated *pro-S* because replacing it with deuterium gives the *S* enantiomer. The hydrogen atom in front of the page is designated *pro-R* because replacing it with deuterium gives the *R* enantiomer. A prochiral center cannot be converted into a single chiral compound by a symmetrical (achiral) reagent. But the enzymes that catalyze biochemical reactions are chiral. These enzymes can distinguish between the enantiotopic groups of a prochiral center. Enzymes have specific binding sites into which substrates fit. For a molecule such as ethanol, when the CH_3 and OH groups "fit" into the enzyme binding site, the prochiral hydrogen atoms are located in different environments of the chiral enzyme. Hence a reaction might occur at one prochiral hydrogen atom, for example, and not at the other.

The concept of prochirality is also important in describing the biochemical reactions of molecules that already have one or more chiral centers. Formation of a second chiral center at an achiral site could lead to a mixture of diastereomers. The two equivalent groups at the achiral site are designated as **diastereotopic**.

The hydrogen atoms at the C-3 atom of (*R*)-2-butanol are diastereotopic. Consider replacing either one of them by deuterium. Replacing the C-3 hydrogen atom on the right in the structure gives the *R* configuration. That hydrogen atom is *pro-R*. The diastereomeric 2*R*,3*S* compound results from replacing the C-3 hydrogen atom on the left, which is *pro-S*.

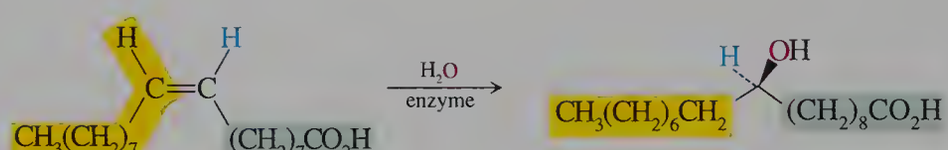


Next we consider a reaction at an sp^2-hybridized carbon atom as it is converted into a product with an sp^3-hybridized carbon atom. Although the trigonal carbon atom of a carbonyl group is not a stereogenic center, the reduction of that group forms an alcohol with a stereogenic center. Consider the formation of a C—H bond in the reduction of ethanal that has been deuterated at the C-1 atom. Bond formation at one face gives one enantiomer; formation of a C—H bond at the opposite face gives the other enantiomer.



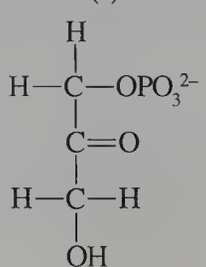
To describe the addition reactions at the two possible faces of planar parts of a molecule, we must be able to distinguish the faces. To do this, consider the sequence of groups bonded to the trigonal atom. If, when viewed from one face, the groups are in a clockwise sequence when arranged by priority rules, that face is designated *re*. If the sequence of groups is counterclockwise, the face is designated *si*. Viewing ethanal-*1-d* from above the page as shown above, the face is *si* because the order of the groups O > CH_3 > D is counterclockwise. Thus, we describe a reaction from this direction as attack at the *si* face to give the *R* enantiomer.

Many biochemical reductions occur at sp^2-hybridized carbon atoms. These reactions yield a single enantiomer. For example, the hydration of oleic acid yields exclusively (*R*)-10-hydroxystearic acid.



Problem 9.26

The structure of dihydroxyacetone phosphate, an intermediate in glycolysis, is shown below. Identify the pro-chiral hydrogen atom(s) and label them as H_R and H_S.



Problem 9.27

Is the face to which oxygen adds in the addition of water to oleic acid *si* or *re*?

EXERCISES

Chirality

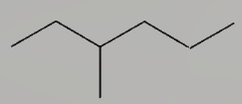
9.1 Which of the following isomeric methylheptanes has a chiral center?
(**a**) 2-methylheptane (**b**) 3-methylheptane (**c**) 4-methylheptane

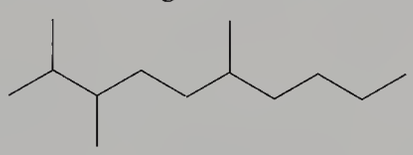
9.2 Which of the following isomeric bromohexanes has a chiral center?
(**a**) 1-bromohexane (**b**) 2-bromohexane (**c**) 3-bromohexane

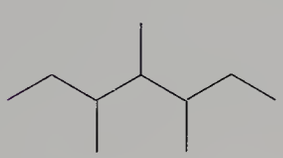
9.3 Which of the compounds with molecular formula $C_5H_{11}Cl$ has a chiral center?

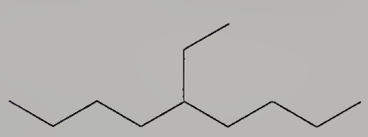
9.4 Which of the compounds with molecular formula $C_3H_6Cl_2$ has a chiral center?

9.5 How many chiral centers does each of the following alkanes have?

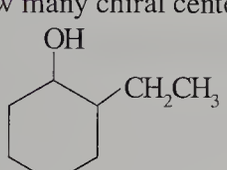
(**a**) 

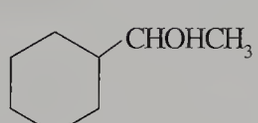
(**b**) 

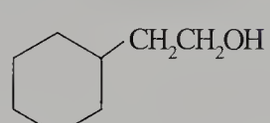
(**c**) 

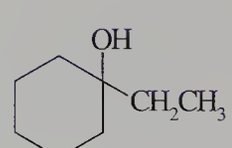
(**d**) 

9.6 How many chiral centers does each of the following cyclic compounds have?

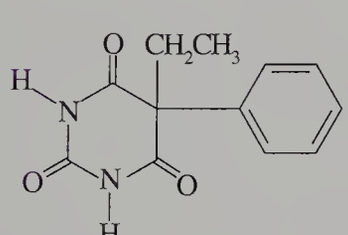
(**a**) 

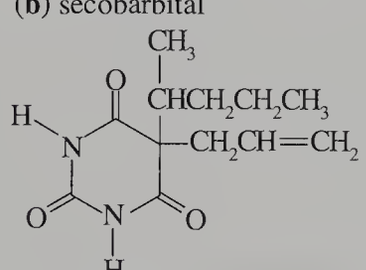
(**b**) 

(**c**) 

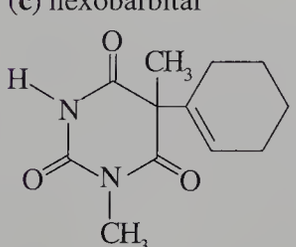
(**d**) 

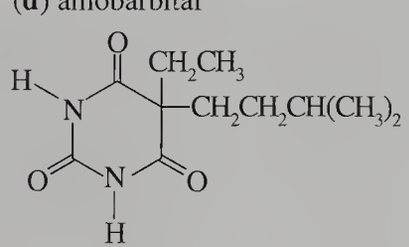
9.7 How many chiral centers does each of the following barbiturates have?
(**a**) phenobarbital (**b**) secobarbital





(**c**) hexobarbital (**d**) amobarbital

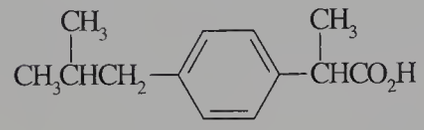




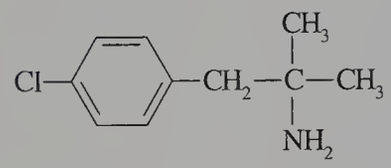
9.8 How many chiral centers does each of the following drugs have?

(**a**) phenylbutazone, used to treat gout

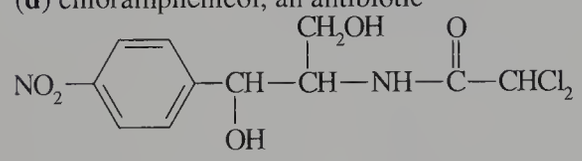
(**b**) ibuprofen, an analgesic



(**c**) chlorphentermine, a nervous system stimulant

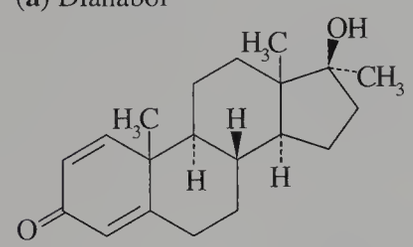


(**d**) chloramphenicol, an antibiotic

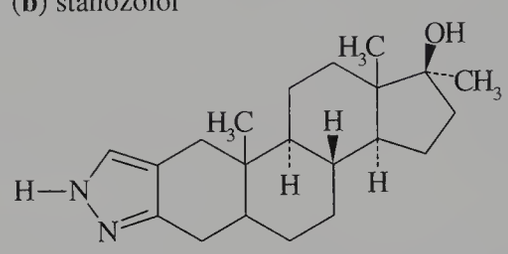


9.9 How many chiral carbon atoms are in each of the following synthetic anabolic steroids?

(**a**) Dianabol

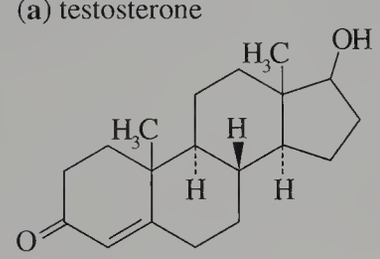


(**b**) stanozolol

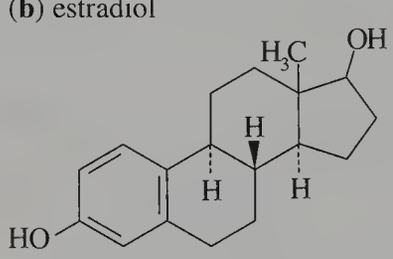


9.10 Determine the number of chiral centers in the male sex hormone testosterone and in the female sex hormone estradiol.

(**a**) testosterone



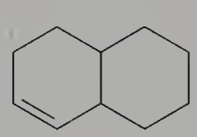
(**b**) estradiol



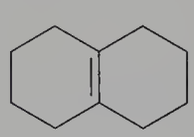
Plane of Symmetry

9.11 Determine whether each of the following compounds has a plane of symmetry.

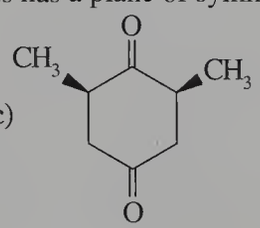
(**a**)



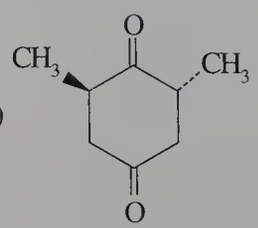
(**b**)



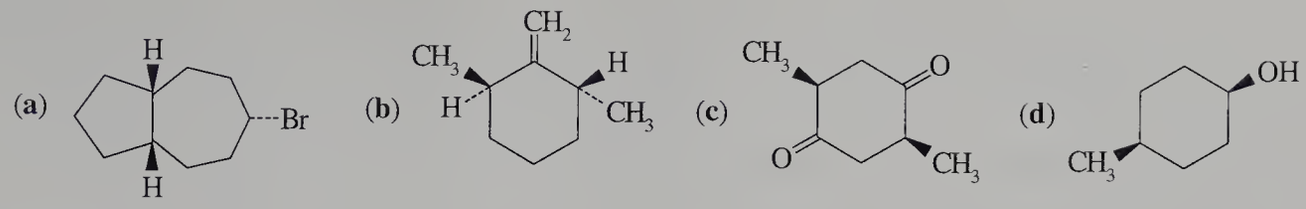
(**c**)



(**d**)



9.12 Determine whether each of the following compounds has a plane of symmetry.



Optical Activity

9.13 Lactic acid in the blood has a specific rotation of +2.6. A sample of lactic acid obtained from sour milk has a specific rotation of −2.6. How do these compounds differ?

9.14 Optically pure (*S*)-(+)-citronellol from citronella oil has a specific rotation of +5.3. An enantiomer of optically pure (*S*)-(+)-citronellol is obtained from geranium oil. What is its specific rotation?

9.15 The configuration of naturally occurring MSG, which has a specific rotation of +24, is *S*. Is the assignment of configuration incorrect?

9.16 Carvone obtained from spearmint oil is the (*R*)-(−) enantiomer. Explain the meaning of both terms within parentheses.

9.17 A solution of 3 g of menthol in 50 mL of ethanol is prepared and a sample is placed in a 10-cm tube. The optical rotation is +3.0. What is the specific rotation of menthol?

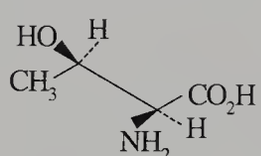
9.18 The specific rotation of (*R*)-2-bromobutane in ethanol is −23.1. A solution of the compound in a 1 dm tube has $\alpha = 55$. What is the concentration of the compound in grams per 100 mL?

9.19 The specific rotation of (+)-2-butanol as a pure liquid is +13.9. A synthetic sample of 2-butanol has an optical rotation of −4.5. What is the composition of the sample?

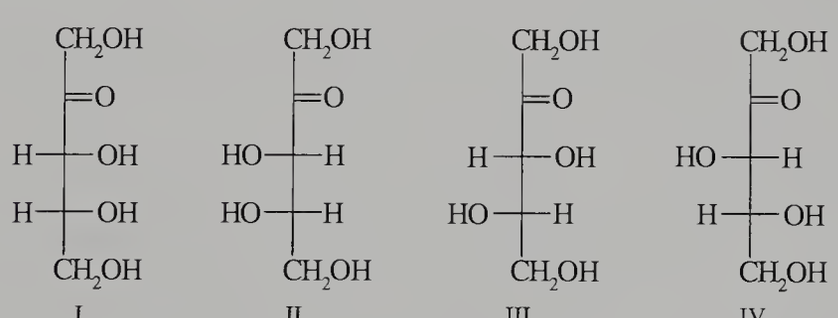
9.20 The specific rotation of the *S* enantiomer of MSG, a flavor enhancer, is +24. What is the optical purity of a synthetic sample whose α is +6? What are the percentages of the two enantiomers in the sample?

Fischer Projection Formulas

9.21 Draw the Fischer projection formula of the following enantiomer of naturally occurring threonine obtained from proteins. Draw all diastereomers as well.



9.22 What stereochemical relationship exists between any and all pairs of the following structures of carbohydrates?



Priority Rules

9.23 Arrange the groups in each of the following sets in order of increasing priority.

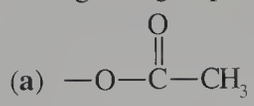
(**a**) —OH, —SH, —SCH_3, —OCH_3

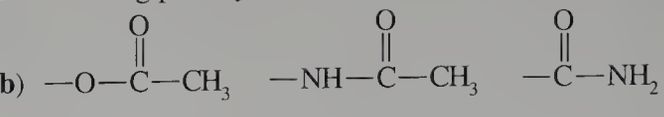
(**b**) —CH_2Br, —CH_2Cl, —Cl, — Br

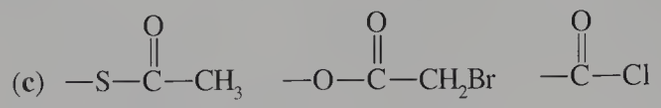
(**c**) —CH_2—CH=CH_2, —CH_2—O—CH_3, —CH_2—C≡CH, —C≡C—CH_3

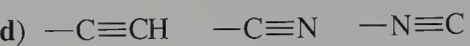
(**d**) —CH_2CH_3, —CH_2OH, —CH_2CH_2Cl, —OCH_3

9.24 Arrange the groups in each of the following sets in order of increasing priority.

(**a**) 

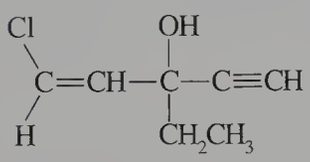
(**b**) 

(**c**) 

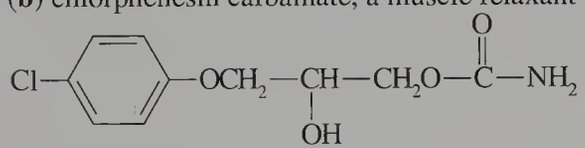
(**d**) 

9.25 Consider the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority.

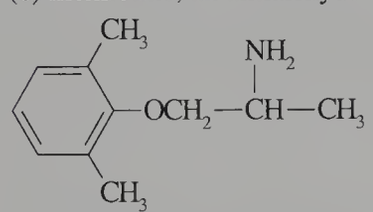
(**a**) ethchlorvynol, a sedative-hypnotic



(**b**) chlorphenesin carbamate, a muscle relaxant

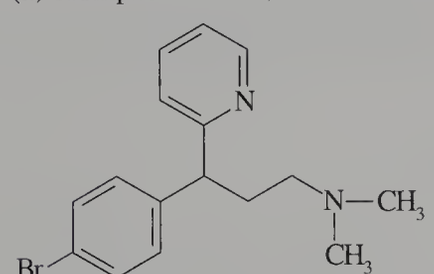


(**c**) mexiletine, an antiarrhythmic

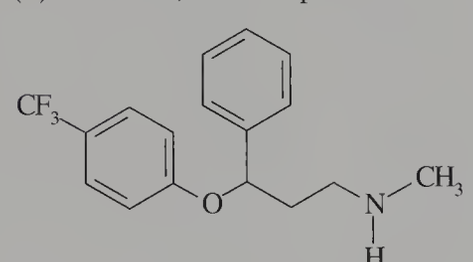


9.26 Consider the chiral carbon atom in each of the following drugs and arrange the groups in order of increasing priority.

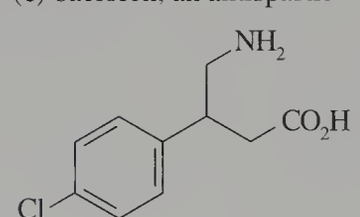
(**a**) brompheniramine, an antihistamine



(**b**) fluoxetine, an antidepressant



(**c**) baclofen, an antispastic

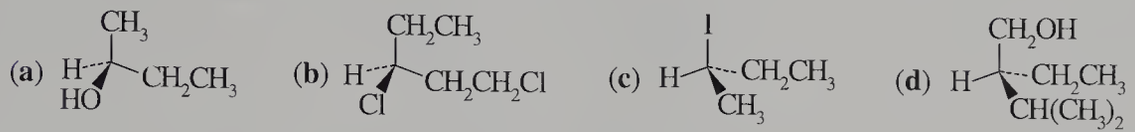


R,S Configuration

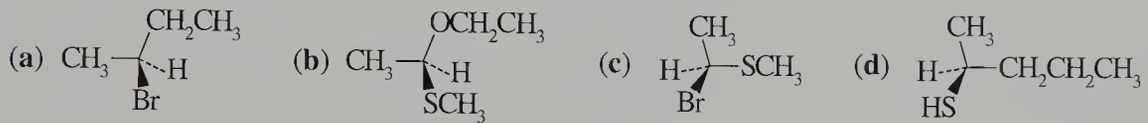
9.27 Draw the structure of each of the following compounds.
(a) (*R*)-2-chloropentane **(b)** (*R*)-3-chloro-1-pentene **(c)** (*S*)-3-chloro-2-methylpentane

9.28 Draw the structure of each of the following compounds.
(a) (*S*)-2-bromo-2-phenylbutane **(b)** (*S*)-3-bromo-1-hexyne **(c)** (*R*)-2-bromo-2-chlorobutane

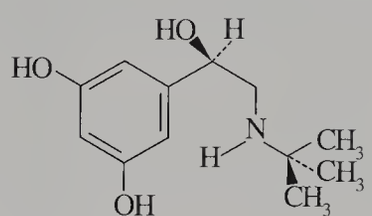
9.29 Assign the configuration of each of the following compounds.



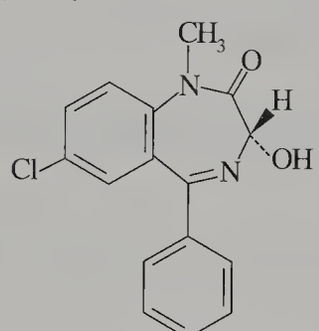
9.30 Assign the configuration of each of the following compounds.



9.31 Assign the configuration of terbutaline, a drug used to treat bronchial asthma.

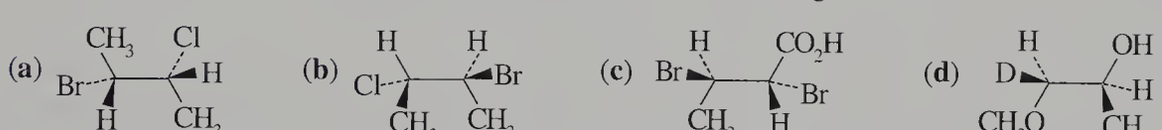


9.32 Assign the configuration of the following hydroxylated metabolite of diazepam, a sedative.

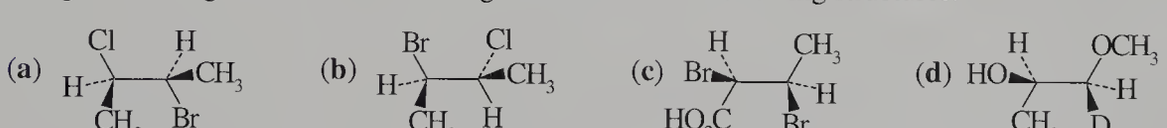


Diastereomers

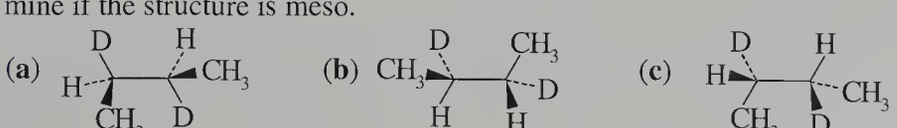
9.33 Assign the configuration of each stereogenic center in the following structures.



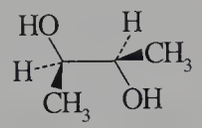
9.34 Assign the configuration of each stereogenic center in the following structures.

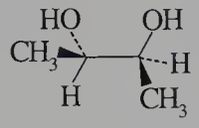


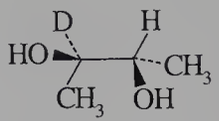
9.35 Assign the configuration of each stereogenic center in the following structures. Based on the assignment, determine if the structure is meso.



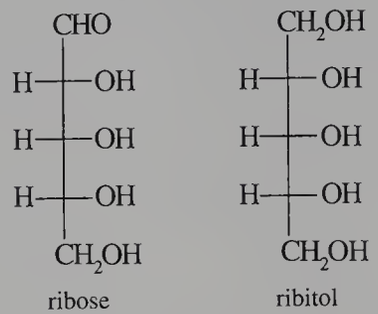
9.36 Assign the configuration of each stereogenic center in the following structures. Based on the assignment, determine if the structure is meso.

(a) 

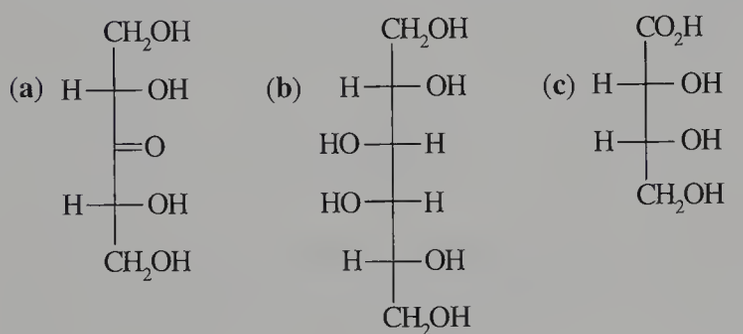
(b) 

(c) 

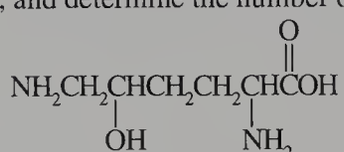
9.37 Ribose is optically active, but ribitol, its reduction product, is optically inactive. Why?



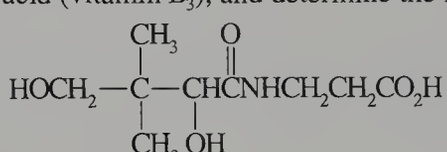
9.38 Which of the following carbohydrate derivatives is/are meso compounds?



9.39 Consider the structure of 5-hydroxylysine, and determine the number of stereoisomers possible.

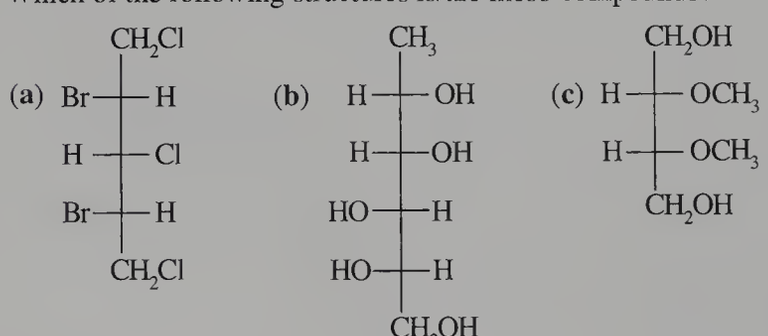


9.40 Consider the structure of pantothenic acid (vitamin B_3), and determine the number of stereoisomers possible.



9.41 There are four isomeric 2,3-dichloropentanes but only three isomeric 2,4-dichloropentanes. Explain why.

9.42 Which of the following structures is/are meso compounds?



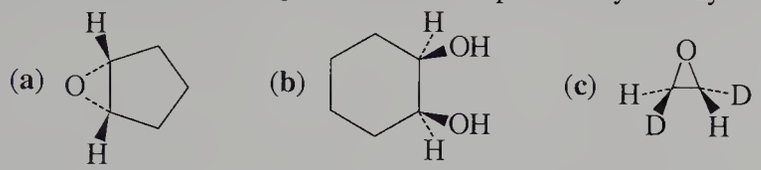
Cyclic Compounds

9.43 Which of the following compounds has a plane of symmetry?

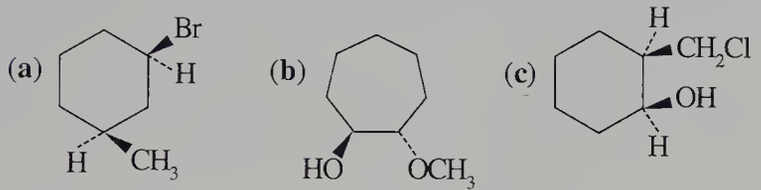
(**a**) *cis*-1,2-dibromocyclobutane (**b**) *trans*-1,2-dibromocyclobutane

(**c**) *cis*-1,3-dibromocyclobutane (**d**) *trans*-1,3-dibromocyclobutane

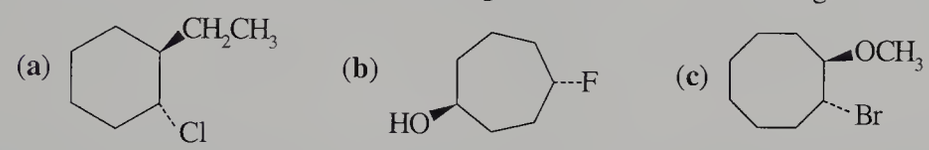
9.44 Which of the following structures has a plane of symmetry?



9.45 Assign the configuration of each stereogenic center in the following structures.



9.46 Assign the configuration of each stereogenic center in the following structures.



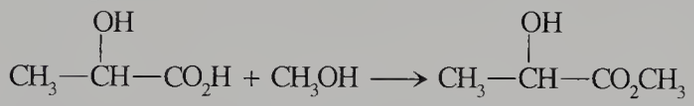
Resolution

9.47 Reaction of a racemic mixture of A_R,A_S with a resolving agent X_R yields diastereomers. The A_S—X_R isomer is less soluble than A_R—X_R. Consequently, the A_S isomer is obtained optically pure. Describe the experimental results if X_S were available as a resolving agent.

9.48 Resolution of a racemic mixture yields one enantiomer with $[\alpha]_D = +44$ and another enantiomer with $[\alpha]_D = -33$. One enantiomer is optically pure. Which one? What is the optical purity of the other enantiomer?

Reactions of Chiral Compounds

9.49 (*R*)-(−)-Lactic acid is converted into a methyl ester when it reacts with methanol. What is the configuration of the ester? Can you predict its sign of rotation?



9.50 Alkyl bromides can be reduced to alkanes using lithium aluminum hydride ($LiAlH_4$). The reaction involves a displacement of bromide ion by a hydride ion. What is the product of reduction of (*R*)-1-bromo-2-methylbutane by $LiAlH_4$?

9.51 Based on the experimental results of the reaction of (*R*)-2-bromooctane with sodium hydroxide (Section 9.9), predict the product of the reaction of (*S*)-2-bromobutane with sodium hydroxide.

9.52 Alcohols can be formed by acid-catalyzed addition of water to alkenes. Predict the stereochemistry of the product of addition of water to 1-octene.

9.53 Free radical chlorination of (*S*)-2-bromobutane gives a mixture of compounds resulting from attack at any of the four nonequivalent carbon–hydrogen bonds. The products of reaction at C-1 and C-4 atoms are both optically active. Explain why.

9.54 Free radical chlorination of (*S*)-2-fluorobutane gives a 31% yield of 2-chloro-2-fluorobutane. What is the expected stereochemistry of the product?

9.55 Free radical chlorination of (*S*)-2-bromobutane at the C-2 atom gives an optically inactive product, but reaction at the C-3 atom gives an optically active product. Explain why.

9.56 Free radical chlorination of (*S*)-2-fluorobutane gives a 40% yield of 2-chloro-3-fluorobutane. The product consists of a 3:2 ratio of the 2*R*,3*S* and 2*S*,3*S* diastereomers. Why are the compounds not produced in equal amounts?

9.57 How many products are possible when HBr adds to the double bond of (*R*)-3-bromo-1-butene? Which are optically active?

9.58 How many products are possible when HBr adds to the double bond of (*R*)-4-methylcyclohexene? Which are optically active?

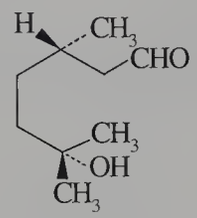
Stereoisomers in Biochemistry

9.59 Natural glucose is a sugar that the body can metabolize. Suggest what would happen if one were to eat its enantiomer.

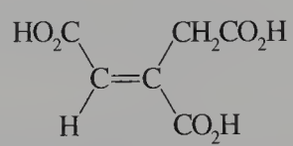
9.60 The mold *Penicillium glaucum* can metabolize one enantiomer of optically active tartaric acid. Explain what would happen if a racemic mixture of tartaric acid were "fed" to the mold.

9.61 Natural adrenaline is levorotatory. The enantiomer has about 5% of the biological activity of the natural compound. Explain why.

9.62 The isomer of hydroxycitronellal shown below has the odor of lily of the valley. Its enantiomer has a minty odor. Explain why.

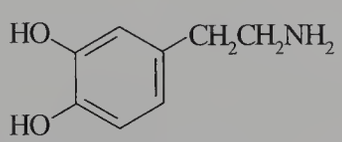


9.63 Enzyme-catalyzed addition of water to aconitic acid gives citric acid, which is optically inactive, and isocitric acid, which is optically active. What are the structures of the two acids. Why are the stereochemical results different?

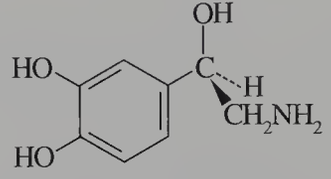


aconitic acid

9.64 The enzymatic hydroxylation of dopamine by dopamine hydroxylase gives (–)-norepinephrine. Explain why. If an achiral reagent were available for a related laboratory synthesis, what would be the stereochemistry of the product?



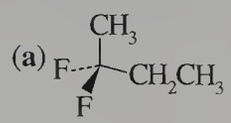
dopamine

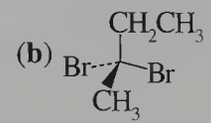


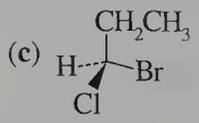
(–)-norepinephrine

Prochiral Centers

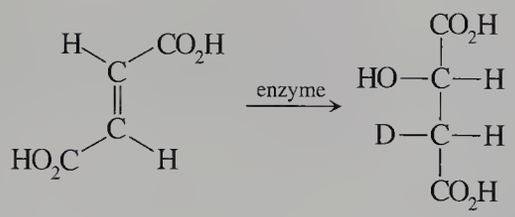
9.65 Consider the atoms in each of the following structures and indicate which are prochiral. Which have enantiotopic groups? Which have diastereotopic groups?







9.66 Addition of water to fumaric acid yields (*S*)-malic acid as part of the citric acid cycle. When D_2O is used, the product is (2*S*,3*R*)-malic acid-*3-d*. Is the addition reaction syn or anti? Are the two carbon atoms of the double bond equivalent or not?



10

Nucleophilic Substitution and Elimination Reactions

10.1 Nucleophilicity and Basicity

In Section 8.9, we first learned that haloalkanes undergo two kinds of reactions: (1) substitution of a halide atom by a nucleophile and (2) elimination of a halide ion and a proton from a β carbon atom to give an alkene. Nucleophilic substitution reactions that occur by an S_N2 mechanism proceed at a rate that depends upon how readily the nucleophile displaces the leaving group from a carbon atom. This property of the nucleophile is called **nucleophilicity**. By virtue of an electron pair that seeks a partially positively charged carbon atom, a nucleophile is also a base. Therefore, nucleophiles may also cause a competitive elimination reaction because, if sufficiently basic, they can competitively extract a proton from a β carbon atom. In this case, the elimination reaction then depends upon the **basicity** of the nucleophile. Note that the terms nucleophilicity and basicity describe different phenomena. Nucleophilicity of a species affects the rate of a substitution reaction at a carbon center. Basicity of a species affects the equilibrium constant for an acid–base reaction between a proton available from the haloalkane and the basic nucleophile in an elimination reaction.

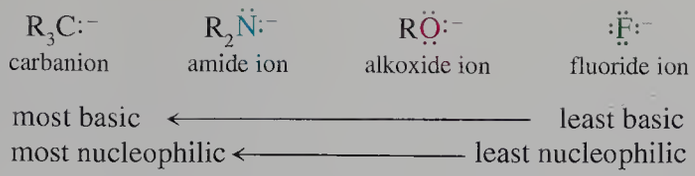
The nucleophilicities and basicities of a series of structurally or chemically related nucleophiles—such as halide ions, oxygen-containing anions, and sulfur-containing anions—are not always related in a simple way. However, trends based on periodic properties of the elements are evident. The relative rates of reaction of various nucleophiles with iodomethane are given in Table 10.1. The reference nucleophile for the substitution reaction is methanol, a poor nucleophile, which is assigned $k_{rel} = 1$.

Table 10.1
Relative Rates of Nucleophiles with Iodomethane

Nucleophile	*Relative rate*
CH_3OH	1
NO_3^-	30
F^-	5×10^2
SO_4^{2-}	3×10^3
$CH_3CO_2^-$	2×10^4
Cl^-	2.5×10^4
NH_3	3.2×10^5
N_3^-	6×10^5
Br^-	6×10^5
CH_3O^-	2×10^6
CN^-	5×10^6
I^-	2.5×10^7
CH_3S^-	1×10^9

Trends Within a Period

When nucleophilic ions having the same charge are in the same period of the periodic table, nucleophilicity and basicity parallel each other and decrease from left to right in the period. For example, we know that hydroxide ion is more basic than fluoride ion. Hydroxide ion is also more nucleophilic. It displaces an iodide ion from methyl iodide about 4000 times as fast as does fluoride ion. The same periodic trend is observed for organic anions.



We recall that the oxygen atom of the hydroxide ion is less electronegative than the fluoride ion because oxygen holds its electrons less firmly than does fluorine. Consequently, we would expect the nonbonding electrons of the oxygen atom of hydroxide ion to be more easily donated to carbon in a nucleophilic substitution reaction than are the nonbonding electrons of fluoride ion. Although the data on nucleophilicity is consistent with this picture, it is also necessary to consider the effect of the solvent (Section 10.3). The solvation of anions by protic solvents such as ethanol decreases the nucleophilicity of anions. A **protic solvent** has a hydrogen atom bonded to a strongly electronegative element such as oxygen. The small fluoride ion, with its more concentrated charge, is strongly solvated by hydrogen bonds between its lone pair electrons and the hydrogen atom of the hydroxyl group (Figure 10.1). In order to react, a solvated nucleophile must lose some solvent molecules so the nucleophile can approach and start to form a bond to the carbon center. As a consequence, its nucleophilicity is greatly decreased.

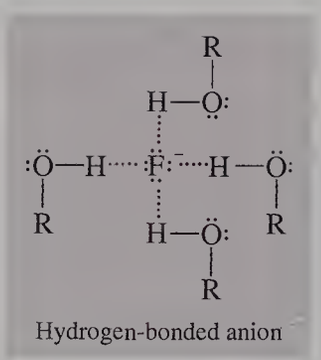
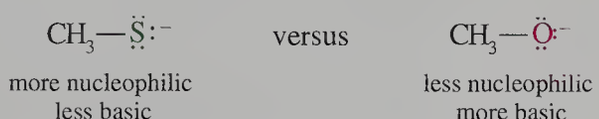


FIGURE 10.1 Solvation of Ions by Protic Solvents
Anions solvated by protic solvents have diminished nucleophilicity as a result of hydrogen bonding between the hydroxyl hydrogen atom of an alcohol and an electron pair of the anion.

Trends Within a Group

The order of nucleophilicity runs opposite to the order of basicity for nucleophiles derived from atoms in the same group of the periodic table. First, consider the nucleophilicities of thiolates (RS^-) and alkoxides (RO^-). Thiols are stronger acids ($pK_a = 10$) than alcohols ($pK_a = 16$), and alkoxides are therefore stronger bases than thiolates. However, thiolates are more nucleophilic than alkoxides (Table 10.1). The ratio of the relative rates for methylthiolate and methoxide in the displacement of iodide from methyl iodide is about 500 to 1.



A similar inverse relationship between basicity and nucleophilicity occurs for the halides. Hydrogen iodide is a strong acid, and hydrogen fluoride is a weak acid. Thus, the iodide ion is a weaker base than the fluoride ion. However, for the series of halide ions, iodide ion is an excellent nucleophile and fluoride ion is a very poor nucleophile. The ratio of relative rates for iodide ion and fluoride ion in the displacement of iodide ion from iodomethane is about 50,000 to 1.

$:\ddot{I}:^-$ $:\ddot{Br}:^-$ $:\ddot{Cl}:^-$ $:\ddot{F}:^-$

least basic ⟶ most basic
most nucleophilic ⟵ least nucleophilic

This order of nucleophilicities within a group of the periodic table can be explained by the polarizability of the atoms. We recall that the atomic radii of elements increase going down a family in the periodic table and, as a result, the electrons are more polarizable. The polarizability of a nucleophile is important in a nucleophilic substitution reaction because an electron pair in the nucleophile forms a bond to the electrophilic carbon atom during the reaction (Figure 10.2). The orbital containing an electron pair in the iodide ion can be distorted to overlap with the back lobe of the sp^3 hybrid orbital of the electrophilic carbon atom. However, fluorine is strongly electronegative, and it tends to maintain its electron pair in its orbital. Therefore, overlap of an orbital of fluorine with the back lobe of the sp^3 hybrid orbital of the carbon atom is less favorable.

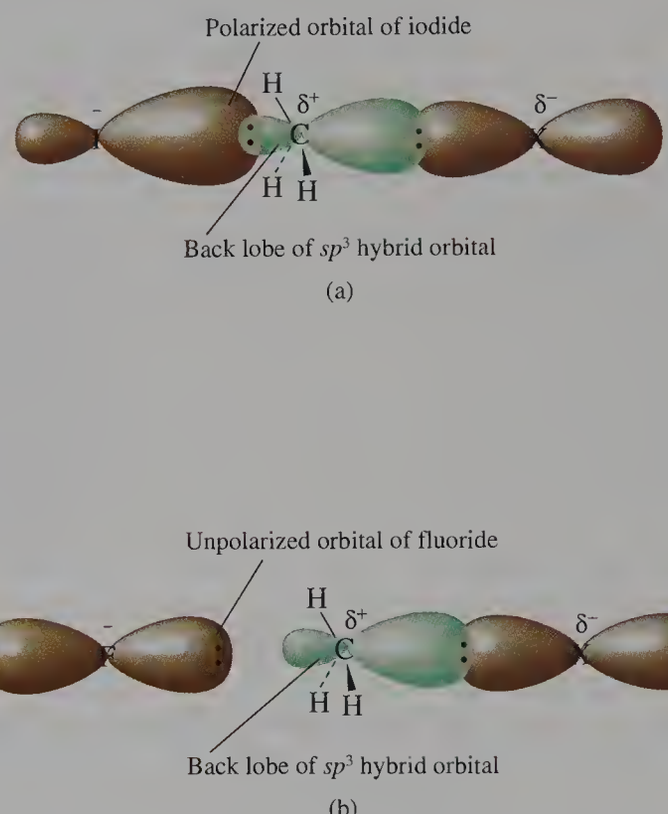


FIGURE 10.2
Polarizability of Nucleophile and Reactivity
The orbitals of the valence electrons of the iodide ion are very polarizable. One of the nonbonding electron pairs can effectively overlap with the sp^3 back lobe of carbon in a nucleophilic displacement reaction. The orbitals of the fluoride ion tightly hold its valence shell electron pairs, and they do not interact effectively with the sp^3 back lobe of carbon at the same distance.

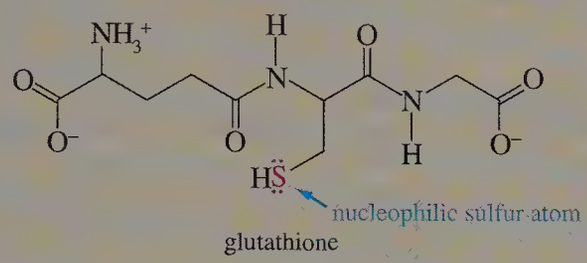
Again, as in the case of the trend of nucleophilicities of anions within a period of the periodic table, the trend of nucleophilicities of anions derived from within a group is also affected by solvation. The larger, more polarizable anions are less strongly hydrogen bonded to protic solvents than are smaller, less polarizable anions. As a result, less energy is required to shed solvent molecules from the larger ion to enable it react as a nucleophile. Thus, large anions are better nucleophiles than smaller anions because they are both more polarizable and less strongly solvated.

Effect of Charge

When a nucleophile can exist as either an anion or its uncharged conjugate acid, the anion is more nucleophilic than the conjugate acid. A negatively charged nucleophile is more strongly attracted to the electrophilic carbon atom than an uncharged nucleophile. For example, alkoxide ions (RO^-) are better nucleophiles than alcohols (ROH).

Biological Substitution Reactions by Sulfur-Containing Nucleophiles

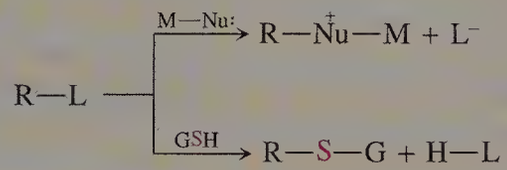
Many biomolecules possess nucleophilic sulfur atoms. Of these, one of the most important is glutathione, which contains a sulfhydryl group (SH). Glutathione is present in a concentration of about 1–5 mM in most animal cells. It participates in several enzyme-catalyzed reactions. In some, glutathione acts as a reducing agent. In others, its nucleophilic sulfhydryl group reacts with various toxic intermediates produced when drugs are metabolized in liver cells. The type of reaction that occurs depends on the cell type and the nature of the enzyme that catalyzes the reaction.



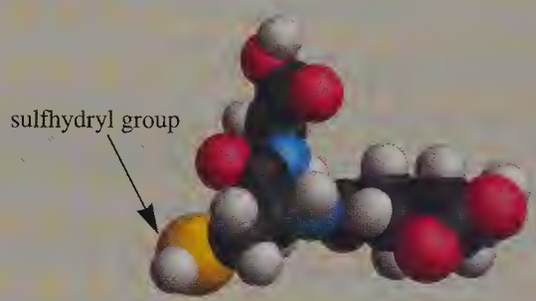
glutathione

The sulfhydryl group of glutathione, often called GSH, is a nucleophile that displaces substituents bonded to carbon. The various leaving groups of reactive metabolites are represented with an L. They are all strongly electron-withdrawing groups, and they make the carbon atom to which they are bonded partially positively charged and susceptible to nucleophilic attack.

The molecule that attacks the reactive metabolite can be an essential macromolecule with a nucleophilic center (M—Nu:) or glutathione (GSH). Thus, glutathione protects cells by reacting with toxic metabolites, represented below by R—L, before they react with other cellular macromolecules (M—Nu:).

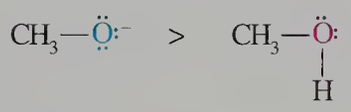


Glutathione also provides some degree of protection against toxic industrial chemicals. Among these are benzyl, allyl, and methyl halides. However, long-term exposure to these chemicals eventually overwhelms the protection provided by glutathione, and damages the organism.



Glutathione

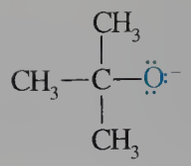
Methoxide ion displaces an iodide ion from methyl iodide about 2×10^6 times as fast as does methanol (Table 10.1). Hydroxide ion is also a better nucleophile than water.



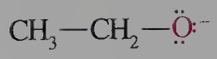
better nucleophile — poor nucleophile

Steric Effects

We recall that the rate of a reaction that occurs via an S_N2 mechanism is strongly affected by bulky groups near the reaction center, which hinder the approach of the nucleophile (Section 8.11). Therefore, the size of the nucleophile is also important as it approaches the reactive carbon center along a path guarded by groups bonded to the carbon center. The steric crowding in the pentacoordinate transition state also increases with the size of the nucleophile. We find, for example, that the larger *tert*-butoxide ion is a poorer nucleophile in S_N2 reactions than the smaller ethoxide ion.



tert-butoxide
(hindered: weak nucleophile)



ethoxide
(unhindered: strong nucleophile)

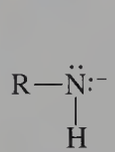
The order of basicities of alkoxides is opposite to the order of nucleophilicity: *tert*-butoxide ion is a stronger base than ethoxide ion. Steric hindrance has little effect on the ease of abstraction of a proton in acid–base reactions. Steric repulsions are less severe when the base approaches a monovalent hydrogen atom than the more crowded environment at a tetravalent carbon atom.

Problem 10.1

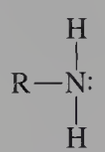
Trimethylamine, $(CH_3)_3N$, is a good nucleophile, but trimethylborane, $(CH_3)_3B$, is not. Explain the difference in the nucleophilicities of these two compounds.

Problem 10.2

Which is expected to be the stronger base, an amide ion or an amine? Which is expected to be the better nucleophile?



an amide ion



an amine

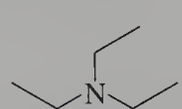
Problem 10.3

Which is expected to be the better nucleophile, diethyl sulfide, $(CH_3CH_2)_2S$, or diethyl selenide, $(CH_3CH_2)_2Se$?

Problem 10.4

Quinuclidine reacts about 50 times faster than triethylamine to displace iodide ion from iodomethane. Suggest a reason for this difference in nucleophilicity of these two compounds, which contain the same number of alkyl groups bonded to the nitrogen atom.

quinuclidine



triethylamine

10.2 Stereochemistry of Substitution Reactions

Part of the evidence for the existence of two possible mechanisms for nucleophilic substitution reactions is the kinetic order of the reaction (Section 8.11). Some substrates react by a mechanism designated S_N2, a one-step process in which the nucleophile attacks the substrate and the leaving group departs simultaneously. In this concerted, bimolecular process, the substrate and the nucleophile are both present in the transition state. The rate of the reaction depends on the concentrations of both nucleophile and substrate.

In other nucleophilic substitution reactions, the rate of the reaction depends only on the concentration of the substrate, not on that of the nucleophile. Such reactions, designated S_N1, occur in two steps. In the first step, the bond between the carbon atom and the leaving group breaks to produce a carbocation and, most commonly, an anionic leaving group. In the second step, the carbocation reacts with the nucleophile to form the product. The first step in an S_N1 reaction, formation of a carbocation, is the slow, or rate-determining step. The second step, formation of a bond between the nucleophile and the carbocation, occurs very rapidly. Since the slow step of the reaction involves only the substrate, the reaction is a first-order process.

Now we will consider important information about the chirality of the reactant and the product that also distinguishes between the S_N2 and S_N1 mechanisms. The stereochemical consequences of the two mechanisms differ because the transition states in the two mechanisms differ. In the S_N2 mechanism, the nucleophile and the substrate form a pentacovalent transition state in the shape of a trigonal bipyramid. In the S_N1 mechanism, the substrate minus the leaving group exists as a planar sp^2-hybridized carbocation. The existence of these two mechanisms was postulated by Hughes and Ingold in the 1940s based on kinetic and stereochemical evidence.

Stereochemistry and the S_N2 Mechanism

In the transition state for the S_N2 mechanism, neither the nucleophile nor the leaving group is fully bonded to carbon. But as the reaction proceeds through the transition state, a bond between carbon and the nucleophile forms and the bond between carbon and the leaving group breaks. Part of the evidence for this transition state is provided by the relative rates of reaction for haloalkanes, which decrease in the order methyl > primary > secondary > tertiary. This trend is attributed to the effect of the alkyl groups bonded to the carbon atom that bears the halogen atom. These alkyl groups shield the back of the carbon atom from attack by nucleophiles along a line collinear with the carbon–halogen bond (Figure 10.3). This steric hindrance blocks the approach of the nucleophile, and slows the rate of the reaction. The alkyl groups would not affect the rate of the reaction as much if the nucleophile attacked from the side of the molecule where the leaving group is bonded.

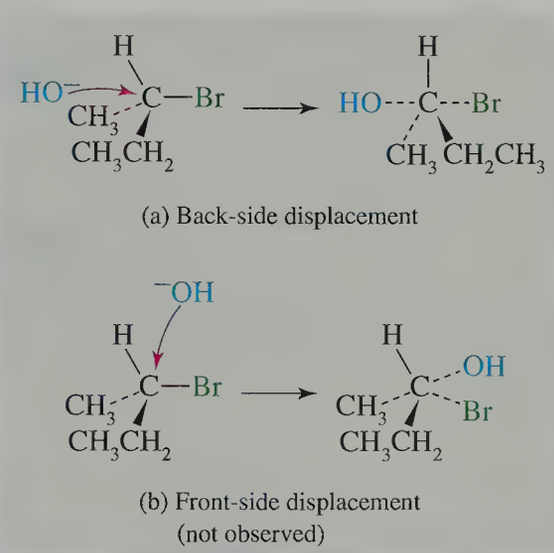
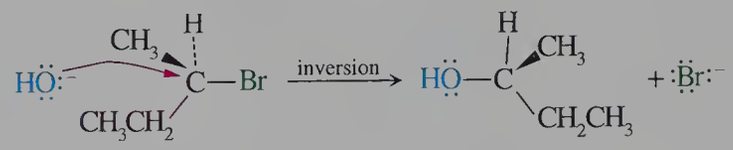


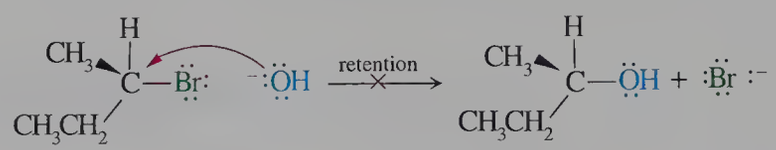
FIGURE 10.3 Steric Hindrance in the S_N2 Reaction
A compound substituted at a secondary center such as 2-bromobutane undergoes bimolecular substitution reactions at a slower rate than a compound substituted at a primary center such as bromoethane. The decreased rate is the result of steric hindrance in a backside displacement by the alkyl groups. A frontside displacement would not be as adversely affected.

The model for the transition state is based on stereochemical facts established by experiment. When (*R*)-2-bromobutane reacts with sodium hydroxide, the substitution product is (*S*)-2-butanol. This stereochemical process is termed **inversion of configuration**. This result indicates that the nucleophile approaches the electrophilic carbon atom from the back side—that is, from the side directly opposite the leaving group. Simultaneously, the leaving group departs from the front side of the substrate.



(*R*)-2-bromobutane (*S*)-2-butanol

If the hydroxide ion had bonded to the carbon atom on the side that was originally occupied by the leaving group, the product would have the same configuration as the reactant. This stereochemical process, termed **retention of configuration**, doesn't occur.



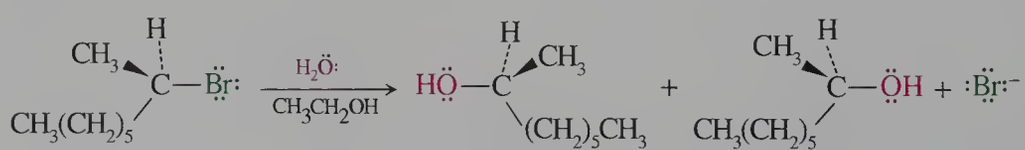
(*R*)-2-bromobutane (*R*)-2-butanol

Stereochemistry and the S_N1 Mechanism

The rate of S_N1 reactions decreases in the order 3° > 2° > 1° > methyl, a finding attributed to the order of stability of the carbocation formed in the rate-determining ionization step (Section 8.11). A relatively stable tertiary carbocation forms faster than a less stable secondary carbocation, which in turn forms very much faster than a highly unstable primary carbocation. However, the existence of a carbocation in an S_N1 mechanism is also supported by stereochemical studies.

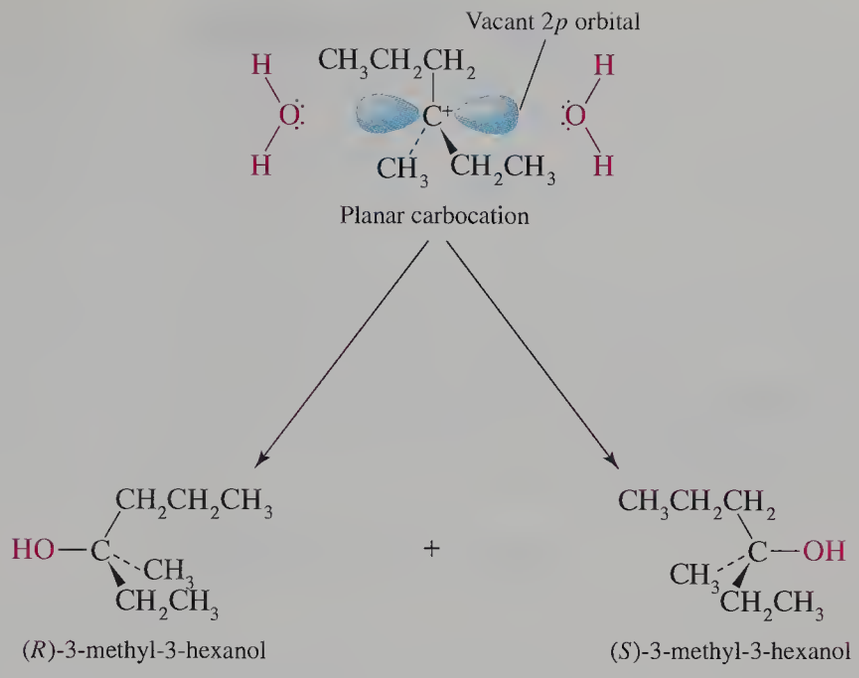
In the preceding section we saw that S_N2 reactions at chiral centers occur with inversion of configuration. In contrast, an S_N1 reaction tends to give a mixture of enantiomers, which has little or no optical rotation. For example, (*S*)-3-bromo-3-methylhexane reacts with water, a poor nucleophile, to give a racemic mixture of 3-methyl-3-hexanol. The reaction occurs via an achiral carbocation intermediate with a plane of symmetry (Figure 10.4). Because the carbocation intermediate has a plane of symmetry, the nucleophile can attack equally well from either side of the plane to give a racemic mixture.

(*S*)-3-bromo-3-methylhexane, which gives a racemic mixture with no optical rotation, is a tertiary alkyl halide. However, for some reactants, the product is partially racemic. That is, the product consists of two enantiomers with some slight excess of the enantiomer with an inverted configuration compared to the reactant. Consider the reaction of (*R*)-(−)-2-bromooctane, a secondary alkyl halide, with water in a mixed solvent of water–ethanol.



(*R*)-(−)-2-bromooctane (*S*)-(+)-2-octanol (83%) (*R*)-(−)-2-octanol (17%)

FIGURE 10.4 Stereochemistry of S_N1 Reaction



The optical rotation of the product is not zero, so only partial loss of optical activity is observed. The enantiomeric excess (see Section 9.3) of the product formed by net inversion is calculated as 66% based on the observed optical activity. The mixture contains 83% *S* and 17% *R* products.

The partial net inversion in S_N1 processes occurs because the carbocation may not be entirely free of the leaving group prior to attack by the nucleophile. Note that in Figure 10.4, the tertiary carbocation was shown as a symmetrical species solvated on both sides. However, in less stable carbocations, such as the secondary carbocation derived from 2-bromooctane, the anion of the leaving group hovers near the side from which it just departed. Hence, that face of the carbocation is shielded by the anion, so the carbocation is captured preferentially by a nucleophile that attacks from the opposite face. The experimental result is formation of a net excess of the product with inversion of configuration.

Although products of S_N1 processes may be only partially racemic, there is a clear stereochemical distinction between the two nucleophilic substitution mechanisms. The pentacoordinate transition state of the S_N2 mechanism results in complete inversion of configuration.

Problem 10.5

The reaction of (*S*)-2-bromobutane in ethanol proceeds via an S_N1 process. Write the structure of the product.

Problem 10.6

The optical rotation of (*S*)-(+)-2-bromobutane after its recovery from a solution of bromide ion in acetone as solvent is smaller than that of the original sample. Explain why. Based on this explanation, what will be the optical rotation after a prolonged period of time?

Sample Solution

The only way that the "original" reactant could lose its optical activity would be if a bromide ion is displaced by a bromide ion. Such a process for a secondary haloalkane occurs with inversion of configuration. The enantiomeric compound results each time a displacement occurs. Eventually, the process will produce a racemic mixture.

Problem 10.7

(*R*)-2-Chloro-3,7-dimethyloctane reacts with water in acetone as solvent to give (*S*)-3,7-dimethyl-2-octanol with 21% optical purity. What is the percentage of the *S* isomer in the reaction mixture? What is the origin of the mixture?

10.3 S_N2 Versus S_N1 Reactions

We have outlined the general properties of S_N2 and S_N1 reactions in Chapter 9. Let's now quantitatively examine which one is likely to occur as a function of structural and experimental variables. We will consider (1) the structure of the substrate, (2) the nucleophile, (3) the leaving group, and (4) the nature of the solvent.

Structure of the Substrate

The occurrence of one substitution mechanism rather than the other is primarily due to the degree of branching of the carbon atom bearing the leaving group. That atom is called the α carbon. Primary haloalkanes almost always react in nucleophilic substitution reactions by the S_N2 mechanism, whereas tertiary haloalkanes react by the S_N1 mechanism. Secondary haloalkanes may react by either mechanism, depending on the nature of the nucleophile and the solvent.

relative rate, S_N2: methyl > primary > secondary > tertiary

relative rate, S_N1: tertiary > secondary > primary > methyl

For displacement of bromide ion by the iodide ion, the S_N2 reactivity of the simplest representative compounds is

	bromomethane	bromoethane	2-bromopropane
relative rate:	2.2×10^5	1.4×10^3	1

The rate for 2-bromo-2-methylpropane is estimated to be more than 10^3 times slower than the rate for 2-bromopropane.

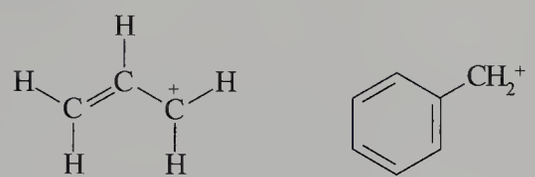
Steric hindrance to attack at the back side of the carbon atom is also easily demonstrated by the S_N2 reactivity of compounds having alkyl branching at the β carbon atom. The reactivities of primary alkyl halides decrease by several orders of magnitude when branching at the β carbon atom is increased (Table 10.2). This de-

Table 10.2
Relative Rates of S_N2 Reaction of Branched Bromoalkanes

Bromoalkane	*Relative rate (I^-)*	*Relative rate ($CH_3CH_2O^-$)*
$CH_3—CH_2—Br$	1	1
$CH_3—CH_2—CH_2—Br$	0.8	0.3
$CH_3—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—CH_2—Br$	0.003	0.03
$CH_3—\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\vert}{C}}}}—CH_2—Br$	0.00001	0.000004

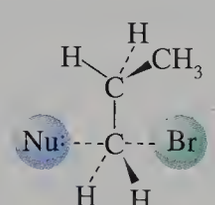
crease in the rate of reaction with increased branching results from steric hindrance. Branching hinders the approach of the nucleophile from the back side, as shown by the conformations in Figure 10.5. Certain conformations of 1-bromopropane and 1-bromo-2-methylpropane allow ready approach of the nucleophile. The methyl groups bonded to the β carbon are not near the path of the approaching nucleophile. However, every conformation of 1-bromo-2,2-dimethylpropane has a methyl group that interferes with the nucleophile.

Structural features that stabilize carbocations favor the S_N1 mechanism over the S_N2 mechanism. According to the Hammond postulate, structural features that stabilize the carbocation also lower the energy of the transition state in which the carbocation forms. Examples illustrating the effect of carbocation stability, and therefore the mechanism of the reaction, include allylic and benzylic compounds. In these compounds, the carbocations generated by unimolecular dissociation of the leaving group are resonance stabilized (Figure 10.6).

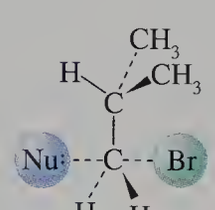


allyl carbocation benzyl carbocation

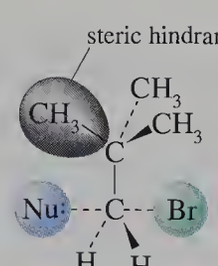
Although both carbocations are primary, substrates that can generate these ions tend to react by an S_N1 mechanism. In fact, these primary carbocations are approximately as stable as secondary alkyl carbocations. Furthermore, secondary resonance-stabilized



1-bromopropane



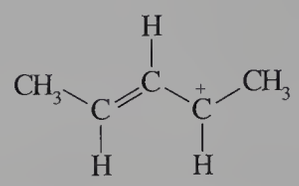
1-bromo-2-methylpropane



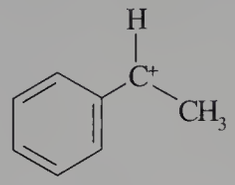
1-bromo-2,2-dimethylpropane

FIGURE 10.5 Steric Effects of β-Substituents in S_N2 Reaction
Both 1-bromopropane and 1-bromo-2-methylpropane have conformations in which the methyl groups do not interfere with the approach of the nucleophile. A methyl group of 1-bromo-2,2-dimethylpropane always interferes with the approach of the nucleophile.

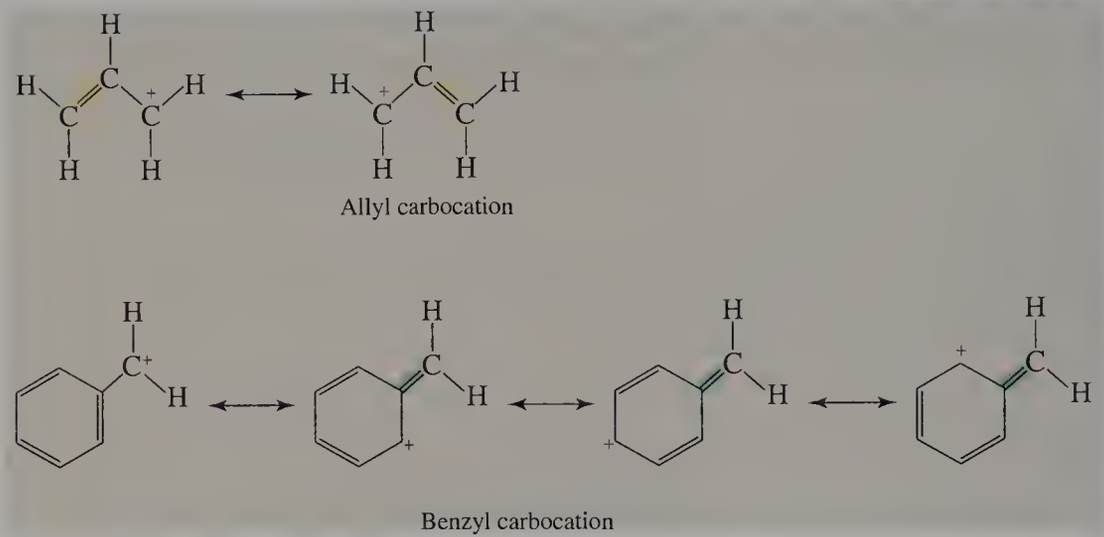
carbocations are as stable as tertiary alkyl carbocations. Any substrate that can form these secondary carbocations reacts by the S_N1 process.



secondary allylic carbocation



secondary benzylic carbocation



Allyl carbocation

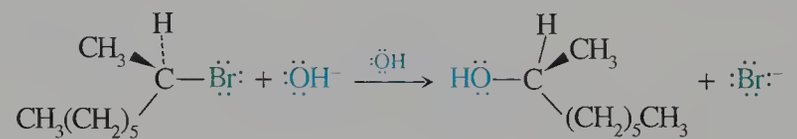
Benzyl carbocation

FIGURE 10.6
Resonance Forms of Allyl and Benzyl Carbocations

Effect of the Nucleophile

The nature of the nucleophile can favor one mechanism over the other, as is often the case for substrates such as secondary alkyl halides. If the nucleophile is a highly polarizable species, such as thiolate ion (RS^-), it tends to react with a substrate by an S_N2 reaction. On the other hand, if the nucleophile is an uncharged species, such as H_2O or CH_3OH, an S_N1 mechanism is more likely with the same substrate.

Section 10.2 described the reaction of the secondary alkyl halide (*R*)-(−)-2-bromooctane with water in a mixed solvent of water–ethanol, which occurs by an S_N1 process with some net inversion of configuration. In the presence of a better nucleophile, such as the hydroxide ion, the configuration of the substitution product is completely inverted. This reaction occurs by an S_N2 mechanism.

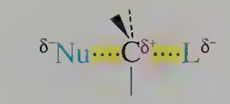


(*R*)-(−)-2-bromooctane

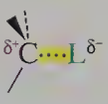
(*S*)-(−)-2-octanol

Effect of the Leaving Group

The leaving group affects the rate of both S_N2 and S_N1 reactions. Most leaving groups are either displaced as anions in S_N2 processes or are generated as anions by ionization in S_N1 processes. In the transition states for both the S_N2 and the S_N1 processes, some negative charge is transferred to the leaving group. Thus, stabilizing the charge of the anion increases the rate of either reaction.



charge development of the transition state for S_N2 reaction



charge development of the transition state for S_N1 reaction

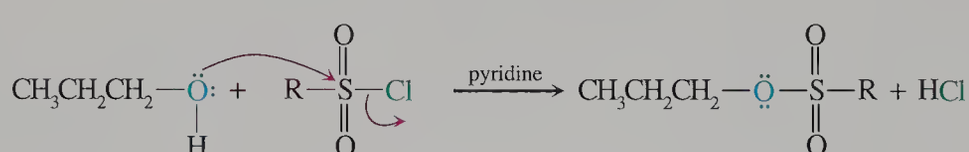
The stability of anions is inversely related to their basicity. As a result, the best leaving groups are the weakest bases. Consider the halide ions. Hydrogen iodide is the strongest acid of the hydrogen halides and iodide ion is the weakest base. Iodide and bromide are excellent leaving groups, chloride ion is a fair leaving group, and fluoride ion is a very poor leaving group. The relative rates of reaction for S_N2 reactions involving these leaving groups in a reaction with a common nucleophile are

leaving group:	I^-	Br^-	Cl^-	F^-
relative rate:	2	1	0.02	1×10^{-5}

The same general relationship is also found for S_N1 reactions, but the rate differences tend to be somewhat greater. In the S_N1 process, the carbon–halogen bond must be completely ruptured, compared to only partial bond breaking, aided by the simultaneous "push" of the nucleophile, in an S_N2 reaction.

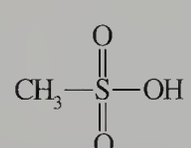
Because the hydroxide ion is a very strong base, it is an exceedingly poor leaving group regardless of the reaction mechanism. To displace oxygen from alcohols, the reaction must be carried out under acidic conditions where the hydroxyl group is protonated. Under these conditions, water is the leaving group. Loss of water as a leaving group occurs at a rate comparable to that of the chloride ion.

The ease with which an oxygen atom of an alcohol leaves can be increased by transforming the hydroxyl group into a sulfonate ester, which is prepared by treating an alcohol with a sulfonyl chloride. The reaction occurs by displacement of a chloride ion from the sulfur atom. Pyridine is used as a base to neutralize the HCl formed.

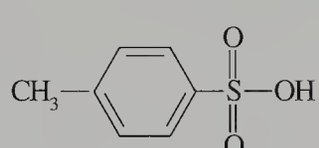


1-propanol (a sulfonyl chloride) (an alkyl sulfonate ester)

Sulfonate esters of sulfonic acids such as methanesulfonic acid or *p*-toluenesulfonic acid are prepared from the related sulfonyl chloride.

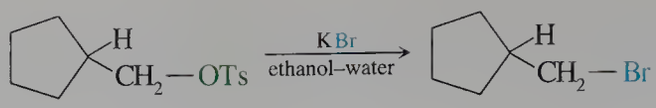


methanesulfonic acid

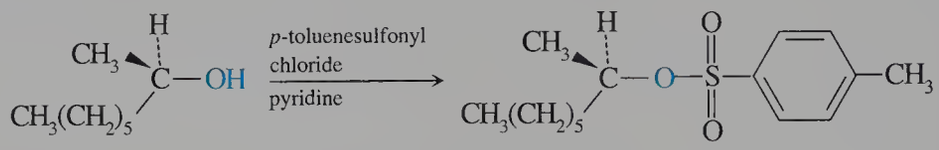


p-toluenesulfonic acid

Sulfonic acids are very strong acids, so the related conjugate bases, substituted sulfonate ions, are very weak bases. Thus, they are readily displaced by halides from alkyl methanesulfonates or alkyl *p*-toluenesulfonates (commonly called tosylates and abbreviated OTs in equations) to give an alkyl halide product. Primary alkyl tosylates react about 10^3 times as fast as even primary alkyl iodides. For example, the following reaction occurs readily.

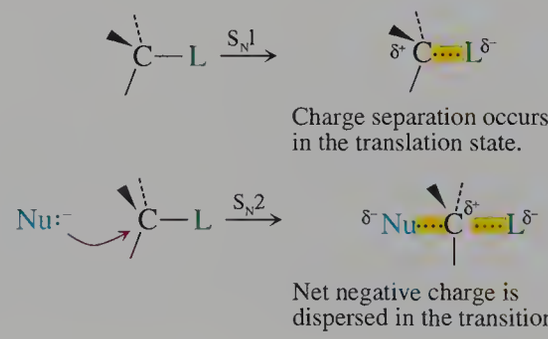


Related substitution reactions of the alcohol under acidic conditions are complicated by rearrangement reactions. Attempted direct conversion of the related alcohol to the bromide using HBr leads to rearrangement of products, including ring expansion, to give cyclohexane derivatives. Such complications are largely avoided by preparing a sulfonate ester of the alcohol and displacing the sulfonate ion with a halide ion. In the conversion of an alcohol into a tosylate, the configuration at a chiral center bonded to oxygen is not affected because the carbon–oxygen bond is not involved. The optical purity of the tosylate will thus equal that of the alcohol.



Effect of Solvent

Until now, we have not considered the role of solvent in nucleophilic substitution reactions, but the choice of solvent can tip the balance in favor of one substitution mechanism or another. We noted that secondary haloalkanes can react by either an S_N1 or an S_N2 mechanism. In these cases, the polarity of the solvent plays an important role. The S_N1 process forms a carbocation intermediate. Because a polar solvent stabilizes charged species better than a nonpolar solvent, a polar solvent increases the rate of S_N1 reactions. Reactions that occur via an S_N2 mechanism are also affected by solvent polarity, but the effect is smaller and depends on charge type. The nucleophilic reactant in an S_N2 reaction is usually negatively charged, and so is the transition state structure, where the negative charge is distributed over several atoms.



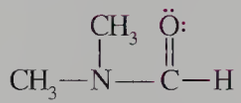
We recall that the dielectric constant (Section 2.9) indicates the ability of a solvent to stabilize charge and allow separation of oppositely charged particles. Thus, there is a correlation between the dielectric constant and the rate of S_N1 reactions such as the reaction of *tert*-butyl chloride with the solvent (Table 10.3).

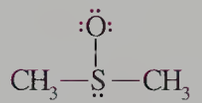
More interesting effects are seen in S_N2 reactions, in which the solvent affects nucleophilicity. Recall that a protic solvent interacts strongly with nucleophilic anions by forming hydrogen bonds with the unshared pairs of electrons on the nucleophiles (Figure 10.1). When the nucleophile is hydrogen bonded to the solvent, its nucleophilicity decreases.

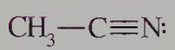
Polar solvents that do not have protons available for hydrogen bonding to nucleophiles are called polar **aprotic solvents**. Examples of polar aprotic solvents include dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetonitrile.

Table 10.3
Relative Rates of S_N1 Reaction and Solvent Polarity

Solvent	*Dielectric constant*	*Relative rate*
acetic acid	6	1
methanol	33	4
formic acid	58	5×10^3
water	78	1.5×10^5


dimethylformamide


dimethyl sulfoxide


acetonitrile

The electron pairs of the oxygen atoms of these aprotic solvents solvate cations, but not anions. For example, these solvents tie up the cation of KCN by orienting their negative ends around it (Figure 10.7). Because there are no electropositive hydrogen atoms in aprotic solvents, the CN^- ion cannot be effectively solvated; it is called a "naked anion". Consequently, the nucleophilicity of CN^- is greater in dimethyl sulfoxide than in ethanol (CH_3CH_2OH). Thus, an aprotic solvent such as dimethyl sulfoxide favors an S_N2 reaction.

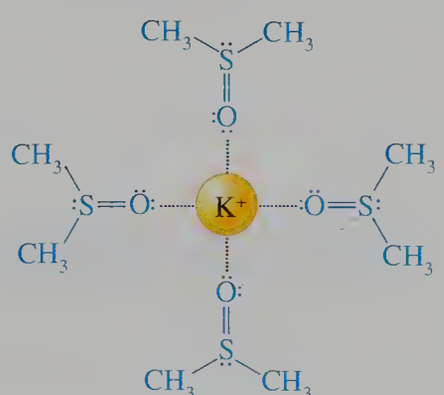
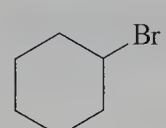


FIGURE 10.7 Solvation of Cations by Aprotic Solvents
Cations are solvated by aprotic solvents. The partner anion that is unsolvated is "naked" and is more nucleophilic.

The rates of substitution of 1-bromobutane by azide ion (N_3^-) in both protic and aprotic solvents, listed in Table 10.4, illustrate the difference in the nucleophilicity of solvated and unsolvated anions. The rates of reaction of the unsolvated anions in aprotic solvents are substantially larger than for the solvated anions in a protic solvent such as water.

Problem 10.8

Explain why the reaction of 3-bromocyclohexene with methanol (CH_3OH) is faster than the reaction of bromocyclohexane with methanol.


bromocyclohexane

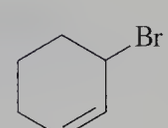

3-bromocyclohexene

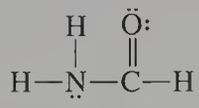
Table 10.4
Effect of Aprotic Solvent on an S_N2 Reaction

$CH_3(CH_2)_2CH_2Br + N_3^- \longrightarrow CH_3(CH_2)_2CH_2N_3 + Br^-$

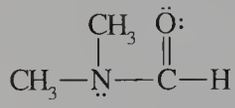
Solvent	*Relative rate*
CH_3OH	1
$H-\overset{\overset{O}{\|}}{C}-NH_2$	12
$H-\overset{\overset{O}{\|}}{C}-NHCH_3$	45
$H-\overset{\overset{O}{\|}}{C}-N(CH_3)_2$	1.2×10^6

Problem 10.9

The relative rates for the conversion of 1-iodobutane into 1-chlorobutane in methanol, formamide, and dimethylformamide are 1, 12, and 1.2×10^6, respectively. Explain the small rate difference between methanol and formamide and the large rate difference between formamide and dimethylformamide.



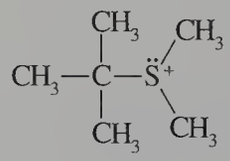
formamide



dimethylformamide

Problem 10.10

The following sulfonium compound reacts in ethanol to produce a mixture of substitution and elimination products 8 times as fast as the rate of reaction of *tert*-butyl chloride in ethanol. Explain why the rates differ for these two reactions, which occur by an S_N1 process.



Sample Solution

Because the reaction occurs by an S_N1 process, the faster rate of reaction for the sulfonium compound indicates that a better leaving group is released. The leaving groups for the two reactions are the chloride ion and CH_3SCH_3. Because HCl is a stronger acid than H_2S, we can predict that Cl^- is a weaker base than HS^-. Thus, the chloride ion is a better leaving group than HS^-. However, the comparison made in this problem is with leaving groups not having the same charge. Neutral leaving groups leave more easily than negatively charged leaving groups, and it is this feature that results in the observed order of reactivity.

Problem 10.11

The azide ion (N_3^-) is an excellent nucleophile. Write the Lewis structure for this linear triatomic ion, and explain the nucleophilicity of the ion using this structure.

10.4 Mechanisms of Elimination Reactions

In Chapter 8, we learned that the dehydrohalogenation reaction is used to prepare alkenes. The dehydration reaction is less useful because rearrangement of the carbocation, which is common, leads to mixtures of products having different carbon skeletons. However, the elimination of a hydrogen halide from an alkyl halide is a complex process. We must consider regiochemistry and stereoelectronic effects. These effects are related to the mechanism of the reaction, which may be either E2 or E1.

In this section, we will use concepts developed in the consideration of S_N2 and S_N1 reactions and consider how experimental variables affect the product formed in a dehydrohalogenation reaction. The structural features that control S_N2 and S_N1 substitution and E2 and E1 elimination reactions are related.

Like the S_N2 reaction mechanism, the E2 mechanism is a one-step, concerted process. In an E2 dehydrohalogenation reaction, the base (nucleophile) removes a proton on the β carbon atom. As the proton is removed, the leaving group departs and a double bond forms. The rate of an E2 reaction depends on the concentrations of the substrate and the base. If the substrate concentration is doubled, the reaction rate also doubles, as in S_N2 processes. Thus, the rates of E2 and S_N2 mechanisms are affected in the same way, and the two mechanisms compete with each other.

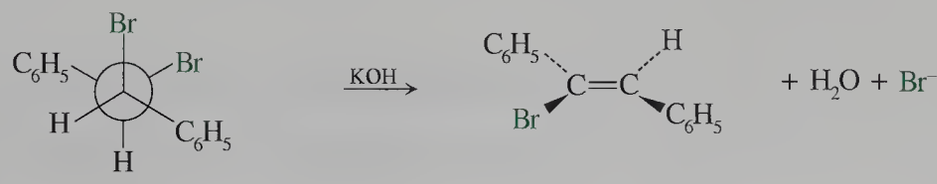
An E1 mechanism occurs in two steps, and the rate-determining step is the formation of a carbocation intermediate. An S_N1 reaction also proceeds in two steps, and the rate-determining step is formation of a carbocation intermediate. Therefore, an E1 mechanism competes with an S_N1 mechanism. Because the rate determining step of an E1 reaction involves only the substrate, the formation of the carbocation is a unimolecular reaction. The carbocation can either react with a nucleophile to form a substitution product or lose a proton to give an elimination product.

Stereoelectronic Effects in Elimination Reactions

Now we will consider important information about the chirality of the reactant and the product, which also clearly distinguishes between the E2 and E1 mechanisms. The stereochemical consequences of the two mechanisms differ because of the different structures of the intermediates and transition states in the respective mechanisms.

We recall that an E2 reaction requires a precise molecular arrangement, termed a stereoelectronic effect, which we illustrated using cyclic compounds such as *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexanes (Section 8.19). An E2 reaction is favored by the anti periplanar arrangement of the hydrogen and halogen atoms because this arrangement aligns the orbitals properly for the formation of the π bond. The anti periplanar arrangement is easily seen in a Newman projection formula (Figure 10.8). In terms of "electron pushing", we can visualize the process as removal of the proton to provide an electron pair that attacks the neighboring carbon atom from the back side to displace the leaving group in a reaction resembling an S_N2 process.

The stereoelectronic effect of the E2 reactions can also be established with conformationally flexible molecules, provided they have chiral centers. Consider the dehydrobromination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane. A specific staggered conformation is required to properly align the sp^3 hybrid orbitals of the C—H and C—Br bonds. This alignment can yield only the *Z* isomer in a concerted E2 reaction.



(1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane (*Z*)-1-bromo-1,2-diphenylethene

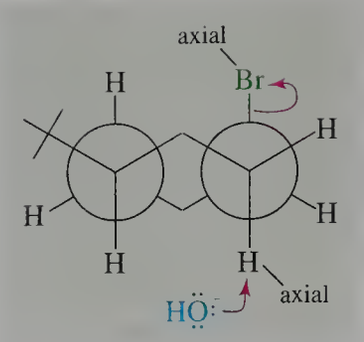


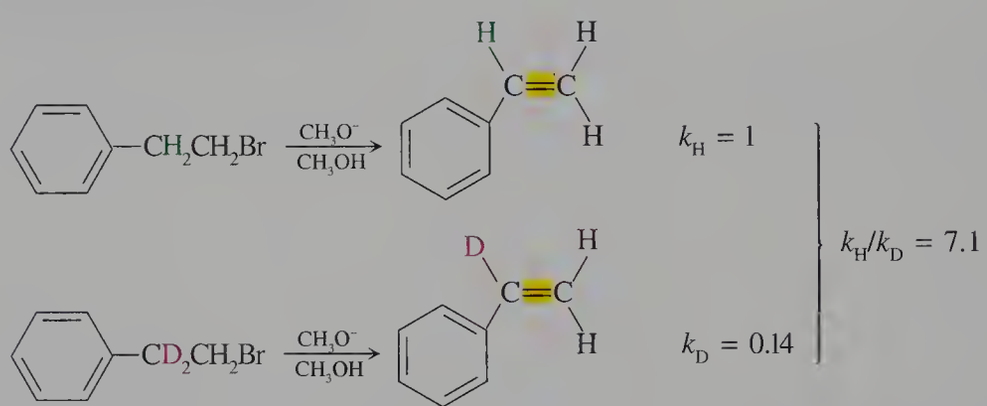
FIGURE 10.8 Stereoelectronic Effects in Elimination Reactions
The E2 reaction is most favorable when the hydrogen atom and the leaving group are anti periplanar as in *cis*-1-bromo-4-*tert*-butylcyclohexane. The Newman projection formula shows this favorable arrangement.

There is no special geometric requirement for an E1 reaction. Once the carbocation forms, any of the hydrogen atoms on carbon atoms adjacent to the positive center can be lost.

Deuterium Isotope Effect

The two elimination mechanisms can also be distinguished by a **primary deuterium isotope effect**, which measures the degree to which C—H and C—D bonds are broken in the rate-determining step. The carbon–hydrogen bond is slightly weaker than the carbon–deuterium bond. If a C—H bond is broken in a rate-determining step, then the corresponding C—D bond in the isotopically substituted compound would require more energy to reach the transition state. The deuterium-labeled compound therefore would react at a slower rate. If a C—H (or C—D) bond cleavage occurs in a fast step after the rate-determining step, the rates would be the same. This means that we can distinguish between the E2 and E1 reactions by placing deuterium where it can be abstracted by a base.

Let's see how the deuterium isotope effect is used to establish a mechanism for an elimination reaction. The rates of dehydrobromination of 1-bromo-2-phenylethane and 1-bromo-2,2-dideuterio-2-phenylethane are different.



The deuterium isotope effect, expressed as k_H/k_D, equals 7.1. This result tells us that the C—H and C—D bonds are broken in the rate-determining step.

There is no deuterium isotope effect in an E1 process. There is still a difference in the rates at which the C—H and C—D bonds are broken, but we can't directly measure it because the cleavage occurs after the rate-determining step.

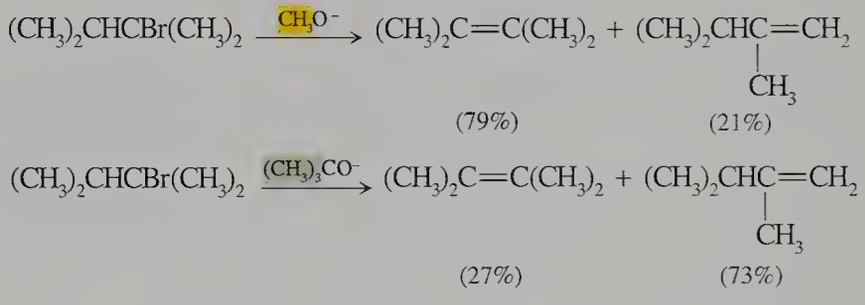
Base Strength and Competing E2 and E1 Mechanisms

Because the base participates in the rate-determining step of an E2 reaction, the rate of the reaction depends on the strength of the base. The steric size of the base af-

fects the regiochemistry of the reaction. Because the base is not involved in the rate-determining step of the E1 reaction, it might appear reasonable to expect no effect on the composition of the product mixture. Such a conclusion is valid if the base is weak, such as an alcohol solvent. Without a strong base, a proton transfer occurs from the carbocation to the solvent in the E1 process. However, a strong base causes a competing E2 reaction. As a result, the products arise from two competing processes.

Steric Effect of Base on Regiochemistry

In Section 10.1, we learned that the difference in the sizes of the methoxide ion and the *tert*-butoxide ion causes marked differences in the rates of S_N2 reactions. We noted that steric factors are much less important in determining the ease of abstraction of a proton. However, such effects do exist, and they are in the direction that we would expect. More highly hindered bases tend to abstract the least sterically hindered protons. This fact is established for the reaction of 2-bromo-2,3-dimethylbutane with various alkoxide ions. The major product with methoxide ion is the more highly substituted alkene—the Zaitsev product. However, with *tert*-butoxide, the major product is the least substituted alkene.



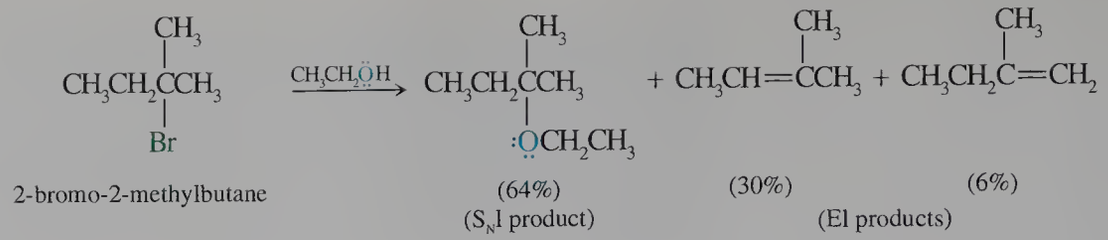
Thus, we have now established that sterically hindered bases not only tend to increase the proportion of E2 to S_N2 products but they also increase the amount of the least substituted alkene—the "non-Zaitsev" product.

10.5 Effect of Structure on Competing Reactions

Let's now examine the variety of product mixtures that result from competing substitution and elimination processes. We will divide our discussion according to the type of haloalkane undergoing reaction.

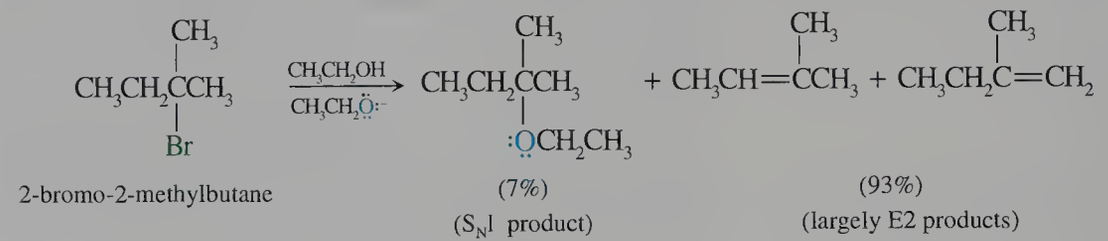
Tertiary Haloalkanes

Tertiary haloalkanes undergo substitution reactions only by an S_N1 mechanism because there is too much steric hindrance for an S_N2 reaction to occur. However, a tertiary haloalkane can undergo an elimination reaction by either an E2 or an E1 process. The mechanism depends on the basicity of the nucleophile and the polarity of the solvent. If the nucleophile is a weak base, S_N1 and E1 processes compete, and the amounts of the two types of products depend only on the carbocation formed. For example, 2-bromo-2-methylbutane reacts in ethanol to give about 64% of the product from an S_N1 process. The ratio of S_N1 to E1 product is about 2:1.



2-bromo-2-methylbutane (64%, S_N1 product) + (30%) + (6%) (El products)

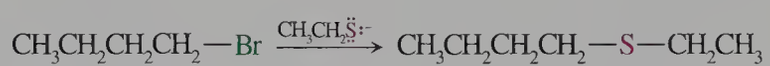
However, if sodium ethoxide, a strongly basic nucleophile, is added to the ethanol, an E2 process competes with the substitution reaction. The amount of elimination product is increased to a total of about 93% of the product mixture. Only 7% of the ether product is formed. Most of the elimination product is derived from the E2 process.



2-bromo-2-methylbutane (7%, S_N1 product) + (93%, largely E2 products)

Primary Haloalkanes

Primary haloalkanes can undergo either S_N2 or E2 reactions. They do not undergo S_N1 or E1 reactions because a primary carbocation is very unstable. Primary haloalkanes react with strongly nucleophilic, weakly basic reactants, such as ethyl thiolate ($CH_3CH_2S^-$), exclusively by an S_N2 process. However, a primary haloalkane reacts with ethoxide ion, a weaker nucleophile but a stronger base than ethyl thiolate, to give some elimination product.



1-bromobutane (exclusive product, S_N2 mechanism)

1-bromobutane (90%, S_N2 mechanism) + (10%, E2 mechanism)

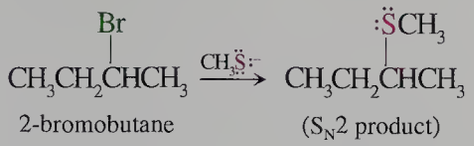
If a primary haloalkane is treated with *tert*-butoxide ion instead of ethoxide, the amount of elimination product increases significantly. The *tert*-butoxide ion is not only more basic than the ethoxide ion, it is also much more sterically hindered. The combination of these two factors favors elimination by an E2 process over substitution by an S_N2 process.

1-bromobutane (15%, S_N2 product) + (85%, E2 product)

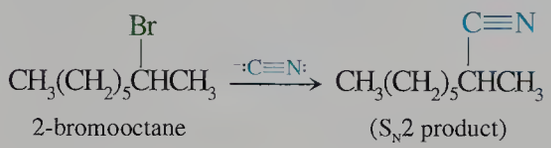
Secondary Haloalkanes

Secondary haloalkanes can react by S_N2, E2, S_N1, and E1 mechanisms, and it is sometimes difficult to predict which of these processes will occur in a given reaction. How-

ever, secondary haloalkanes tend to react with strong nucleophiles that are weak bases, such as thiolates or cyanide ion, by an S_N2 process.

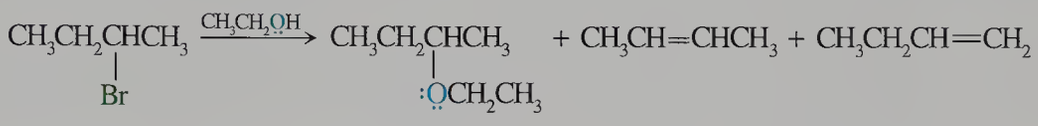


2-bromobutane (S_N2 product)



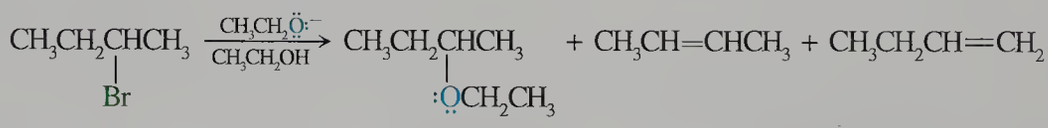
2-bromooctane (S_N2 product)

On the other hand, a secondary haloalkane tends to react with weak nucleophiles that are also weak bases, like ethanol, by an S_N1 process with some accompanying E1 product.



(95%) (S_N1 product) (4%) (1%) (El products)

We can tip the scales in the other direction by adding sodium ethoxide to ethanol. By adding this strong base, we find that the product of the S_N1 reaction drops to 18% of the total, and E2 products account for the rest.



(18%) (S_N1 product) (66%) (16%) (E2 products)

Problem 10.12

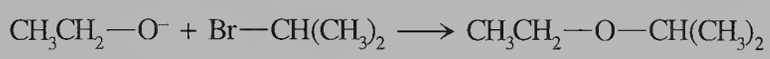
The ratio of elimination to substitution products for the reaction of 2-bromo-2-methylbutane depends on the concentration of the base. For 0.05 M and 1.0 M sodium ethoxide, the percentages of elimination product are 56% and 98%, respectively. Explain these data.

Problem 10.13

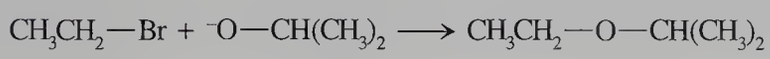
The amount of elimination product for the reaction of 1-bromooctadecane with an alkoxide in the corresponding alcohol solvent is about 1% for methoxide ion and 85% for *tert*-butoxide ion. Explain these data.

Problem 10.14

Which of the following two methods of preparing the ether $CH_3CH_2OCH(CH_3)_2$ will give the better yield?



ethoxide 2-bromopropane



bromoethane isopropoxide

Sample Solution

The reactants in both reactions are a haloalkane and the conjugate base of an alcohol, an alkoxide. The ether has two different alkyl groups bonded to oxygen, one from the alkoxide and the other from the haloalkane.

The first reaction is a nucleophilic displacement at a secondary center by a nucleophile that is also a strong base. A competing elimination reaction to yield propene will also occur, thus decreasing the yield of the ether product. The second reaction occurs by an S_N2 reaction at a primary center, which tends to occur with little competition from an elimination reaction. Therefore, the second reaction is the better way to make the desired product.

EXERCISES

Nucleophilicity

10.1 Hydroxylamine (NH_2OH) is a nucleophile. Write its Lewis structure. Which atom supplies the electrons in nucleophilic substitution reactions?

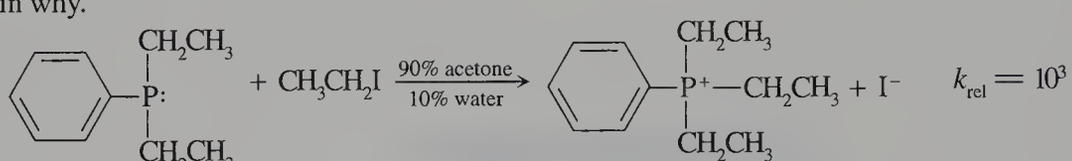
10.2 The thiocyanate ion (SCN^-) reacts with alkyl halides to give thiocyanate products (R—SCN). The cyanate ion (OCN^-) reacts to form isocyanate products (R—NCO). Write the Lewis structures of the ions. Explain the difference in the sites of reactivity for the two ions.

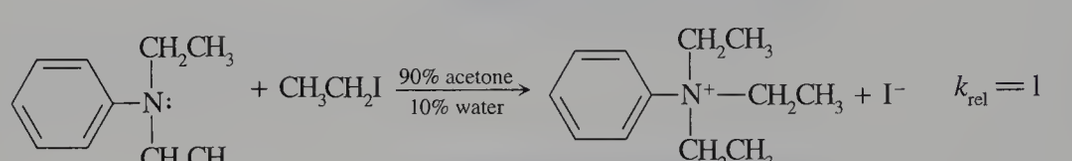
10.3 Reaction of methoxide ion with an alkyl halide to give an ether product is about 100 times as fast as reaction of acetate ion with an alkyl halide to give an ester. Explain why.

$$CH_3O^- + CH_3{-}I \longrightarrow CH_3{-}O{-}CH_3$$

$$CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O^- + CH_3{-}I \longrightarrow CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O{-}CH_3$$

10.4 Diethylphenylphosphine reacts with iodoethane about 10^3 times as fast as the nitrogen analog, diethylaniline, does. Explain why.





10.5 Dimethyl sulfide, $(CH_3)_2S$, reacts with iodomethane to displace iodide ion twice as fast as diethyl sulfide, $(CH_3CH_2)_2S$, does. Explain why.

10.6 Triethylarsine, $(CH_3CH_2)_3As$, reacts with iodomethane only four times as fast as dimethyl selenide, $(CH_3)_2Se$, does. Compare this difference in rate with the rate difference of ammonia relative to water, about 3×10^5.

Stereochemistry of Substitution Reactions

10.7 Reaction of (*R*)-(−)-2-butanol with HBr yields a mixture of 87% (*S*)-(+)-2-bromobutane and 13% (*R*)-(−)-2-bromobutane. What is the optical purity of the product? What is the mechanism for this substitution reaction?

10.8 Reaction of (*R*)-2-methyl-1-butanol with HBr yields 1-bromo-2-methylbutane. Predict the configuration of the product. What is the mechanism for this substitution reaction?

10.9 The rate of incorporation of radioactive iodide into optically active 2-iodooctane in acetone as solvent was studied by Hughes. He found that the rate of racemization of 2-iodooctane was twice the rate of incorporation of radioactive iodine. Explain how these data support the model of an S_N2 mechanism.

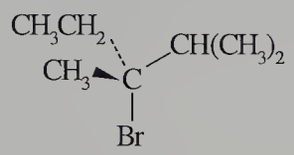
$$R{-}I + {}^*I^- \longrightarrow R{-}{}^*I + I^-$$

10.10 The reaction of (*S*)-2-bromooctane with cyanide ion gives a cyano compound with an *R* configuration. However, reaction of (*S*)-2-bromooctane with iodide ion followed by reaction of the alkyl iodide with cyanide ion gives a cyano compound with the *S* configuration. Explain these data.

10.11 *trans*-1-Chloro-3-methylcyclopentane reacts with sodium iodide in acetone to give *cis*-1-iodo-3-methylcyclopentane. What is the mechanism of this reaction?

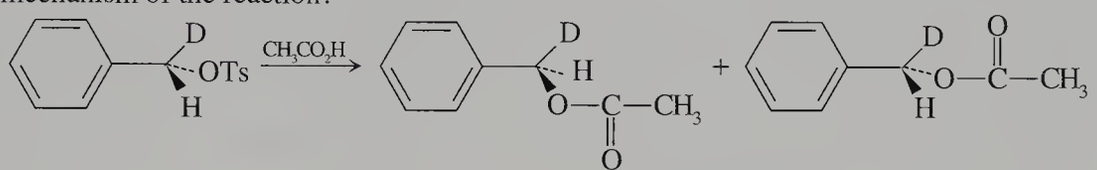
10.12 Write the product expected from the reaction of *cis*-1-bromo-2-methylcyclopentane with cyanide ion.

10.13 The following compound has the *R* configuration. Draw the product expected from the reaction of this compound in ethanol, indicating the stereochemistry.



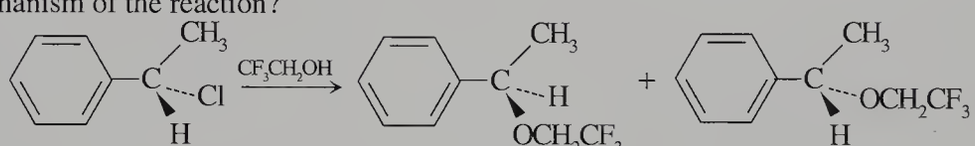
10.14 (*S*)-1-Chloro-1-phenylethane reacts in a 20% water–80% acetone solution to give a 51:49 ratio of (*R*)– and (*S*)-1-phenyl-1-ethanols. Explain why the product is highly racemic in spite of the fact that the reactant is a secondary alkyl halide.

10.15 The reactant in the following reaction has the *S* configuration. Based on the composition of the product mixture, what is the mechanism of the reaction?



(93%) (7%)

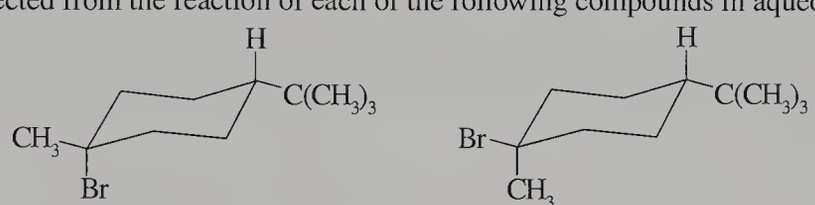
10.16 The reactant in the following reaction has the *S* configuration. Based on the composition of the product mixture, what is the mechanism of the reaction?



(54%) (46%)

10.17 What is the configuration of the tosylate prepared from (*R*)-2-butanol? What is the configuration of the iodide obtained by reacting that tosylate with iodide ion in acetone?

10.18 Write the product expected from the reaction of each of the following compounds in aqueous acetone.



I II

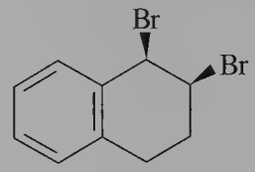
Reactivity in Substitution Reactions

10.19 1-Bromo-1,1-diphenylethane reacts very rapidly in ethanol. Explain why.

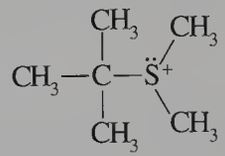
10.20 4-Chloro-2,2,4,6,6-pentamethylheptane reacts in aqueous acetone about 500 times as fast as *tert*-butyl chloride does. Explain why.

10.21 3-Bromo-1-butene and (*E*)-1-bromo-2-butene react at the same rate in aqueous acetone. Explain why. An identical mixture of two substitution products is obtained from either compound. What are the structures of the products?

10.22 The following compound reacts in methanol to rapidly replace one of the two bromine atoms by a methoxy group. Which bromine atom is replaced?



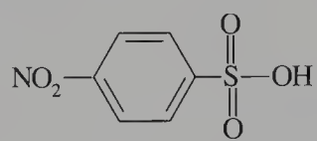
10.23 The following sulfonium ion reacts in 80% ethanol–20% water to give 36% 2-methyl-1-propene. The remaining 64% of the product is a mixture of two substitution products. What are the substitution products? *tert*-Butyl chloride reacts under the same conditions to give the identical mixture of products. Why?



10.24 The relative rates of substitution of bromide by ethoxide in ethanol for methyl, ethyl, propyl, and butyl bromides are 1, 0.057, 0.018, and 0.013, respectively. Explain these data, taking into account the magnitude of the change in the relative rates between each member of this homologous series.

10.25 Trifluoromethanesulfonyl chloride reacts with alcohols to form sulfonate esters. Would you expect the "trifylates" to be more or less reactive than the methanesulfonate esters?

10.26 A nitro group is electron withdrawing. Would you expect the sulfonate esters of the following sulfonic acid to be more or less reactive than the tosylates?

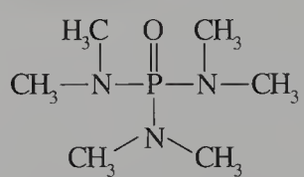


Solvent Effect in Substitution Reactions

10.27 Explain why ethanol (CH_3CH_2OH) can solvate both cations and anions. Explain why dimethyl ether, $(CH_3)_2O$, is a poorer solvent for ionic compounds. Discuss the solvation characteristics of both solvents for both cations and anions.

10.28 *trans*-1-Iodo-3-methylcyclopentane reacts with KF in DMF to give a fluoro compound. What is its configuration? The iodo compound reacts with KF in ethanol to give products that do not contain fluorine. Explain these data.

10.29 The structure of hexamethylphosphoramide is shown below. Its dielectric constant is 30. Compare the expected solvent properties with those of other solvents discussed in Section 10.3.



10.30 The rate constant for the displacement of iodide from iodomethane by fluoride ion is 10^6 times faster in dimethylformamide as it is in methanol. Explain why.

10.31 Methyl tosylate reacts with halide ions in water. The rate constants for the reaction in water stand in the order $k_{I^-} > k_{Br^-} > k_{Cl^-}$. The rate constants for the reactions in acetone stand in the order $k_{I^-} < k_{Br^-} < k_{Cl^-}$. Explain these data.

10.32 The equilibrium constant for the following reaction is 15 in water and 0.6 in acetone. Explain these data.

$$CH_3Br + I^- \rightleftharpoons CH_3I + Br^-$$

Elimination Reactions

10.33 Attempted displacement of iodide ion by fluoride in acetone usually fails because elimination products result. Explain why elimination is favored over substitution.

10.34 The product mixture obtained in the reaction of isobutyl bromide with sodium ethoxide in ethanol contains 62% 2-methyl-1-propene. The reaction using potassium *tert*-butoxide in *tert*-butyl alcohol contains 92% 2-methyl-1-propene. Explain why.

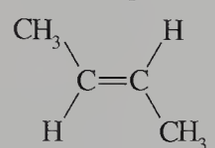
10.35 The product mixture obtained in the reaction of *sec*-butyl bromide with 1 M sodium ethoxide in ethanol contains 78% unsaturated material. What are the products and which of them should predominate? Using 4 M sodium ethoxide in ethanol, the product mixture is 91% unsaturated material. Why?

10.36 The unsaturated compounds obtained in the reaction of 2-bromo-2,3-dimethylbutane with the alkoxide of 3-ethyl-3-pentanol are 92% 2,3-dimethyl-1-butene and 8% 2,3-dimethyl-2-butene. Compare these data with the data for reaction of *tert*-butoxide with the same compound (Section 10.4).

10.37 E2 reactions of tosylates occur using alkoxide ions as bases in the related alcohol solvent. Determine the stereochemistry of the 2-phenyl-2-butene formed from reaction of the tosylate of (2R,3R)-3-phenyl-2-butanol.

10.38 The tosylate of *cis*-2-phenylcyclohexanol undergoes an elimination reaction much more rapidly with *tert*-butoxide in *tert*-butyl alcohol than does the trans isomer. The product is exclusively 1-phenylcyclohexene. Explain these data.

10.39 The following products are obtained from the E2 reaction of (2*S*,3*R*)-2-bromo-3-deuteriobutane using sodium ethoxide in ethanol. Explain why. Predict the products from the E2 reaction of (2*S*,3*S*)-2-bromo-3-deuteriobutane.



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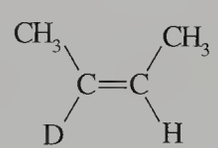
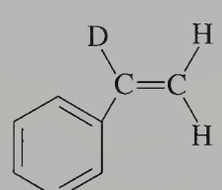
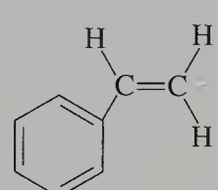


II

10.40 The E2 reaction of 1-bromo-2-deuterio-2-phenylethane gives the following compounds. Explain why the indicated percentage of each compound is formed.

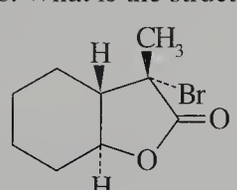


(87%)

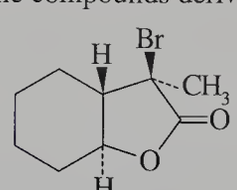


(13%)

10.41 The E2 reaction of each of the following compounds with sodium methoxide in methanol proceeds regiospecifically to give different compounds. What is the structure of the compounds derived from each stereoisomer?

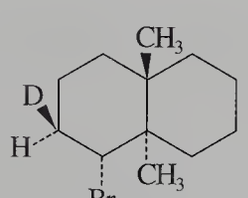


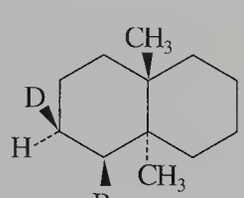
I

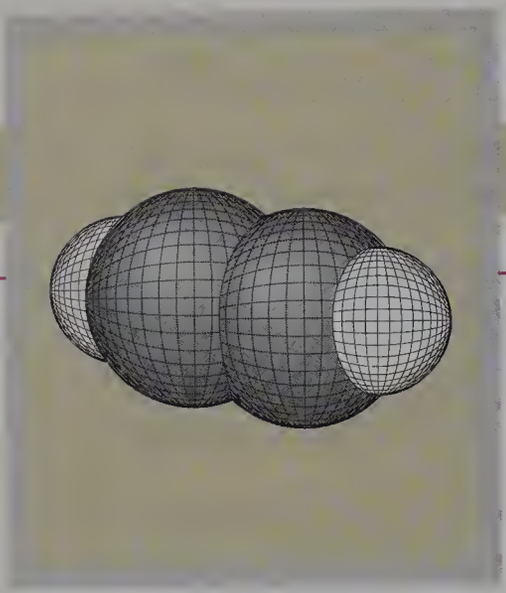


II

10.42 Predict the E2 product formed in the reaction of each of the following compounds. Which compound reacts at the faster rate?





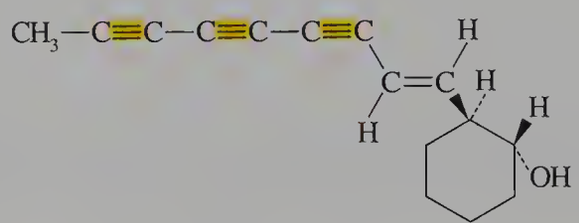


11

Alkynes

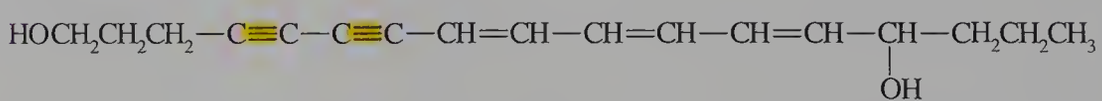
11.1 Occurrence and Uses of Alkynes

Like alkenes, alkynes, which contain one or more triple bonds, are found in natural products, although less commonly and not in petroleum. Many natural alkynes contain several triple bonds, and are physiologically active. For example, the triyne ichthyothereol—secreted from the skin of a species of frog that lives in the Lower Amazon Basin—is a mucous membrane irritant that wards off predators. The Indians of the area coat their arrowheads with the secretion. When the arrow pierces the skin of the prey, the compound acts on the nervous system and causes convulsions.



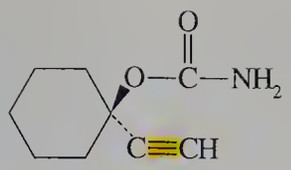
ichthyothereol

Natural products with several triple bonds are also found in plants. Cicutoxin, a poisonous compound contained in water hemlock, is the compound that was used in the execution of Socrates.

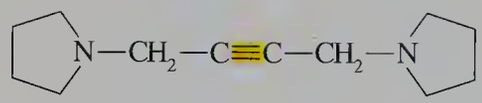


cicutoxin

Some synthetic drugs contain a triple bond. For example, ethinamate is a sedative and hypnotic drug, and tremorine is used to treat Parkinson's disease.

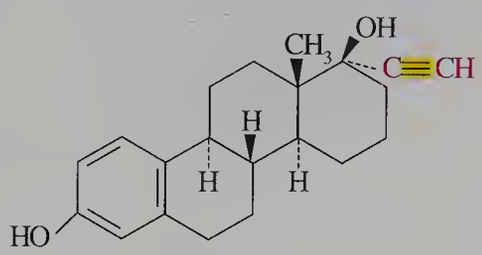


ethinamate

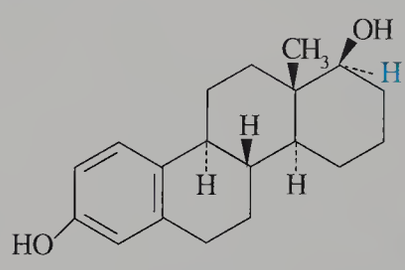


tremorine

Synthetic estrogens such as 17-ethynylestradiol are birth control agents. Estradiol, the female sex hormone, is a secondary alcohol that cannot be administered orally because it would be rapidly oxidized by the liver. The synthetic estrogens contain an ethynyl group (—C≡CH), and are tertiary alcohols that are not oxidized in metabolic reactions. The ethynyl group in these compounds is located so that the hydroxyl group has the same stereochemistry as the natural estradiol.



17-ethynylestradiol



estradiol

11.2 Structure and Properties of Alkynes

The simplest alkyne, C_2H_2, is commonly called acetylene. Unfortunately, the common name ends in -ene, which suggests that the compound contains a double bond. Such confusion is one reason IUPAC names are so important for clear communication in chemistry. The IUPAC name for C_2H_2 is ethyne.

The four atoms of acetylene are collinear. Each H—C≡C bond angle is 180°. In alkynes, the two triple-bonded carbon atoms and the two atoms directly attached to them all lie in a straight line. The *sp* hybridization of the carbon atoms of acetylene is described in Section 1.18. The contributions of the *sp* hybrid orbitals and 2*p* orbitals to the triple bond in acetylene are illustrated in Figure 11.1.

Classification of Alkynes

The classes of alkynes are more limited than the classes of alkenes because only one alkyl group can bond to each *sp*-hybridized carbon atom of the triple bond. If one alkyl group is bonded to one of the carbon atoms of the triple bond, the compound is a **monosubstituted** alkyne (R-C≡C-H). This is also called a **terminal** alkyne because the triple bond is at the end of the carbon chain. When alkyl groups are bonded to both carbon atoms of the triple bond, the compound is a **disubstituted**, or **internal**, alkyne (R—C≡C—R).

Hybridization, Bond Length, and Bond Energy

The *sp* hybrid orbital has 50% *s* character, which is greater than the 33% and 25% *s* characters of the sp^2 and sp^3 hybrid orbitals, respectively. We recall that as the percent *s* character of hybrid orbitals increases, the electrons in the hybrid orbitals are closer to the nucleus. Therefore, the bonding electrons in an *sp* hybrid orbital of a C—H bond in acetylene are closer to the nucleus than the electrons in the hybrid or-

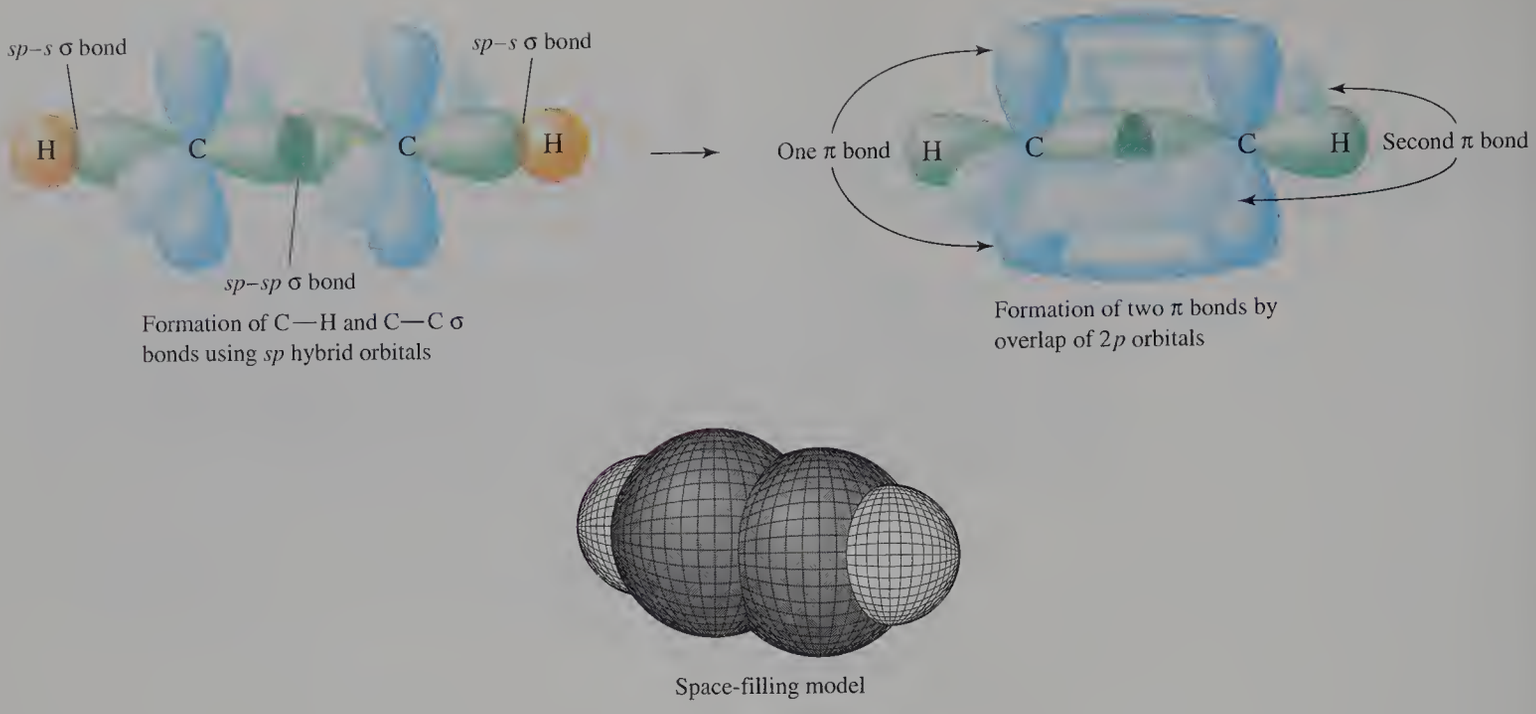
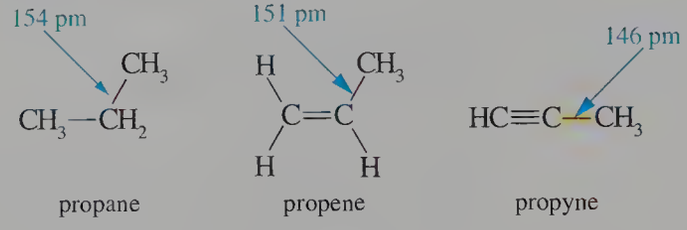


FIGURE 11.1 Structure of Acetylene

bital of the C—H bonds of ethylene or ethane. The greater *s* character of the σ bonds of acetylene and alkynes affects their physical properties.

The length of a bond between a carbon atom and another atom is shortest for a carbon atom with *sp* hybrid orbitals. The carbon–hydrogen bond lengths for acetylene, ethylene, and ethane are 105, 109, and 111 pm, respectively. The C—H bond energy of acetylene is 536 kJ mole^{-1} (128 kcal mole^{-1}), larger than the 470 and 422 kJ mole^{-1} values for the C—H bond energies of ethylene and ethane.

The length of a σ carbon–carbon bond depends on the hybridization of both carbon atoms. For example, the *sp*-*sp*^{3} C—C bond of propyne is shorter than both the *sp*^{2}-*sp*^{3} C—C bond of propene and the *sp*^{3}-*sp*^{3} C—C bond of propane.



The carbon–carbon bond length of acetylene is 121 pm, shorter than the 134 and 153 pm of ethylene and ethane, respectively. The shorter carbon–carbon triple bond length of acetylene is partly due to the *sp* hybridization of the two orbitals used to form the C—C σ bond. The decrease in bond length caused by one *sp*-hybridized carbon atom in propyne (compared to propane) could lead us to predict that the length of a σ bond between two *sp*-hybridized carbon atoms would be about 138 pm. However, the larger number of bonds joining the carbon atoms further decreases the carbon–carbon bond length of acetylene. The shared pairs of electrons in the two π bonds draw the nuclei of the carbon atoms closer together than does the single shared electron pair in the π bond of ethylene.

The C≡C bond energy of acetylene is 820 kJ mole^{-1} (196 kcal mole^{-1}), and the C—C bond energy of ethane is 368 kJ mole^{-1} (88 kcal mole^{-1}). The σ bond

energies should increase slightly with increasing *s* character. Thus, the σ bond energy of acetylene must be equal to or slightly larger than 368 kJ mole^{-1}. Because the C≡C bond energy is less than three times that of the C—C bond energy of ethane, we conclude that each of the two π bonds is substantially weaker than the σ bond.

Heats of Formation

We recall that the heat of formation is the enthalpy change for the formation of one mole of a compound from its elements in their standard states. Heats of formation often are calculated by the arithmetic combination of heats of reactions because physical measurement of the direct combination reaction to form a compound is frequently not possible. A case in point is the heat of formation of alkynes, which cannot be synthesized by direct combination of carbon and hydrogen.

Most organic compounds have negative heats of formation. However, a few low molecular weight compounds have positive heats of formation because they contain multiple bonds that are less stable than carbon–hydrogen and carbon–carbon single bonds. For example, the heats of formation of acetylene and ethylene are +227 and +52.1 kJ mole^{-1}, respectively, whereas the heat of formation of ethane is −84.3 kJ mole^{-1}. The positive heats of formation of ethylene and acetylene indicate that the π bonds of these unsaturated compounds are not as stable as σ bonds. The heats of formation of some alkynes are listed in Table 11.1.

TABLE 11.1
Heats of Formation of Alkynes

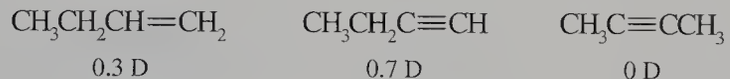
Compound	ΔH_f° *(kJ mole^{-1})*
propyne	185.0
1-butyne	165.7
2-butyne	147.7
1-pentyne	144.0
2-pentyne	128.6
3-methyl-1-butyne	136.1
1-hexyne	123.4
1-heptyne	102.8
1-octyne	82.2
1-nonyne	61.7
1-decyne	41.1

Physical Properties of Alkynes

The general molecular formula for alkynes is C_nH_{2n-2} because an alkyne has four fewer hydrogen atoms than an alkane with the same number of carbon atoms. The physical properties of the homologous series of alkynes are similar to those of the homologous series of alkenes (C_nH_{2n}) and alkanes (C_nH_{2n+2}). Unsaturated hydrocarbons are essentially nonpolar.

The members of each series containing fewer than five carbon atoms are gases at room temperature. The boiling points of the alkynes, like those of alkanes and alkenes, increase as the number of carbon atoms increases because the London forces increase (Table 11.2). Branching tends to decrease the boiling point.

Terminal alkynes have dipole moments that are larger than the dipole moments of terminal alkenes. Disubstituted alkynes with identical or even similar alkyl groups have no dipole moment.



Chemical Properties of Alkynes

We have learned that the π bond of alkenes reacts in characteristic ways with electrophiles, free radicals, oxidizing agents, and reducing agents. Alkynes, with two π bonds, undergo similar regiospecific reactions. However, both π bonds of alkynes can react, and this fact requires consideration of experimental conditions (Sections 11.6 and 11.7). First, do the conditions for the addition of a reagent to one π bond to give an alkene allow addition to the second π bond? Second, we have to consider the regiospecificity of the addition reactions to the first and second π bonds. Third, we have

TABLE 11.2
Physical Properties of Alkynes

Compound	*Boiling point (°C)*	*Density (g/cm³)*
1-butyne	8.1	0.678
2-butyne	27	0.691
1-pentyne	40.2	0.690
2-pentyne	56.1	0.711
3-methyl-1-butyne	29	0.666
1-hexyne	71.3	0.716
2-hexyne	84	0.732
3-hexyne	81.5	0.723
4-methyl-1-pentyne	61.1	0.709
4-methyl-2-pentyne	72.0	0.716
3,3-dimethyl-1-butyne	39.5	0.669
1-heptyne	99.7	0.733
2-heptyne	112	0.748
3-heptyne	105.5	0.753
5-methyl-1-hexyne	92	0.727
5-methyl-2-hexyne	102	0.738
2-methyl-3-hexyne	95.2	0.726
4,4-dimethyl-1-pentyne	76.1	0.714
4,4-dimethyl-2-pentyne	82.3	0.718
3-ethyl-1-pentyne	88	0.724

to learn how to control the stepwise progression of such reactions. Fourth, because alkenes can form as either *E* or *Z* isomers, we need to establish the stereospecificity of the first addition reaction.

Problem 11.1

Based on hybridization considerations alone, predict the C-2 to C-3 bond length of 1-buten-3-yne.

$$CH_2{=}CH{-}C{\equiv}CH$$

1-buten-3-yne

Problem 11.2

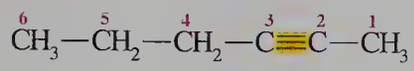
The heats of formation of 1-butyne and 2-butyne are 165.2 and 145.9 kJ $mole^{-1}$, respectively. Which compound is more stable? Assuming that the two compounds could be equilibrated, estimate the equilibrium constant at 25 °C. What assumption is required for this estimate?

11.3 Nomenclature

The IUPAC rules for naming alkynes are similar to those for alkenes. As a branching group, the unit —C≡CH is named ethynyl. The next homolog, $—CH_2—C{\equiv}CH$, is 2-propynyl; the common name is propargyl.

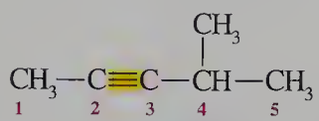
1. Use the longest continuous chain containing the triple bond as the parent.
2. Give the parent the same stem name as an alkane, but replace *-ane* with *-yne*.

3. Number the carbon atoms consecutively from the end of the chain nearer the triple bond. Use the number of the first carbon atom with the triple bond as a prefix separated by a hyphen from the parent name.



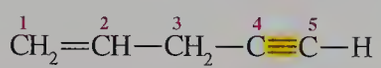
This compound is numbered from right to left. It is 2-hexyne.

4. Alkyl groups are named, and their positions on the chain determined, by the numbering established by rule 3.



This compound is 4-methyl-2-pentyne.

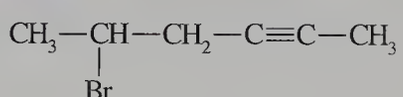
5. Compounds with multiple triple bonds are diynes, triynes, and so on. Compounds with both double and triple bonds are called enynes, not ynenes. Start the numbering of compounds with both double and triple bonds from the end nearer the first multiple bond, regardless of type. When a choice is possible, assign double bonds lower numbers than triple bonds.



This is 1-penten-4-yne, not 4-penten-1-yne.

Problem 11.3

Why is 2-bromo-4-hexyne an incorrect name for the following compound? What is the correct IUPAC name?



Sample Solution

The name is incorrect because it is based on using bromine rather than the triple bond to establish the numbering of the carbon chain. Starting from the right carbon atom places the triple bond at the C-2 atom. The bromine atom is on the C-5 atom and the correct name is 5-bromo-2-hexyne.

Problem 11.4

1,3,11-Tridecatriene-5,7,9-triyne is a compound found in safflowers and used as a chemical defense against nematode infestations. Write the structure of the compound.

Problem 11.5

Write the structure of each of the following compounds.

(a) 1-ethynylcyclohexanol (b) cyclododecyne (c) 4-methyl-1,6-heptadiyne

11.4 Acidity of Terminal Alkynes

Terminal alkynes are weak acids, but a very strong base may remove a proton from the terminal carbon atom to give a carbanion called an **alkynide** ion. The common name for an alkynide ion is the **acetylide** ion.

$$R{-}C{\equiv}C{-}H + B^- \rightleftharpoons R{-}C{\equiv}C{:}^- + BH$$

(an alkynide ion)

Formation of a carbanion, the conjugate base of a hydrocarbon, is generally less favorable than the ionization of acids in which a hydrogen atom is bonded to electronegative atoms such as oxygen or nitrogen. Because carbon is less electronegative than these two elements, the K_a values of hydrocarbons are very small.

$CH_3{-}CH_3$	$CH_2{=}CH_2$	$HC{\equiv}CH$
$K_a \approx 10^{-50}$	$K_a \approx 10^{-44}$	$K_a \approx 10^{-25}$

The C—H acid dissociation constant, K_a, related to the hybridization of the carbon atom, increases for carbon atoms in the order $sp^3 < sp^2 < sp$. This order of acidities parallels the percent *s* character of the hybrid orbitals. Because an *sp* hybrid orbital has more *s* character than an sp^2 or sp^3 orbital, its electrons are located closer to the nucleus, and a hydrogen atom bonded to an *sp*-hybridized carbon atom can be more easily removed as a proton.

Although acetylene and terminal alkynes are much stronger acids than other hydrocarbons, they are still very weak acids. The hydroxide ion is not a strong enough base to convert a terminal alkyne to its conjugate base to any significant degree.

$$R{-}C{\equiv}C{-}H + {:}\ddot{O}H \rightleftharpoons R{-}C{\equiv}C{:}^- + HOH \qquad K_{eq} \approx 10^{-9}$$

In fact, the conjugate base of an alkyne rapidly and quantitatively converts to the alkyne whenever it reacts with compounds containing hydroxyl groups (such as water, alcohols, and carboxylic acids).

$$R{-}C{\equiv}C{:}^- + H_2O \longrightarrow R{-}C{\equiv}C{-}H + HO^-$$

From the periodic trends of acidity we discussed earlier, we know that an N—H bond is a weaker acid than an O—H bond. Therefore NH_2^-, the conjugate base of ammonia, a very weak acid, is a stronger base than OH^-, the conjugate base of water, a weak acid. The K_a of ammonia is 10^{-36}. Thus, amide ion quantitatively removes a proton from a terminal alkyne because its K_a value is about 10^{-25}.

$$\underset{K_a \approx 10^{-25}}{R{-}C{\equiv}C{-}H} + H_2\ddot{N}{:} \rightleftharpoons R{-}C{\equiv}C{:}^- + \underset{K_a \approx 10^{-36}}{{:}NH_3} \qquad K_{eq} \approx 10^{11}$$

We will return to this feature of alkynes in Section 11.9, which describes the use of alkynides to synthesize higher molecular weight alkynes.

Problem 11.6

Grignard reagents of terminal alkynes can be prepared by the following reaction. Explain why the reaction is favorable. Estimate the equilibrium constant.

$$CH_3{-}C{\equiv}C{-}H + CH_3{-}MgBr \rightleftharpoons CH_3{-}C{\equiv}C{-}MgBr + CH_4$$

11.5 Oxidation of Alkynes

Oxidizing agents attack the π electrons of the triple bond of alkynes much as they do the π electrons of alkenes. Thus, both alkenes and alkynes can be oxidized under conditions that do not destroy the carbon chain. We recall that the oxidation of alkenes by neutral potassium permanganate yields diols (Section 7.9). Under similar conditions, alkynes yield diones. We will not discuss the mechanism of this reaction, as it is not central to our study of organic chemistry.

$$CH_3{-}C{\equiv}C{-}CH_3 \xrightarrow{KMnO_4} CH_3{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}CH_3$$

At higher temperatures, or under more acidic conditions, the dione breaks between the two carbonyl carbon atoms to give carboxylic acids.

When ozone bubbles through an alkyne in an inert solvent such as dichloromethane, the triple bond breaks. Internal alkynes form carboxylic acids. A terminal alkyne forms one molar equivalent of CO_2.

$$R{-}C{\equiv}C{-}R' \xrightarrow[2.H_2O]{1.\ O_3} RCO_2H + R'CO_2H$$

$$R{-}C{\equiv}C{-}H \xrightarrow[2.\ H_2O]{1.\ O_3} RCO_2H + CO_2$$

Problem 11.7

A mixture of propyne and propadiene (allene) is used in torches requiring a higher temperature than produced by propane. Explain why this commercial mixture is effective for this purpose.

$$CH_2{=}C{=}CH_2$$

propadiene

Problem 11.8

Ozonolysis of a compound with molecular formula $C_{18}H_{30}O_4$ gives nonanedioic acid (azelaic acid) . What is the structure of the compound?

$$HO{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_7{-}\overset{O}{\overset{\|}{C}}{-}OH$$

nonanedioic acid

Sample Solution

Only 9 of the original 18 carbon atoms are shown in the product. Therefore, the original compound must have been symmetrical. That compound also contained four oxygen atoms, indicating that some of the oxygen atoms in the product were contained in the same type of functional group in the reactant. Because ozonolysis of an alkyne gives a carboxylic acid, one of the two carboxylic acid groups in the product was present in the reactant. We obtain the original structure by "discarding" two oxygen atoms and joining two units of nonanedioic acid at one of the carbon atoms of the carboxyl group.

$$HO{-}\overset{O}{\overset{\|}{C}}{-}(CH_2)_7{-}C{\equiv}C{-}(CH_2)_7{-}\overset{O}{\overset{\|}{C}}{-}OH$$

The Oxyacetylene Torch

All hydrocarbons react exothermically with oxygen. However, to achieve the high temperatures needed for welding, which requires heating metal to its melting point, welding torches use a mixture of oxygen and acetylene rather than more saturated compounds. Let's find out why. Compare the heats of combustion of ethane, ethylene, and acetylene.

$$CH_3CH_3 + \tfrac{7}{2}O_2 \longrightarrow 2\,CO_2 + 3\,H_2O \qquad \Delta H^\circ = -1560 \text{ kJ mole}^{-1}$$

$$CH_2{=}CH_2 + 3\,O_2 \longrightarrow 2\,CO_2 + 2\,H_2O \qquad \Delta H^\circ = -1410 \text{ kJ mole}^{-1}$$

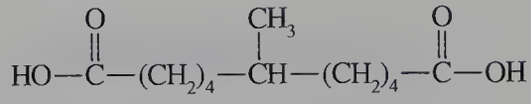
$$HC{\equiv}CH + \tfrac{5}{2}O_2 \longrightarrow 2\,CO_2 + H_2O \qquad \Delta H^\circ = -1325 \text{ kJ mole}^{-1}$$

From the ΔH° for the three reactions, we see that acetylene provides the smallest amount of heat energy per mole of compound. However, the requirement for a welding torch is a reaction that gives the highest possible temperature. The heat energy liberated per mole of reactant is only one factor affecting flame temperature. Temperature also depends on the number of product molecules among which the energy spreads. Note that water is a product in all three reactions, but in unequal amounts. It has a high heat capacity, which means that a large amount of energy is required to raise its temperature. Because fewer moles of water are produced per mole of hydrocarbon for acetylene, the heat energy produces higher temperature products than those from the oxidation of the other two hydrocarbons.

acetylene

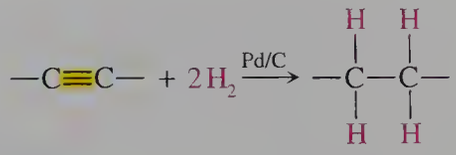
Problem 11.9

Ozonolysis of a compound with molecular formula $C_{12}H_{20}$ gives the following dicarboxylic acid. Write the structure of the compound.



11.6 Hydrogenation of Alkynes

Like alkenes, alkynes react with hydrogen gas to give more saturated compounds. Alkynes are completely reduced to alkanes by reaction with two molar equivalents of hydrogen gas in the presence of a palladium catalyst.



The reaction occurs with the stepwise addition of hydrogen to first give an alkene. The second step occurs even faster than the first. Therefore, catalytic hydrogenation with transition metal catalysts cannot be used to partially hydrogenate alkynes and "stop" at an alkene. The hydrogenation goes all the way to the alkane.

$$CH_3(CH_2)_3C{\equiv}CH + 2\,H_2 \xrightarrow{Pd/C} CH_3(CH_2)_3CH_2{-}CH_3 \qquad \Delta H^\circ = -290 \text{ kJ mole}^{-1}$$

In the hydrogenation of alkynes, the two π bonds break, along with the hydrogen–hydrogen bond of two hydrogen molecules. Four carbon–hydrogen bonds form. The hydrogenation reaction is exothermic regardless of the structure of the alkyne because the four carbon–hydrogen bonds that form are stronger than the combined strength of the bonds that break. The overall heat evolved for the hydrogenation reaction is reported as a positive quantity called the **heat of hydrogenation** ($\Delta H^\circ_{\text{hydrogn.}}$), but ΔH° for the reaction is negative.

The relative stabilities of the two π bonds of an alkyne can be compared to the single π bond of an alkene. The heat of hydrogenation of 1-hexyne, 290 kJ mole^{-1}, is more than twice the heat of hydrogenation of 1-hexene, 126 kJ mole^{-1}.

$$CH_3(CH_2)_3CH{=}CH_2 + H_2 \xrightarrow{Pd/C} CH_3(CH_2)_3CH_2{-}CH_3 \qquad \Delta H^\circ = -126 \text{ kJ mole}^{-1}$$

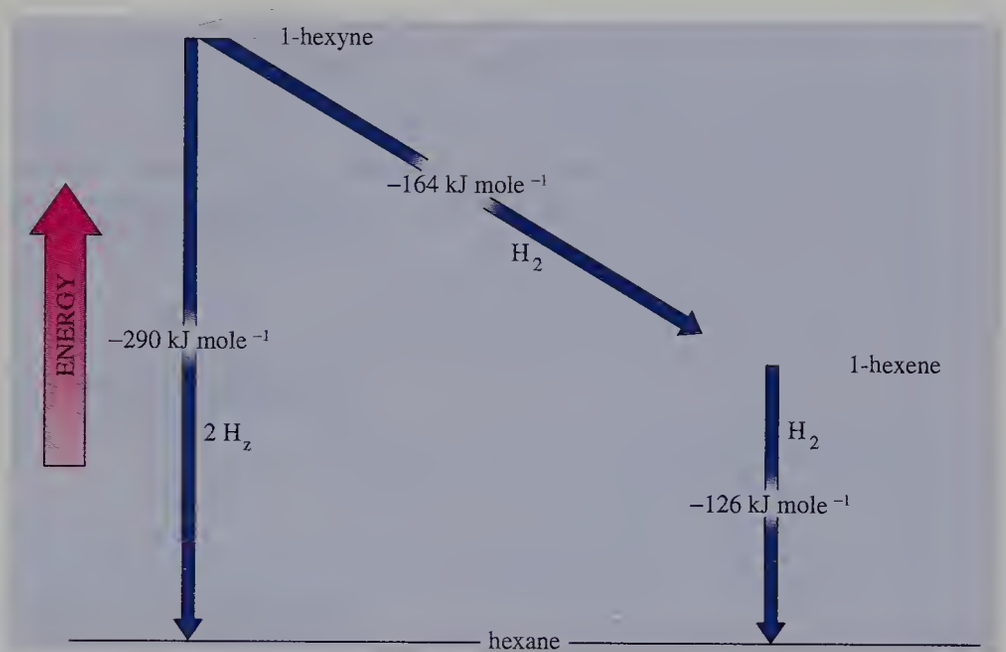


FIGURE 11.2 Stability of Alkenes and Alkynes

The heat evolved by addition of the first mole of hydrogen to 1-hexyne, 164 kJ mole^{-1}, can be calculated using Hess's law.

$$CH_3(CH_2)_3C{\equiv}CH + 2\,H_2 \longrightarrow CH_3(CH_2)_3CH_2{-}CH_3 \qquad \Delta H^\circ = -290 \text{ kJ mole}^{-1}$$

$$CH_3(CH_2)_3CH_2{-}CH_3 \longrightarrow CH_3(CH_2)_3CH{=}CH_2 + H_2 \qquad \Delta H^\circ = +126 \text{ kJ mole}^{-1}$$

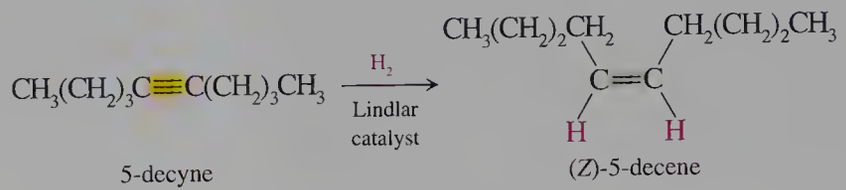
$$CH_3(CH_2)_3C{\equiv}CH + H_2 \longrightarrow CH_3(CH_2)_3CH{=}CH_2 \qquad \Delta H^\circ = -164 \text{ kJ mole}^{-1}$$

We find that the first step in the hydrogenation of an alkyne is more exothermic than the hydrogenation of an alkene. Thus, we conclude that the single π bond of an alkene is more stable than either of the two π bonds of an alkyne. The release of electrons from alkyl groups to the unsaturated carbon atoms explains the higher stability of the π bond of alkenes compared to alkynes. The *sp*-hybridized carbon atoms of alkynes attract electrons more strongly than the sp^2-hybridized carbon atoms of alkenes, but there are fewer alkyl groups available to supply those electrons in alkynes.

Syn Addition of Hydrogen

The catalytic hydrogenation reaction can be stopped after adding one molar equivalent of hydrogen gas to form an alkene with particular palladium preparations. One

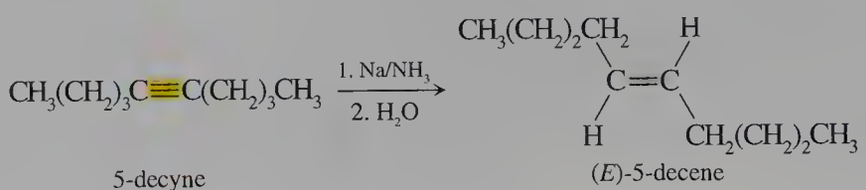
such palladium catalyst, called the **Lindlar catalyst**, has palladium coated on calcium carbonate that contains a small amount of lead acetate. Hydrogenation of an alkyne using the Lindlar catalyst is stereospecific. Syn addition occurs, giving the *Z* (cis) isomer. This syn addition indicates that the reaction occurs on the surface of the palladium catalyst and that both hydrogen atoms bond on the same "face," while the compound remains attached to the catalyst.



5-decyne (*Z*)-5-decene

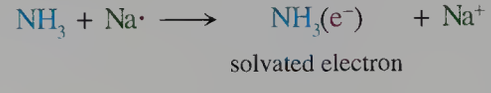
Anti Addition of Hydrogen

Reduction of an alkyne with sodium metal in liquid ammonia gives an alkene formed by anti addition of two hydrogen atoms. The reaction occurs by a very different mechanism than the catalytic hydrogenation reaction.



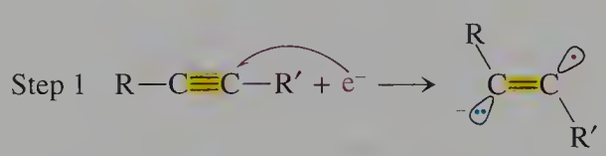
5-decyne (*E*)-5-decene

This reaction occurs in four steps: two are electron transfer reactions and two are acid–base reactions. An electron of the alkali metal moves to ammonia to give a "solvated electron," the active reducing agent. The formation of this solvated electron causes a deep blue color when the metal is placed in ammonia.



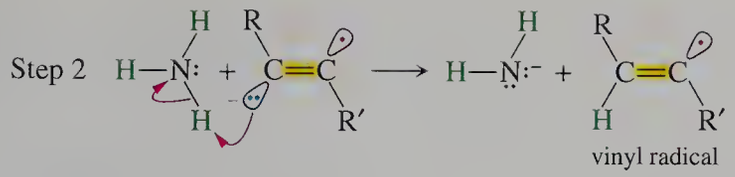
solvated electron

In the first step, an electron adds to the antibonding π orbital of the alkyne to form a radical anion. The two nonbonded orbitals are shown trans to each other. However, the stereochemistry is not critical at this point. Vinyl carbanions are configurationally stable, but vinyl radicals are less so.

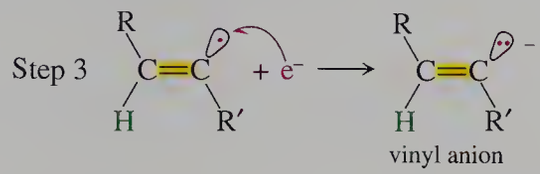


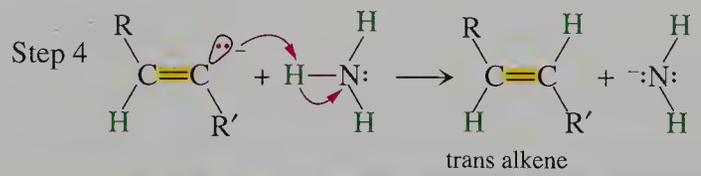
radical anion

The second step is an acid–base reaction. Because C—H bonds of sp^2-hybridized carbon atoms are less acidic than N—H bonds, the equilibrium lies to the right. At this point, even if the vinyl radical is not configurationally stable, the two alkyl groups are more stable trans to each other because steric hindrance would result if they were cis to each other.



In the third step, a second electron transfer occurs to form a vinyl anion in which the alkyl groups are trans. Finally, an acid–base reaction occurs to protonate the vinyl anion.





Problem 11.10

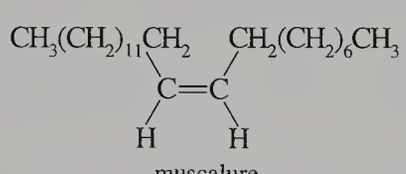
The heats of hydrogenation of 1-butyne and 2-butyne are 292 and 274 kJ mole^{-1}, respectively. Which compound is more stable? Why?

Problem 11.11

One of the intermediate compounds in the synthesis of the spruce budworm sex pheromone is (*E*)-11-tetradecen-1-ol. How can this compound be produced from a substituted alkyne? Name the alkyne.

Problem 11.12

The IUPAC name of muscalure, the sex hormone of the housefly, is (*Z*)-9-tricosene. How can this compound be produced from a structurally related alkyne? Name the alkyne.



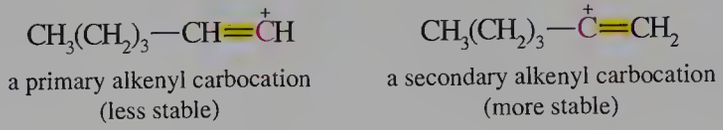
11.7 Electrophilic Addition Reactions

In Chapter 7, we considered the addition of HBr, Br_2, and H_2O to double bonds. These reagents react with alkenes by common, well-established mechanisms. We will now use this information to consider the addition reactions of alkynes.

Addition of Hydrogen Halides

Hydrogen bromide adds to alkynes at a slightly slower rate than it adds to alkenes. This regioselective reaction is a Markovnikov addition.

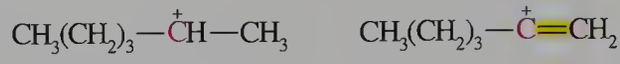
The reaction occurs when a proton adds to the triple bond to form an alkenyl carbocation, which the nucleophilic bromide ion subsequently captures. Of the two possible carbocations, the secondary is more stable than the primary because the alkyl group stabilizes the more highly substituted carbocation. The more stable intermediate forms in the rate-determining step of the reaction because it has a lower energy barrier.



a primary alkenyl carbocation (less stable)

a secondary alkenyl carbocation (more stable)

Hydrogen bromide adds to alkynes more slowly than to alkenes. To understand why, consider the carbocations formed in the addition of a proton to 1-hexene and 1-hexyne.

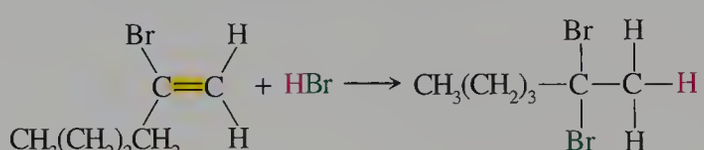


(an alkyl carbocation)

(an alkenyl carbocation)

The positive carbon atoms of the alkyl and alkenyl carbocations are sp^2- and sp-hybridized, respectively. The sp hybrid orbital is of lower energy than the sp^2 hybrid orbital. If electrons were present in these orbitals, the ones in the sp hybrid orbital would be more strongly attracted to the carbon atom. Because the carbocation does not have electrons in the hybrid orbital, the alkenyl carbocation requires more energy to form than the alkyl carbocation. That is, the alkenyl carbocation is less stable than an alkyl carbocation. For this reason, the rate-determining step forming the alkenyl carbocation is somewhat slower than the step forming the alkyl carbocation.

The addition product of one mole of HBr to an alkyne can be isolated because the electron-withdrawing bromine atom diminishes the reactivity of the product toward electrophiles. The electronegative bromine atom withdraws electron density from the π bond of the alkenyl bromide, thereby decreasing the availability of π electrons to electrophiles. Nevertheless, when the alkenyl bromide does react with a second mole of HBr, the second step is also a regiospecific Markovnikov addition.

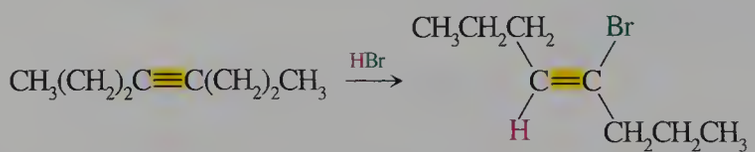


2-bromo-1-hexene

2,2-dibromohexane

Although the bromine atom is electron withdrawing, the secondary carbocation resulting from adding a proton to the C-1 atom is still more stable than the primary carbocation that would result from addition of a proton to the C-2 atom.

Now let's consider the stereochemistry of the addition of the first mole of HBr. The bromide ion tends to add trans to the proton, although the stereoselectivity may be low in some cases.



4-octyne

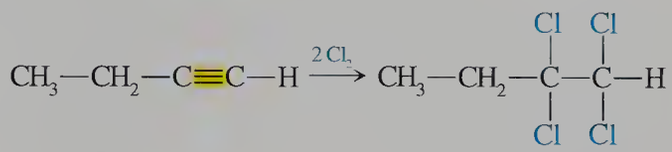
(Z)-4-bromo-4-octene

Adding excess bromide ion to the reaction mixture tends to increase the percentage of anti addition product. The increased stereoselectivity may result from the simul-

taneous attack of the entering bromide ion on the developing carbocation as the proton is transformed to the π electrons.

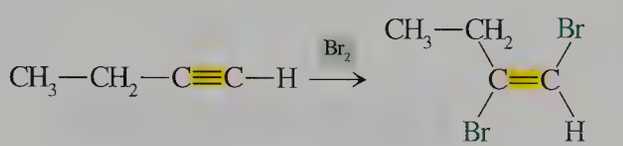
Addition of Halogens

Alkynes react with chlorine or bromine to produce tetrahaloalkanes, which contain two halogen atoms on each of the original carbon atoms of the triple bond. Hence, the reaction consumes two molar equivalents of the halogen.



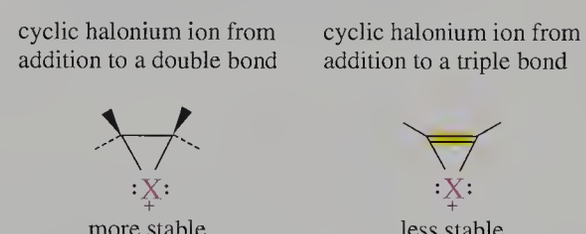
1-butyne 1,1,2,2-tetrachlorobutane

If only one molar equivalent of the halogen is used, the reaction product has the halogen atoms on the opposite sides of the double bond. The reaction rate is distinctly slower than the reaction rate for adding a halogen to an alkene.



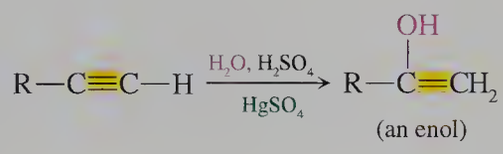
1-butyne (*E*)-1,2-dibromo-1-butene

The model for the stereoselectivity of the addition of bromine to a triple bond relates to that for the anti addition of bromine to a double bond. A cyclic halonium ion forms as an intermediate, and the nucleophilic halide ion attacks the electrophilic carbon atom from the side opposite the bridged halogen atom. The rate of formation of the intermediate is slower for an alkyne because the double bond in the cyclic halonium ion intermediate is highly strained. Because the intermediate is less stable, the transition state also reflects the same ring strain, and the energy barrier for its formation is higher. Thus, the rate of the reaction is slower.



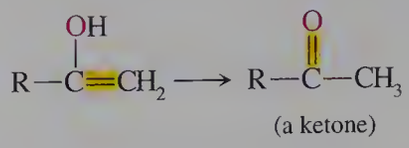
Hydration of Alkynes

Water adds to one of the π bonds of a triple bond in aqueous sulfuric acid in the presence of mercuric sulfate catalyst. However, the alcohol that forms has its —OH group bonded to the double-bonded carbon atom of an alkene. This type of compound is called an **enol**, a name that includes both the *-ene* suffix of a double bond and the alcohol suffix *-ol*.



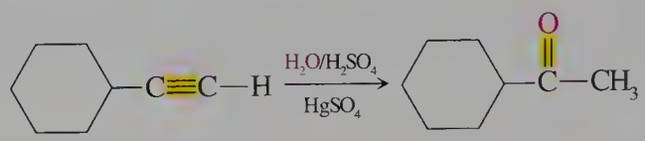
(an enol)

Enols are unstable compounds that rapidly rearrange to isomeric carbonyl compounds (Section 8.1). We will discuss this reaction further in Chapter 23.



(a ketone)

Thus, the product of hydration of an alkyne is a ketone. The more substituted carbon atom of the alkyne is converted into a carbonyl carbon atom.



Problem 11.13

Alkynes can react with HBr by way of a peroxide-catalyzed mechanism similar to that discussed for alkenes (Section 7.11). Predict the product of the free radical addition of HBr and 1-hexyne. Write the structure of the alkenyl radical formed in the chain reaction.

Problem 11.14

The addition of two equivalents of HBr to 3-hexyne occurs regiospecifically. Under the same reaction conditions, the reaction with 3-heptyne yields two products. Explain why.

Problem 11.15

Write the structure of the product formed in the reaction of excess chlorine with each of the following compounds.

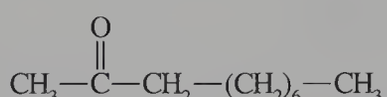
(a) ethynylcyclohexane (b) propargylcyclopentane (c) 1,5-hexadiyne

Problem 11.16

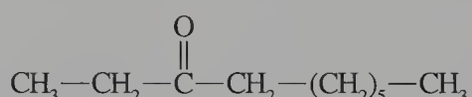
Consider the regioselectivity of the hydration of 2-decyne. Write the products of the reaction. Predict the percentage of each compound in the product mixture.

Sample Solution

The initial hydration of an alkyne places the hydroxyl group on the more substituted carbon atom. This carbon atom is the eventual site of the carbonyl group. In 2-decyne, both the C-2 and C-3 atoms are substituted to the same degree. The C-2 atom is bonded to a methyl group; the C-3 atom is bonded to a heptyl group. As a consequence, hydration can occur either of two ways and two products, 2-decanone and 3-decanone, are formed.



2-decanone



3-decanone

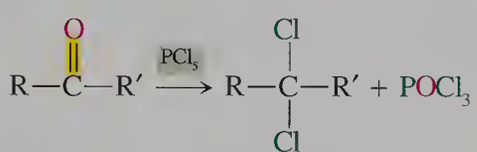
Although the heptyl group is larger than a methyl group, it is a primary alkyl group. Thus, the steric sizes of the heptyl group and the methyl group are not dramatically different. We would expect approximately equal amounts of the two ketones.

11.8 Synthesis of Alkynes

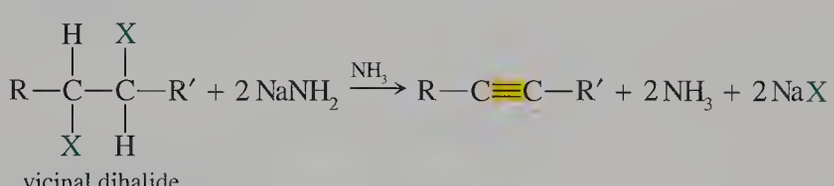
Some synthetic methods introduce the carbon–carbon triple bond by functional group transformations such as the dehydrohalogenation reaction. Other methods construct complex alkynes by forming carbon–carbon single bonds between two molecules, one of which already contains a triple bond. We discuss both synthetic methods in this section.

Elimination Reactions of Dihalides

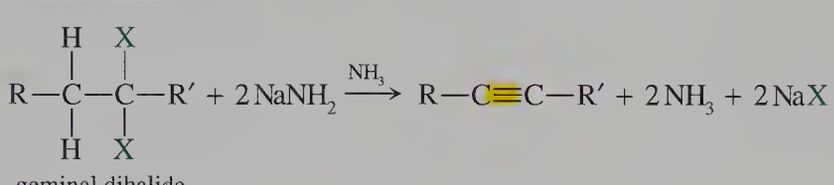
Alkynes can be prepared by elimination reactions under conditions similar to those used to form alkenes. Because an alkyne has two π bonds, two molar equivalents of HX must be eliminated from the starting material. One such suitable reactant is a **vicinal** dihalide, a compound with halogen atoms on adjacent carbon atoms. We recall that such compounds result from the addition of a halogen to the double bond of an alkene (Section 7.6). A **geminal** dihalide, which has both halogens on the same carbon atom, can also be used to synthesize alkynes. Geminal dichlorides can be made by reaction of phosphorus pentachloride with an aldehyde or ketone.



The most commonly used base to eliminate two moles of hydrogen halide from either a vicinal or geminal dihalide is sodium amide in liquid ammonia as the solvent. Potassium *tert*-butoxide in dimethyl sulfoxide can also be used.

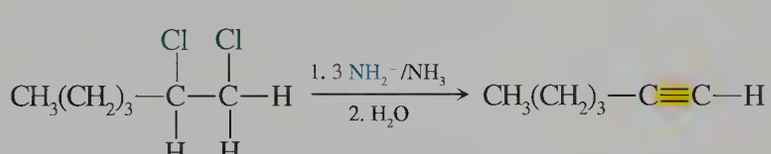


vicinal dihalide



geminal dihalide

A terminal alkyne can be synthesized from a 1,2-dihalo compound. We recall that this starting material can be synthesized in an addition reaction of a halogen to a monosubstituted (terminal) alkene. For example, 1,2-dichlorohexane can be prepared by addition of chlorine to 1-hexene. The double dehydrohalogenation of 1,2-dichlorohexane yields 1-hexyne.



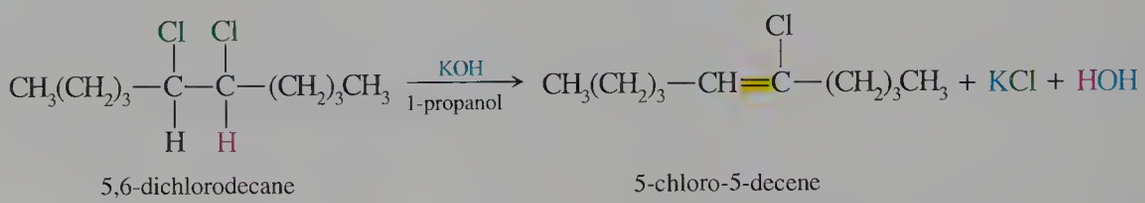
1,2-dichlorohexane 1-hexyne

Note that the synthesis of this terminal alkyne requires a total of three equivalents of

base. The double dehydrohalogenation itself requires two equivalents. However, a third equivalent is required because, as the alkyne forms, its acidic hydrogen atom reacts with the amide ion to convert the alkyne to its conjugate base. Without the "extra" equivalent of amide ion, the reaction would not go to completion. The water in the workup step acts as an acid to protonate the alkynide and to convert any excess amide ion to ammonia.

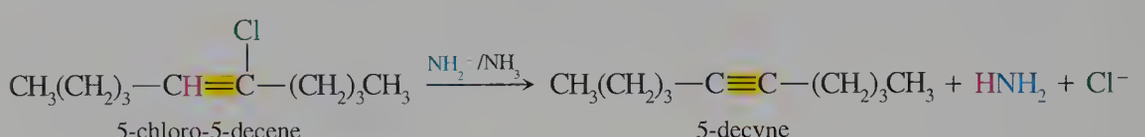
$$CH_3(CH_2)_3{-}C{\equiv}C{:}^- + H_2O \longrightarrow CH_3(CH_2)_3{-}C{\equiv}C{-}H + OH^-$$

The double dehydrohalogenation occurs in two distinct steps, the second being slower than the first. The reaction can be stopped at the first step using a weaker base, such as hydroxide ion, if a vinyl chloride compound is the objective of the synthesis.



5,6-dichlorodecane — 5-chloro-5-decene

Vinyl halides are intermediates in the double dehydrohalogenation by strong base. If the vinyl halide obtained by reaction with a weaker base is treated with a strong base, the partially dehydrohalogenated material is further dehydrohalogenated.



5-chloro-5-decene — 5-decyne

Alkylation of Alkynes

To prepare alkynes by a functional group transformation, the required hydrocarbon skeleton must be available in the form of a geminal or vicinal dihalide. Now we will see how to combine smaller structural units, one of which already has a carbon–carbon triple bond, to build an alkyne having a more complex structure.

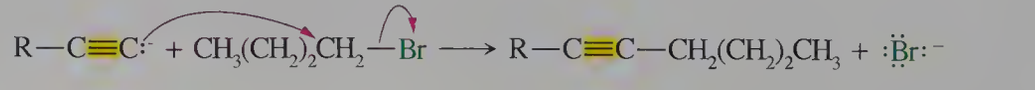
The attachment of an alkyl group to a selected molecular structure is called **alkylation**. We will encounter this method of forming carbon–carbon bonds repeatedly in later chapters dealing with other functional groups. Alkylation is one of the fundamental reactions used to construct complex structures.

The alkylation reaction considered here replaces the hydrogen atom of a terminal alkyne by an alkyl group derived from an alkyl halide. In the first step, the alkynide ion forms. We recall that sodium amide in ammonia is a strong base that quantitatively abstracts protons from C—H bonds of *sp*-hybridized carbon atoms.

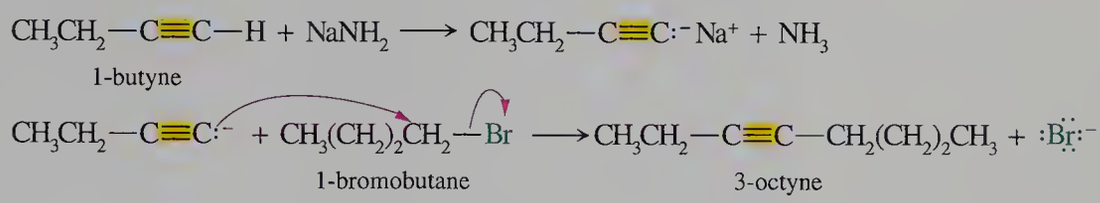
$$R{-}C{\equiv}C{-}H + NaNH_2 \longrightarrow R{-}C{\equiv}C{:}^-Na^+ + NH_3$$

sodium alkynide

In the second step, the alkynide ion acts as a nucleophile, displacing a halide ion from an alkyl halide subsequently added to the reaction mixture.



For example, 3-octyne can be prepared by joining two four-carbon units. One reactant is 1-butyne, which is converted into an alkynide ion. The alkynide ion then displaces a bromide ion from 1-bromobutane in the second step.



The displacement of a halide from alkyl halides by the alkynide ion occurs through an S_N2 mechanism. The reaction works only on primary alkyl halides because the nucleophilic alkynide ion is also a strong base. It preferentially eliminates hydrogen halide from secondary and tertiary alkyl halides rather than serving as a nucleophile.

Problem 11.17

The double dehalogenation of a geminal dihalide can be used to form alkynes. Write the steps for the reaction of 1,1-dichlorohexane and NH_2^-/NH_3. What limitations might one encounter if the reaction were attempted with 2,2-dichlorohexane?

Problem 11.18

Write the structure of the product formed by the elimination of one equivalent of HCl from (3*R*,4*R*)-3,4-dichlorohexane using *tert*-butoxide in *tert*-butyl alcohol.

Problem 11.19

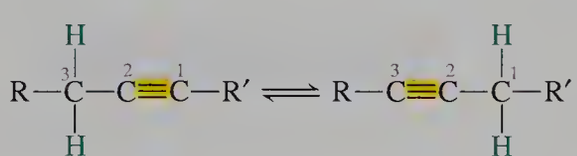
Sodium amide reacts with acetylene to give sodium acetylide. Removal of a second proton by the amide ion does not occur under ordinary conditions. Explain why.

Problem 11.20

Suggest a method to prepare 5-methyl-2-hexyne using reagents containing no more than four carbon atoms.

11.9 Rearrangement of Alkynes

Alkynes can isomerize to form mixtures of constitutional isomers with different locations for the triple bond. The conditions are severe; strong bases at high temperatures are required. Thus under equilibrium conditions, a mixture of triple-bonded isomers can result. A general equation representing this migration of the triple bond is



The migration of the triple bond occurs through a carbanion formed by abstraction of a proton from the carbon atom bonded to the *sp*-hybridized carbon atom (Figure 11.3). The resonance-stabilized anion can be protonated to yield either the original alkyne or an isomeric allene. Deprotonation of the allene yields another

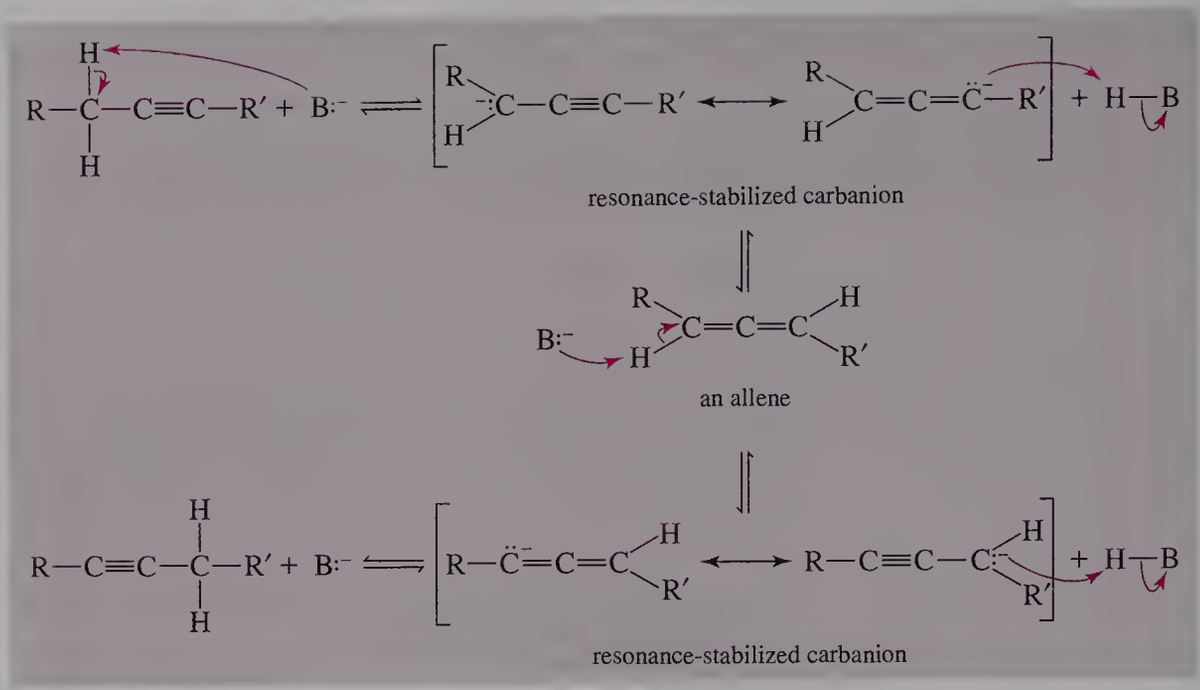


FIGURE 11.3 Mechanism of Alkyne Isomerization

resonance-stabilized carbanion, which can then be protonated to give the allene or an alkyne isomeric with the original alkyne.

Unfortunately, the isomerization reaction can occur under the conditions used to prepare alkynes by the dehydrohalogenation of vicinal or geminal dihalides. Thus, the isolated product depends on the strength of the base, the relative rates of the dehydrohalogenation and isomerization reactions, and the time that the reaction product remains in the basic medium.

Under equilibrium conditions, the composition of a mixture of alkynes formed by isomerization of the double bond depends on two factors. If a terminal alkyne is not structurally possible, the composition of the mixture reflects the thermodynamic stability of the isomers and does not depend on the strength of the base. However, the composition of the reaction mixture may not reflect thermodynamic stability if a terminal alkyne can form and the base is the amide ion. Although a terminal alkyne is thermodynamically less stable than a disubstituted alkyne, it forms because a terminal alkyne is converted to its alkynide salt by the strong base. As expected from Le Châtelier's principle, removal of the terminal alkyne from the equilibrium system by formation of the salt results in formation of additional terminal alkyne. With the addition of water in the workup of the reaction, the alkynide salt yields the terminal alkyne product. If the base used for dehydrohalogenation is hydroxide, then the alkynide salt of a terminal alkyne cannot form. In this case, the more stable substituted alkyne forms in preference to the terminal alkyne.

Problem 11.21

Write the mechanism for the isomerization of 2-pentyne to give 1-pentyne using sodium amide. Which isomer would result in the larger amount after a prolonged reaction time?

Problem 11.22

What is the major product of the reaction of 1,1-dibromopentane or of 2,2-dibromopentane using potassium hydroxide as the base?

EXERCISES

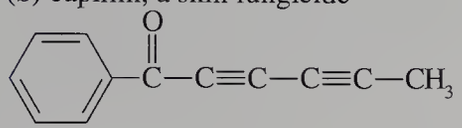
Structures of Alkynes

11.1 What is the molecular formula of each of the following compounds that contain carbon–carbon triple bonds?

(a) mycomycin, an antibiotic

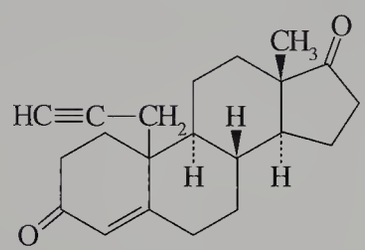
$$H{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2CO_2H$$

(b) capillin, a skin fungicide

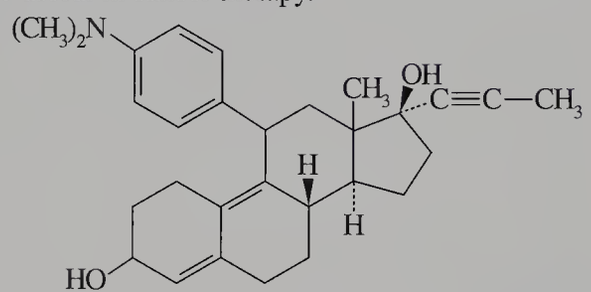


(c) ichthyothereol, a convulsant (See Section 11.1.)

11.2 Classify the triple bond in each of the following drugs. MDL 18962 is a drug used in breast cancer therapy. RU 486 is a drug used to induce abortion and may be useful in cancer therapy.



MDL 18962



RU 486

11.3 What is the molecular formula for the compound with each of following structural features?

(a) six carbon atoms and one double bond

(b) five carbon atoms and two double bonds

(c) seven carbon atoms, a ring, and one double bond

(d) four carbon atoms and one triple bond

11.4 What is the molecular formula for the compounds with each of the following structural features?

(a) four carbon atoms and two triple bonds

(b) four carbon atoms, a double bond, and a triple bond

(c) ten carbon atoms and two rings

(d) ten carbon atoms, two rings, and five double bonds

Properties of Alkynes

11.5 Predict the C-2 to C-3 bond length of 1,3-butadiyne.

11.6 The bond dissociation energies of the C—Cl bonds in chloroethane and chloroethene are 341 and 368 kJ mole^{-1}, respectively. Explain why. Are these data consistent with the relative acidities of the C—H bonds of ethane and ethene?

11.7 The heats of formation of 1-pentyne and 2-pentyne are 144 and 128.6 kJ mole^{-1}, respectively. Which compound is the more stable? Based on this information, which compound has the larger heat of combustion?

11.8 The heats of formation of 1-pentyne and 1,4-pentadiene are 144 and 106 kJ mole^{-1}, respectively. What does this information indicate about the relative stability of a triple bond compared to two double bonds?

11.9 Acetylene can be made by heating methane gas for a short period of time at 1500 °C. The by-product of the reaction is hydrogen gas. Write a balanced equation for the reaction. The $\Delta H°$ for this reaction is positive. Explain why the reaction occurs.

11.10 The heats of formation of 1-propyne and 1,2-propadiene (allene) are 185 and 190 kJ mole^{-1}, respectively. Assuming that an equilibrium can be established, which compound would be present in the larger amount?

11.11 Predict the direction of the dipole moment of 1-propyne. Why is its dipole moment larger than that of 1-propene?

11.12 The boiling points of 1-alkynes are higher than those of the 1-alkenes with the same number of carbon atoms. Suggest reasons for this fact.

11.13 The boiling points of 3,3-dimethyl-1-butyne and 1-hexyne are 39.5 and 71.3 °C, respectively. Explain why the values are so different for these two isomeric compounds.

11.14 The boiling points of terminal alkynes are lower than the boiling points of isomeric internal alkynes. Is this fact consistent with the dipole moments of the compounds? If not, what other structural factors might contribute to the difference in the boiling points?

Nomenclature

11.15 Name each of the following compounds.

(a) $CH_3CH_2CH_2C{\equiv}CH$

(b) $(CH_3)_3CC{\equiv}CCH_2CH_3$

(c) $CH_3{-}C{\equiv}C{-}\underset{\displaystyle CH_2{-}CH_3}{\underset{|}{CH}}{-}CH_3$

11.16 Name each of the following compounds.

(a) $CH_3CHBrCHBrC{\equiv}CCH_3$ (b) $Cl(CH_2)_2C{\equiv}C(CH_2)_3CH_3$ (c) $CH_3{-}\underset{\displaystyle CH_2{-}CH_3}{\underset{|}{CH}}{-}CH_2{-}C{\equiv}C{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CH_3$

11.17 Write the structural formula for each of the following compounds.
(a) 2-hexyne (b) 3-methyl-1-pentyne (c) 5-ethyl-3-octyne

11.18 Write the structural formula for each of the following compounds.
(a) 3-heptyne (b) 4-methyl-1-pentyne (c) 5-methyl-3-heptyne

11.19 Write the structural formula for 4-ethynyl-1,5-nonadien-7-yne.

11.20 Write the structural formula for 1-ethyl-3-(2-propynyl)cyclopentene.

11.21 What is the IUPAC name for the group $-C{\equiv}C-CH_3$?

11.22 Which of the drugs listed in Exercise 11.2 contains a propargyl group?

Acidity of Alkynes

11.23 Would the percent conversion of an alkyne to an alkynide be larger or smaller using *tert*-butoxide ion as a base instead of a methoxide ion?

11.24 The diisopropylamide ion is a strong base commonly used in organic reactions. Is it expected to be a stronger or weaker base than the amide ion?

11.25 Suggest an experimental procedure to prepare 1-deuterio-1-propyne.

11.26 Suggest an experimental procedure that could be used to separate a mixture of a terminal and an internal alkyne.

Oxidation of Alkynes

11.27 The ozonolysis of stearolic acid yields nonanoic acid and nonanedioic acid. What is the structure of stearolic acid?

$CH_3(CH_2)_7{-}CO_2H$ nonanoic acid $\qquad$ $HO_2C(CH_2)_7CO_2H$ nonanedioic acid

11.28 The ozonolysis of tariric acid yields undecanoic acid and hexanedioic acid. What is the structure of tariric acid?

$CH_3(CH_2)_9CO_2H$ undecanoic acid $\qquad$ $HO_2C(CH_2)_4CO_2H$ hexanedioic acid

11.29 The ozonolysis of some alkynes gives a single carboxylic acid product. What types of alkynes are these?

11.30 Write the structure of the product of the ozonolysis of cyclododecyne.

Hydrogenation Reactions

11.31 How many moles of hydrogen gas will react with each of the following compounds?
(a) $CH_3{-}CH{=}CH{-}C{\equiv}CH$ (b) $HC{\equiv}C{-}C{\equiv}CH$
(c) $CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2$ (d) $HC{\equiv}C{-}C{\equiv}C{-}C{\equiv}CH$

11.32 How many moles of hydrogen gas will react with each of the compounds listed in Exercise 11.1?

11.33 The heat of hydrogenation of cyclodecyne for the addition of two moles of hydrogen gas is about 41 kJ $mole^{-1}$ more exothermic than the heat of hydrogenation of 5-decyne. Explain why. Based on your hypothesis, predict whether the difference between the heats of hydrogenation of cyclooctyne and 4-octyne will be larger or smaller than the difference for the ten-carbon analogs.

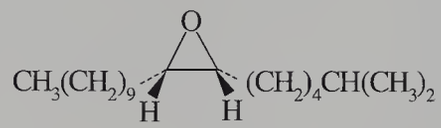
11.34 Which compound should have the larger heat of hydrogenation for the addition of two moles of hydrogen gas, 1-pentyne or 1,4-pentadiene? Why?

11.35 Stearolic acid is converted to oleic acid by hydrogenation using the Lindlar catalyst. Elaidic acid is the product obtained by sodium/ammonia reduction of stearolic acid. Write the structures of oleic and elaidic acids.

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$$

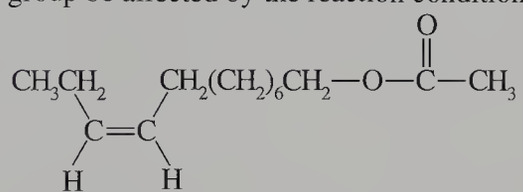
stearolic acid

11.36 Disparlure, the pheromone of the gypsy moth, can be prepared by reduction of an alkyne followed by epoxidation of the alkene. What alkyne is required? What is the configuration of the alkene? What reagents are required for reduction of the alkyne?



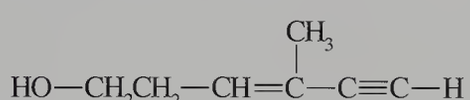
disparlure

11.37 The pheromone of the grape berry moth is indicated below. How could this compound be prepared from a related alkyne. Would the ester functional group be affected by the reaction conditions?

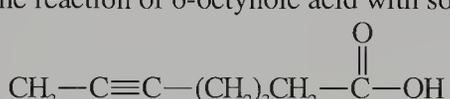


11.38 (*E*)-11-Tetradecen-1-ol is one of the intermediate compounds required to synthesize the sex pheromone of the spruce budworm. How could this compound be prepared from an appropriate alkyne? Would the reaction conditions affect the hydroxyl group?

11.39 Draw the structure of the product of the reaction of the following compound with hydrogen using the Lindlar catalyst.



11.40 Draw the structure of the product of the reaction of 6-octynoic acid with sodium in liquid ammonia.



11.41 Which of the following set of reactions would give a meso compound as the final product starting from 2-butyne?
(a) reduction using hydrogen and the Lindlar catalyst, followed by epoxidation using *m*-chloroperbenzoic acid
(b) reduction using hydrogen and the Lindlar catalyst, followed by addition of bromine
(c) reduction using hydrogen and the Lindlar catalyst, followed by dihydroxylation using OsO_4

11.42 Which of the following set of reactions would give a meso compound as the final product starting from 2-butyne?
(a) reduction using Na/NH_3, followed by dihydroxylation using $KMnO_4$
(b) reduction using Na/NH_3, followed by catalytic hydrogenation using D_2
(c) reduction using Na/ND_3, followed by catalytic hydrogenation using H_2

Electrophilic Addition Reactions

11.43 Addition of one mole of HCl to 2-hexyne gives a mixture of two products in approximately equal amounts. Draw their structures.

11.44 Draw the structure of the addition of one mole of DBr to 1-propyne.

11.45 Draw the structure of the addition product of HBr and 1-octyne in the presence of peroxides.

11.46 Draw the structures of the addition products of HBr with 2,2-dimethyl-3-hexyne in the presence of peroxides. Considering steric effects, predict which compound would be produced in the larger amount.

11.47 Predict the product of the addition of one mole of Br_2 to 1-penten-4-yne.

11.48 Draw the structure of the compound resulting from the addition of one molar equivalent of bromine to acetylene dicarboxylic acid. What is the dipole moment of the product?

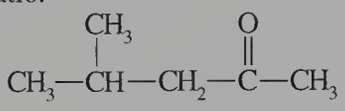
$$HO_2C{-}C{\equiv}C{-}CO_2H$$

acetylene dicarboxylic acid

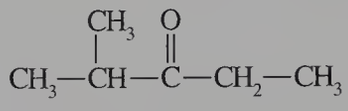
11.49 Hydration of one of the following two compounds yields a single ketone product. The other compound yields a mixture of ketones. Which one yields only the single ketone product? Why?

$CH_3CH_2{-}C{\equiv}C{-}CH_2CH_3$ (I) $\qquad$ $CH_3{-}C{\equiv}C{-}CH_2CH_2CH_3$ (II)

11.50 Hydration of 4-methyl-2-pentyne gives the following compounds in the indicated amounts. Suggest a reason for the observed product ratio.



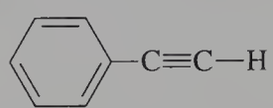
(55%)



(45%)

Preparation of Alkynes

11.51 Write the structure of all compounds that could yield the following alkyne upon dehydrohalogenation.



11.52 Which isomer, 2,2-dibromopentane or 3,3-dibromopentane, would give the better yield of 2-pentyne using sodium amide as the base?

11.53 Would the following reaction provide a good yield of the indicated product? Explain.

$$CH_3CH_2CH_2CBr_2CH_3 \xrightarrow{NaNH_2} CH_3CH_2C{\equiv}CCH_3$$

11.54 What conditions are required to produce 1-octyne from 2-octyne?

11.55 Write the product of the reaction of 1,6-dibromohexane with excess sodium acetylide.

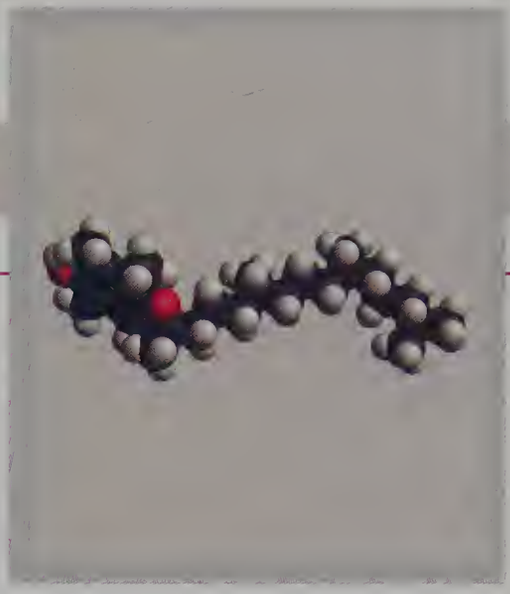
11.56 Predict the product of the reaction of one equivalent of the alkynide of 1-propyne and 1-bromo-5-fluoropentane.

11.57 Draw the structure of the final product of the following series of reactions.

$$HC{\equiv}CH \xrightarrow[2.\ CH_3CH_2CH_2I]{1.\ NaNH_2} \xrightarrow[2.\ CH_3CH_2I]{1.\ NaNH_2}$$

11.58 Outline the steps of a synthesis of 2,2-dimethyl-3-octyne using reactants having no more than six carbon atoms.

12



Dienes and Allylic Compounds

12.1 Classes of Dienes

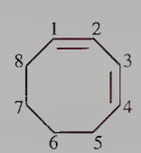
Compounds with two double bonds form the class **alkadienes**, commonly called dienes. Dienes in which more than one single bond separates the two double bonds, called **isolated**, or **nonconjugated,** react like alkenes. On the other hand, dienes in which only one single bond separates the two double bonds, called **conjugated,** react differently from simple alkenes. Conjugated dienes are the major subject of this chapter. Dienes can also have two double bonds that share a common atom. Such **cumulated** compounds are relatively rare, and we will discuss them only briefly in this chapter.

a conjugated diene
$CH_2{=}CH{-}CH{=}CH{-}CH_3$
1,3-pentadiene

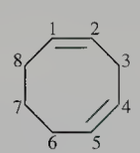
a nonconjugated diene
$CH_2{=}CH{-}CH_2{-}CH{=}CH_2$
1,4-pentadiene

a cumulated diene
$CH_2{=}C{=}CH{-}CH_2{-}CH_3$
1,2-pentadiene

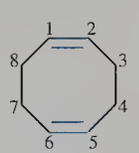
As shown in the above examples, we name alkadienes by replacing the *-ane* ending of the alkane with *-adiene*. Two numbers placed as a prefix indicate the locations of the double bonds. Polyenes are similarly named, using the suffix *-atriene*, *-atetraene*, and so forth, along with the appropriate numbers as a prefix. Cyclic dienes (and polyenes) are named by selecting one carbon atom of one of the double bonds as the reference atom. The prefix includes this number, in contrast to cyclic compounds with one double bond.



1,3-cyclooctadiene



1,4-cyclooctadiene

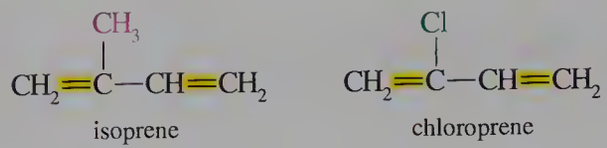


1,5-cyclooctadiene

Isoprene and Terpenes

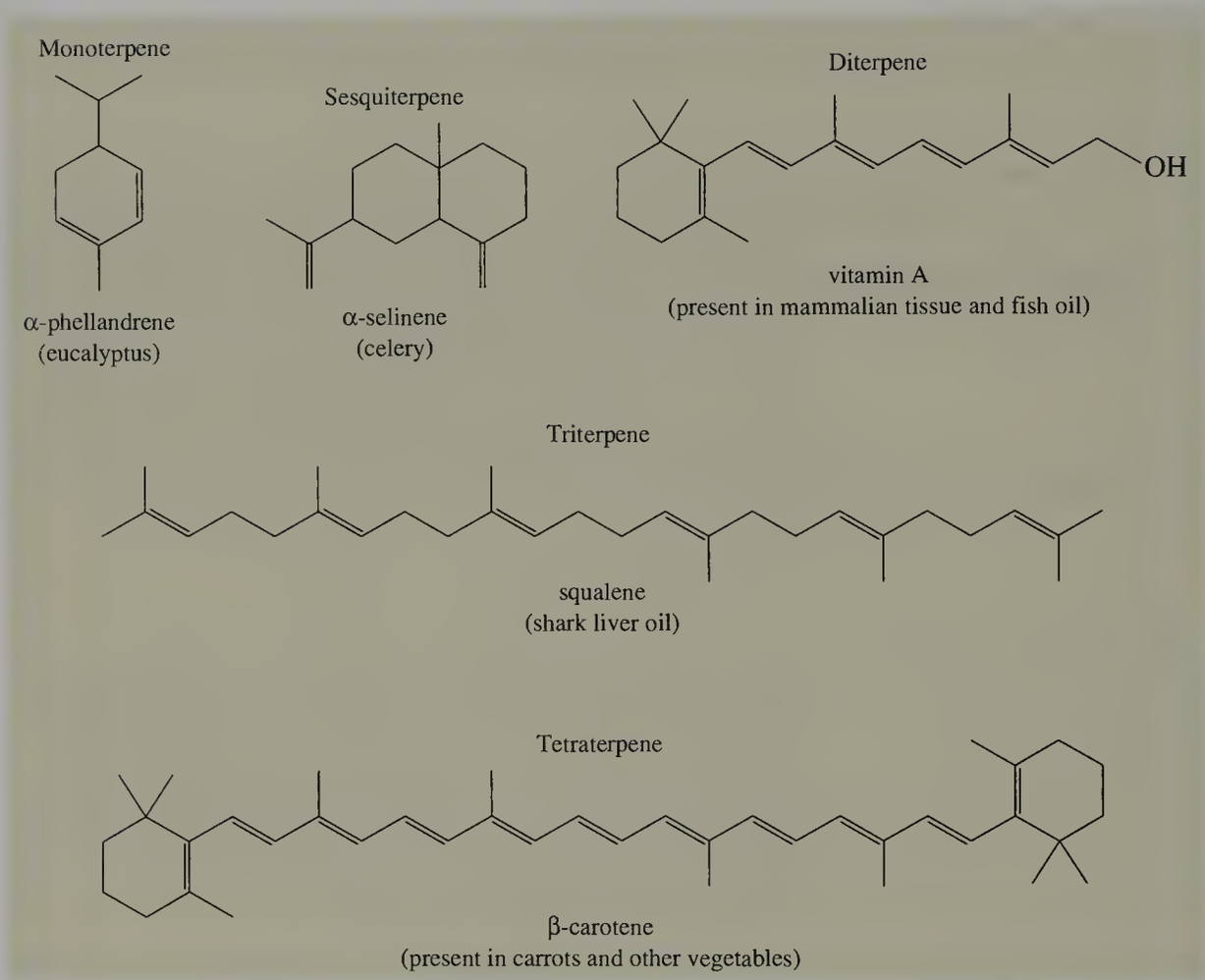
Natural rubber is a polymer of isoprene, a conjugated diene. Synthetic rubbers called neoprenes are produced by the polymerization of chloroprene, a synthetic conjugated

diene. Neoprene is used in a number of products, from industrial hoses to wet suits for scuba diving.

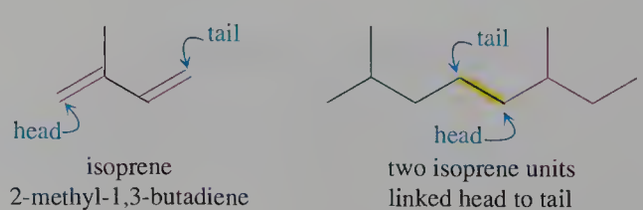


Terpenes have two or more isoprene units as their common structural feature. They can have different degrees of unsaturation and a variety of functional groups. Terpenes are classified according to the number of carbon atoms, in units of 10. **Monoterpenes**, the simplest class, contain two isoprene units or 10 carbon atoms. **Diterpenes**, **triterpenes**, and **tetraterpenes** contain four, six, and eight isoprene units, respectively. **Sesquiterpenes** contain 15 carbon atoms (three isoprene units). Figure 12.1 shows examples of the structures of some terpenes.

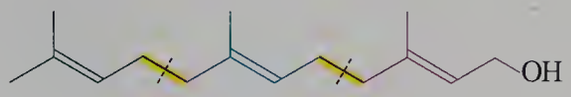
FIGURE 12.1
Classification of Terpenes



The two or more isoprene units of terpenes usually bond head to tail. Although the structures contain a variety of functional groups, the isoprene units are usually easy to identify.

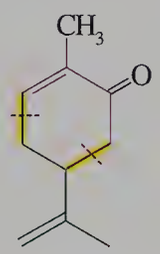


Farnesol contains three isoprene units joined head to tail. Dashed lines indicate where the three units are joined.



isoprene units in farnesol

We can mentally dissect many terpenes that contain one or more rings—carvone, for example—into isoprene units.

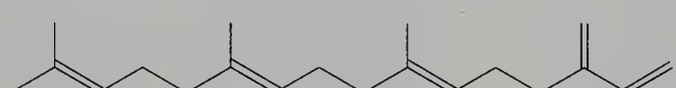


carvone
(oil of caraway)

Terpenes are abundant in the oils of plants and flowers, and they have distinctive odors, flavors, and colors. They are responsible for the odor of pine trees and for the colors of carrots and tomatoes. β-Carotene, found in carrots, and vitamin A are both terpenes (Section 6.1). A biochemical reaction in mammals splits and oxidizes β-carotene into two molecules of vitamin A.

Problem 12.1

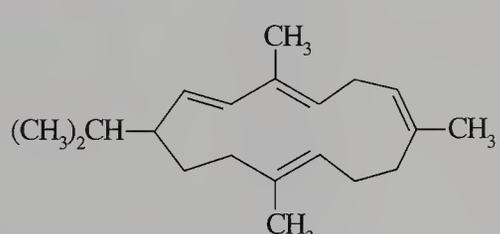
Classify the double bonds found in β-springene, a sex attractant secreted by the dorsal gland of the springbok, a South African gazelle.



β-springene

Problem 12.2

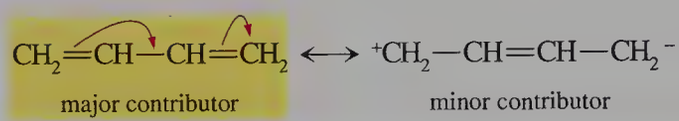
Classify the following terpene and indicate its division into isoprene units.



12.2 Stability of Conjugated Dienes

We saw in Section 6.13 that we can determine the relative stabilities of isomeric alkenes using their heats of hydrogenation ($\Delta H^\circ_{\text{hydrogn}}$) because the hydrogenation of isomeric alkenes yields the same product. We also learned that we can compare the heats of hydrogenation of nonisomeric alkenes because these values fall within categories that reflect the substitution pattern of the double bond.

The calculated heats of hydrogenation for the terminal double bonds of 1,4-pentadiene and (*E*)-1,3-pentadiene are indicated in Figure 12.2. The figure also includes the heat of hydrogenation of the second double bond of each compound to form pentane. The average heat of hydrogenation of a terminal monosubstituted double bond is about 126 kJ mole^{-1} (30 kcal mole^{-1}). Thus, the heats of hydrogenation of both the first and the second double bond of 1,4-pentadiene are typical for a monosubstituted double bond. The heat of hydrogenation of the double bond of *trans*-2-pentene also lies within the range for trans-disubstituted alkenes. However, the monosubstituted (terminal) double bond of (*E*)-1,3-pentadiene releases about 15 kJ mole^{-1} (3.6 kcal mole^{-1}) less on hydrogenation than expected for such a double bond. The molecule is said to be resonance stabilized by an interaction of the two double bonds. This 15 kJ mole^{-1} is the **resonance energy** of the molecule. We will see in the next section that the resonance energy results from a distribution of electrons over more than two atoms in molecular orbitals, a phenomenon called delocalization. Thus, resonance energy describes the extra stability of compounds with conjugated double bonds. The following contributing resonance forms depict the interaction of the two double bonds. The dipolar form is the minor contributor.



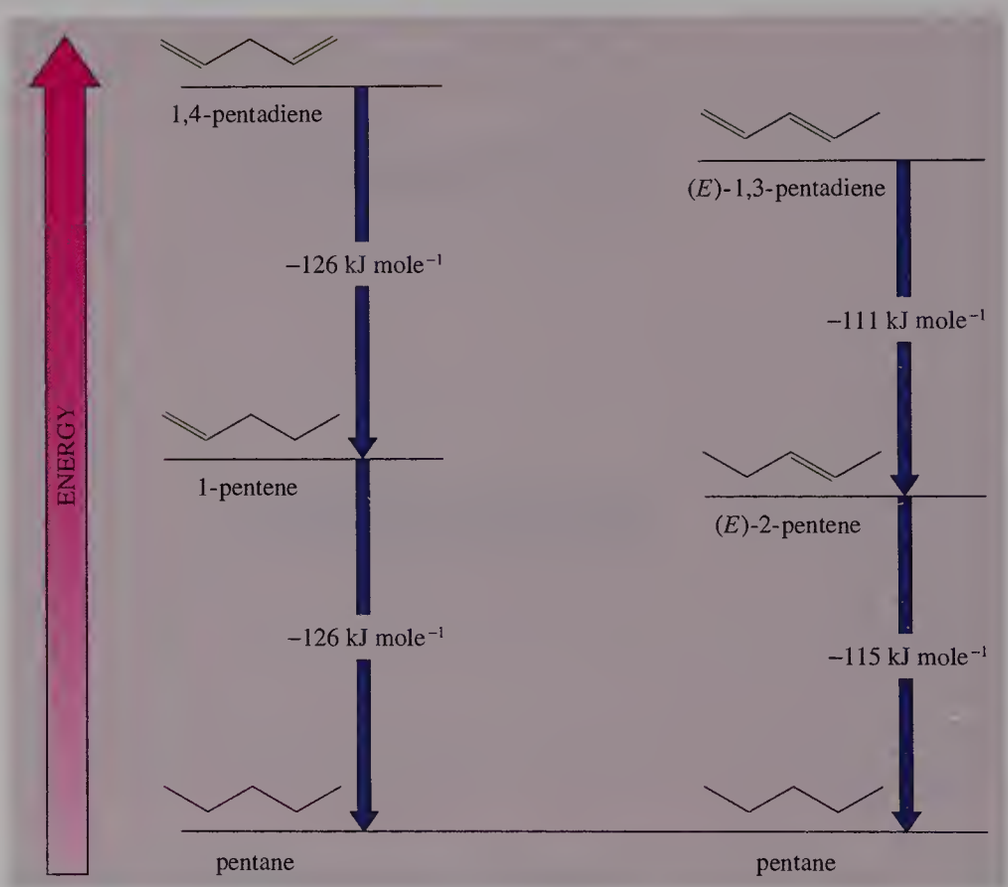


FIGURE 12.2 Heats of Hydrogenation and Resonance Energy
The relative energies of the isomeric (*E*)-1,3-pentadiene and 1,4-pentadiene are different because of both the degree of substitution of the double bonds and the presence or absence of conjugation. Conjugated double bonds result in stabilization by an amount of energy called the resonance energy.

Note that the entire system of conjugated double bonds is resonance stabilized, not a specific bond. Knowing typical heats of hydrogenation for terminal double bonds, we expect the heat of hydrogenation of 1,4-pentadiene to be about 250 kJ mole^{-1} (60 kcal mole^{-1}). The measured value is very close to that number. We can predict that the sum of the heats of hydrogenation for a terminal monosubstituted double bond and a trans-disubstituted double bond is about 241 kJ mole^{-1}. However, the total heat of hydrogenation of (*E*)-1,3-pentadiene is 226 kJ mole^{-1}. The difference between the

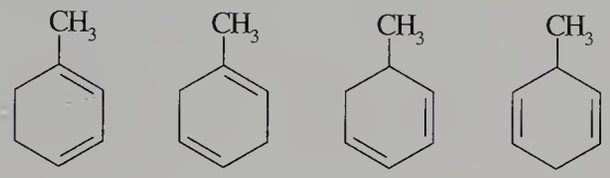
experimental value and the predicted value—assuming no orbital interaction between the two double bonds—is 15 kJ mole^{-1}. This is the resonance energy.

Problem 12.3

Estimate the total heats of hydrogenation of 2*E*,4*E*-heptadiene and of 2*E*,5*E*-heptadiene.

Problem 12.4

Arrange the following methylcyclohexadienes in order of decreasing heats of hydrogenation to form methylcyclohexane.



I II III IV

Sample Solution

Conjugation of double bonds and the degree of substitution of double bonds are two structural features that result in lower heats of hydrogenation. Compounds I and III are conjugated dienes and are resonance stabilized. Their heats of hydrogenation should be smaller than for the two nonconjugated dienes. Compound I should have the lowest heat of hydrogenation because it has a higher degree of substitution at the double bond than compound III. For the same reason, the heat of hydrogenation of compound II should be less than for compound IV. The order should be IV > II > III > I.

Problem 12.5

Arrange the following compounds in order of increasing heats of hydrogenation.

I 1,6-dimethyl-1,3-cycloheptadiene
II 3,6-dimethyl-1,4-cycloheptatdiene
III 2,7-dimethyl-1,4-cycloheptadiene
IV 1,3-dimethyl-1,3-cycloheptadiene
V 2,4-dimethyl-1,4-cycloheptadiene

12.3 Molecular Orbital Models of Polyenes

Lewis structures do not reveal the origin of the resonance energy of conjugated dienes. To better understand such π systems and others, such as benzene (Chapter 13), we must use molecular orbital theory. We introduced this term in Chapter 1, but that was a long time ago. So let's review the molecular orbital picture of ethylene and extend the analysis to 1,3-butadiene.

Molecular Orbitals of Ethylene

Molecular orbitals can be mathematically expressed by a process called a **linear combination of atomic orbitals (LCAO)**. The wave functions for the molecular orbitals result from adding or subtracting the wave functions of the atomic orbitals of several atoms. If we combine the wave functions for n atomic orbitals, we obtain the wave functions for n molecular orbitals. For example, the wave functions of two atomic orbitals represented by A_1 and A_2 produce the wave functions of two molecular orbitals M_1 and M_2.

$$M_1 = c_1A_1 + c_2A_2$$
$$M_2 = c_1A_1 - c_2A_2$$

The coefficients c_1 and c_2 are weighting factors that indicate the degree to which the atomic orbitals contribute to the molecular orbital. Both coefficients are equal for ethylene, but are not necessarily equal for conjugated systems.

The molecular orbitals of ethylene are visually represented using the $2p$ orbitals of the two carbon atoms and then "overlapping" them (Figure 12.3). There are two ways of doing this, which correspond to the addition (in-phase combination) or subtraction (out-of-phase combination) of the wave functions of the atomic orbitals. The plus and minus signs placed within each lobe of a $2p$ orbital indicate the phase of the wave function in that volume of space, not electrical charges. Overlap of the "+" with "+", or "–" with "–", reinforces the wave function to give **constructive overlap**. This arrangement of orbitals forms a **bonding molecular orbital** (MO), designated π_1. The second possibility corresponds to subtraction of wave functions. It is represented by the overlap of "+" with "–", and therefore "–" with "+". In this case, the wave functions of the atomic orbitals cancel, a condition called **destructive overlap**. This arrangement of orbitals forms an **antibonding molecular orbital** (MO), designated π_2. Ethylene has two electrons not involved in the σ bonds of the framework. They are paired in π_1, which has a lower potential energy than π_2. The antibonding MO, often represented as π^*, is vacant.

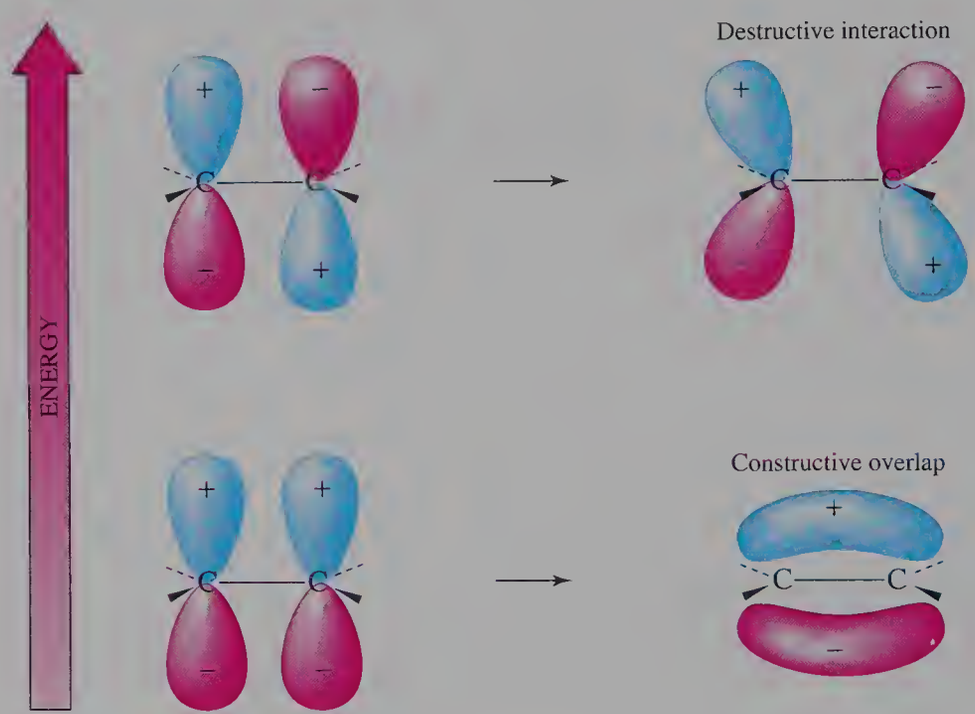


FIGURE 12.3 Molecular Orbitals of Ethylene
The sideways overlap of two $2p$ orbitals in ethylene leads to two molecular orbitals. A constructive overlap gives the bonding molecular orbital. The destructive overlap of the two orbitals gives a higher energy antibonding molecular orbital.

Symmetry of Wave Functions

Now let's consider the probability distribution of electrons in a molecular orbital. In quantum theory the square of the wave function gives the probability of finding an electron at a particular position. For symmetric molecules such as ethylene, the value of the square of the wave function must be the same at symmetrical points. For example, the electron density at a point 100 pm above the plane of the molecule and directly above one carbon atom is the same as the electron density 100 pm below the

plane and below that atom. It is also the same 100 pm above and below the plane at the second carbon atom.

Although the square of the wave function is identical at points related by symmetry, the wave function itself may not have the same sign at these points. Consider the relationship between the signs of the lobes of the atomic orbitals with respect to the horizontal nodal plane located in the plane of the molecule. The wave function has a value of zero in a nodal plane. In π_1 and π_2, the magnitude of the wave function on opposite sides of the plane is the same, but the sign of the wave function is different. The wave function is said to be **antisymmetric** with respect to this nodal plane. Now consider the symmetry of the two wave functions with respect to a vertical plane placed perpendicular to the plane of the molecule (Figure 12.4). In the case of π_1, there is no change in sign, and the wave function is symmetric with respect to the vertical plane. For π_2, the sign changes, and the wave function is antisymmetric with respect to the vertical plane. Note that in this case the vertical plane is a nodal plane.

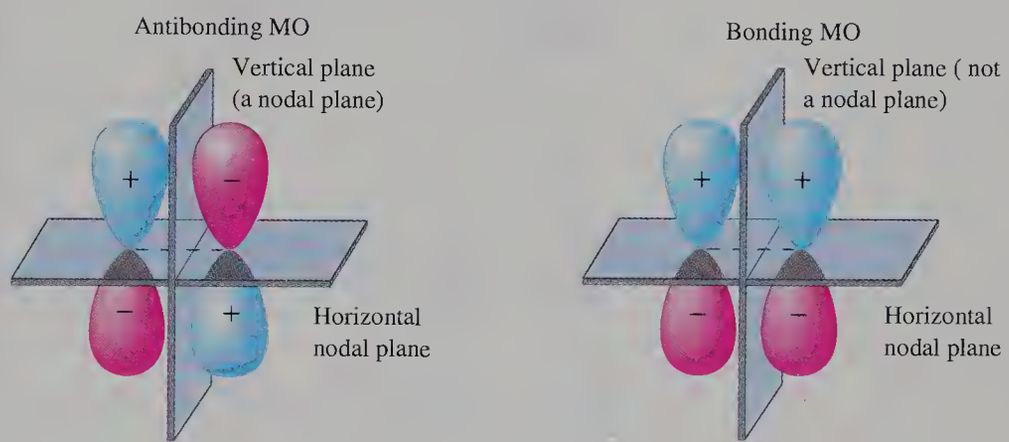
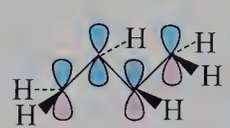


FIGURE 12.4 Symmetry of Molecular Orbitals
Both π molecular orbitals of ethylene are antisymmetric with respect to the nodal plane in the plane of the molecule. The symmetries of the molecular orbitals with respect to a plane perpendicular to the molecule and bisecting the molecule differ. The bonding orbital is symmetric; the antibonding orbital is antisymmetric.

Table 12.1 summarizes several important consequences of molecular orbital theory and the description of molecular orbitals. These guidelines help us to depict the molecular orbitals of conjugated systems.

Molecular Orbitals of 1,3-Butadiene

We can use the guidelines in Table 12.1 to construct the four π molecular orbitals resulting from a linear combination of the four 2*p* orbitals of 1,3-butadiene. Although butadiene is not linear, it is common practice to draw the 2*p* atomic orbitals in a straight line. In this representation, the carbon–hydrogen bonds are not shown because these σ bonds are not part of the π system.



2*p* orbitals of 1,3-butadiene

representation of 2*p* orbitals
used to depict π molecular orbitals

Linear combinations of the four $2p$ orbitals of butadiene give four molecular orbitals: two bonding and two nonbonding. In the lowest energy molecular orbital, designated π_1, all lobes of the $2p$ atomic orbitals overlap constructively (Figure 12.5). However, the coefficients of the equation for π_1 are not equal because the relative contributions of the $2p$ orbitals to the wave function are not equal. We indicate this effect by varying the sizes of the atomic orbitals to show which atoms have a higher electron density in that molecular orbital. The π_1 orbital of 1,3-butadiene is symmetric with respect to a vertical plane placed between the C-2 and the C-3 atom, even though there are no vertical nodal planes for this molecular orbital.

TABLE 12.1
Guidelines for Formationof Molecular Orbitals

1. The number of molecular orbitals is the same as the number of $2p$ orbitals used to form them.
2. The energies of the molecular orbitals are symmetrically distributed above and below the energy of the atomic $2p$ orbitals.
3. The energies of bonding molecular orbitals are lower than the energies of antibonding molecular orbitals.
4. Each molecular orbital has a horizontal nodal plane that contains the carbon nuclei.
5. The molecular orbitals for polyenes containing n atoms can have from zero to $n - 1$ vertical nodal planes.
6. The energies of the orbitals increase with the number of vertical nodal planes.
7. Each molecular orbital must be symmetric or antisymmetric with respect to a vertical plane placed between the atoms at the center of the π system.

The π_1 molecular orbital has the lowest energy because it has no vertical nodal planes. Hence, some double bond character exists between each pair of adjacent carbon atoms. Substantial double bond character occurs between the C-2 and C-3 atoms, a feature not represented by the Lewis structure of the major resonance contributor of butadiene. The π_2 molecular orbital, higher in energy, also has two electrons. It is antisymmetric with respect to a nodal vertical plane between C-2 and C-3. Bonding interactions occur both between C-1 and C-2 and between C-3 and C-4. Therefore, the Lewis structure resembles this molecular orbital. The antibonding π_3 and π_4 molecular orbitals have more vertical nodal planes and are of higher energy than the bonding molecular orbitals. The π_3 molecular orbital contains two antibonding interactions and one bonding interaction. The π_4 molecular orbital is totally antibonding.

Because 1,3-butadiene has only four π electrons and they are found only in π_1 and π_2, the two antibonding orbitals are empty. It is the sum of bonding interactions of both π_1 and π_2 between these two sets of atoms that accounts for the double bonds. An antibonding interaction exists between C-2 and C-3 atoms in π_2, which partially offsets the strong bonding interaction of π_1 between the same atoms. The sum of the two molecular orbitals predicts some residual double bond character between C-2 and C-3 atoms, a structural feature detectable in some physical properties of 1,3-butadiene, which we will discuss in the next section.

Problem 12.6

How many molecular orbitals of 1,3,5-hexatriene contain bonding π electrons? Sketch each of them, showing vertical nodal planes, and determine the symmetry of each wave function.

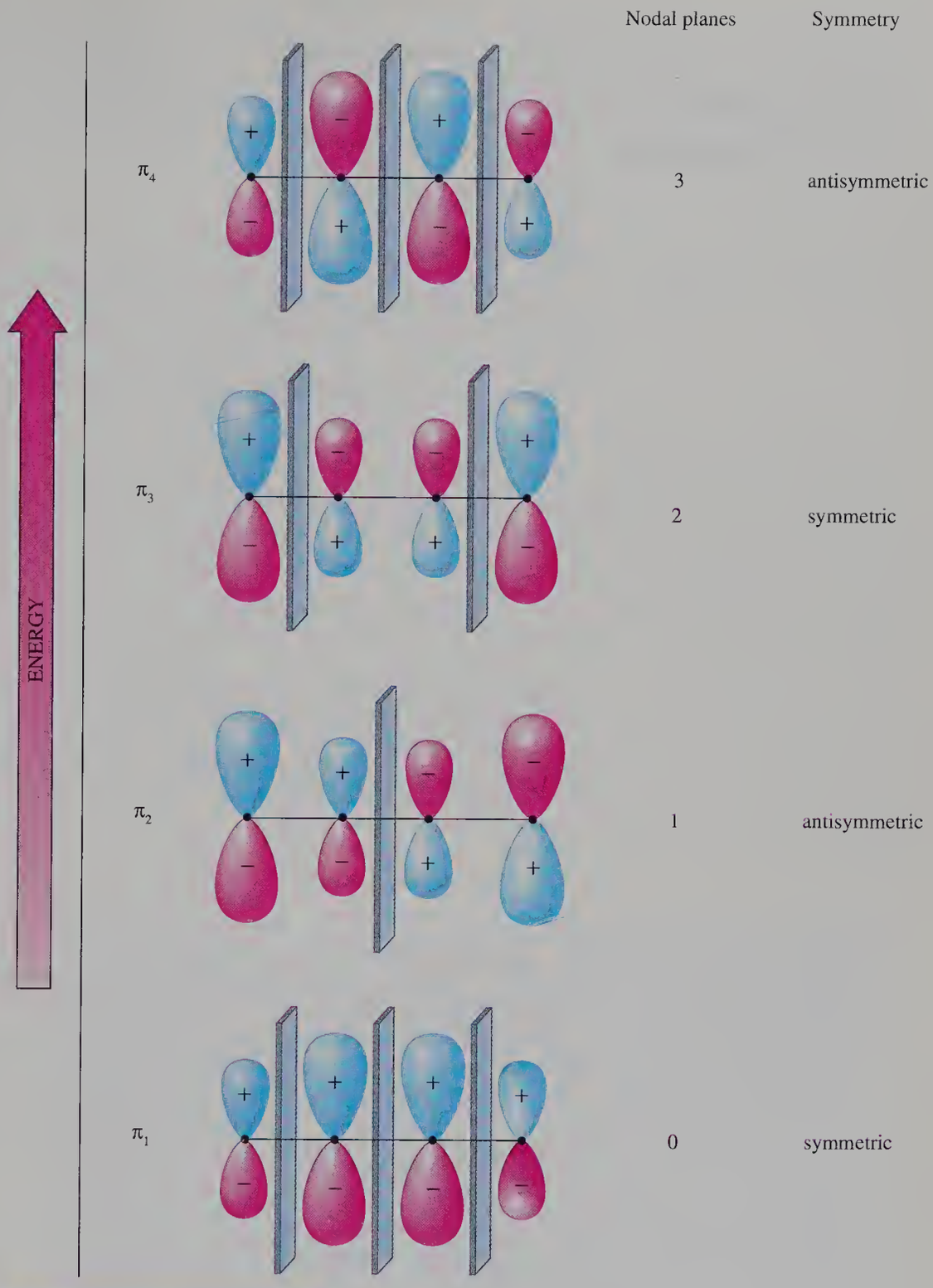


FIGURE 12.5 Molecular Orbitals of 1,3-Butadiene
The sizes of the 2*p* atomic orbitals represent the degree to which the orbitals contribute to the molecular orbital. A bonding interaction results from constructive overlap of 2*p* orbitals of the same sign. Nodal planes are shown between carbon atoms where destructive overlap occurs.

Problem 12.7

What is the symmetry of the highest energy molecular orbital containing electrons in 1,3,5,7-octatetraene?

Sample Solution

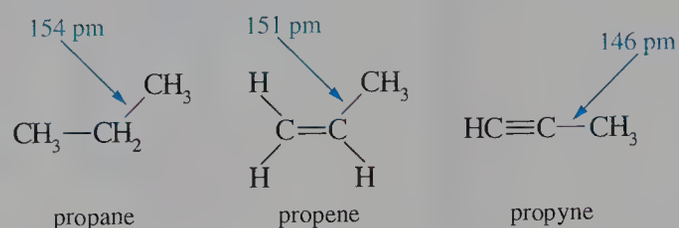
The eight π electrons of the tetraene are located in four molecular orbitals, the highest energy one being π_4. We know that π_1 of linear conjugated polyenes is symmetric and that the symmetry of consecutive orbitals alternates with increasing energy. Thus, π_2 is antisymmetric, π_3 is symmetric, and π_4 is antisymmetric.

12.4 Structural Effects of Conjugation

Using the molecular orbital model, we predict that the contribution of π_1 to the total bonding of butadiene will cause an increase in the C-2 to C-3 bond order of butadiene. That is, the C-2 to C-3 bond is predicted to have some double bond character. Several properties of the C-2 to C-3 bond support this model.

Effect on Bond Length

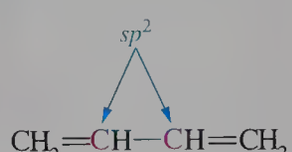
We recall that the length of carbon–carbon σ bonds depends on the hybridization of both carbon atoms, as illustrated by the bond between the sp^3-hybridized methyl carbon atom and the sp^3-, sp^2-, and sp-hybridized central carbon atoms of propane, propene, and propyne, respectively.



propane propene propyne

We also recall that a π bond joining the carbon atoms decreases the bond length of the double bond in alkenes because the shared pairs of electrons in a π bond draw the nuclei of the carbon atoms closer together.

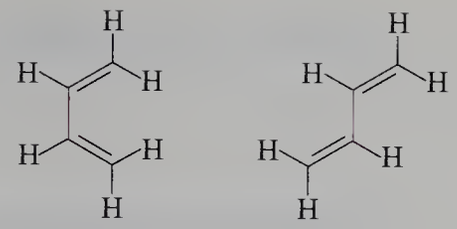
The C-2 to C-3 bond length of 1,3-butadiene is 146 pm. The Lewis structure shows this as a single bond. The hybridization of both atoms is sp^2.



The bond length for sp^2-sp^3 bonded atoms is 3 pm less than that of sp^3-sp^3 bonded atoms, so we expect a bond length of 148 pm for the sp^2-sp^2 bond of 1,3-butadiene. The actual bond length is 2 pm shorter than this prediction because the electron delocalization gives it some partial double bond character due to the π_1 orbital. However, this shortening is substantially less than that resulting from the formation of a "full" π bond in ethylene, which decreases the carbon–carbon bond length by about 19 pm compared to ethane.

Effect on Conformations

Electron delocalization affects the conformations of 1,3-butadiene. We recall that staggered conformations result from rotation around σ bonds of alkanes. The most stable conformations minimize both torsional interactions between bonded pairs of electrons and steric interactions between groups bonded by those electrons. However, to maintain the overlap of the p orbitals required for the π_1 molecular orbital in 1,3-butadiene, the two "vinyl" components must be coplanar. This requirement is fulfilled only in the s-cis and s-trans conformations in which hydrogen atoms and vinyl groups are eclipsed. The letter s in the prefixes s-cis and s-trans refers to the σ bond.



s-cis-1,3-butadiene *s-trans*-1,3-butadiene

We estimate the s-trans conformation to be 12 kJ mole^{-1} more stable than the s-cis conformation because of an unfavorable van der Waals interaction between hydrogen atoms of the C-1 and C-4 atoms in the s-cis conformation.

Effect on Barrier to Rotation

The s-trans and s-cis conformations can interconvert by rotation around the σ bond between the C-2 and C-3 atoms. Rotational barriers for alkanes are 12–16 kJ mole^{-1} (3–4 kcal mole^{-1}). The rotational barrier for 1,3-butadiene, relative to the more stable s-trans conformation, is 28 kJ mole^{-1} (6.7 kcal mole^{-1}). As the molecule undergoes rotation around the C-2 to C-3 bond, it passes through a transition state in which the planes of the two vinyl groups are perpendicular (Figure 12.6). In this "perpendicular conformation," the double bonds are localized because the respective π bonds are perpendicular.

The energy barrier for rotation around the C-2 to C-3 bond reflects both torsional and steric effects for rotation about σ bonds in molecules such as butane and the loss of resonance energy that occurs in the perpendicular conformation. If we know either the energy due to torsional and steric factors or the resonance energy term, we can obtain the other quantity. Subtracting 15 kJ mole^{-1} for the resonance energy (Section 12.2) from the 28 kJ/mole^{-1} rotational barrier, we obtain 13 kJ mole^{-1}, in the range expected for rotation around a σ bond.

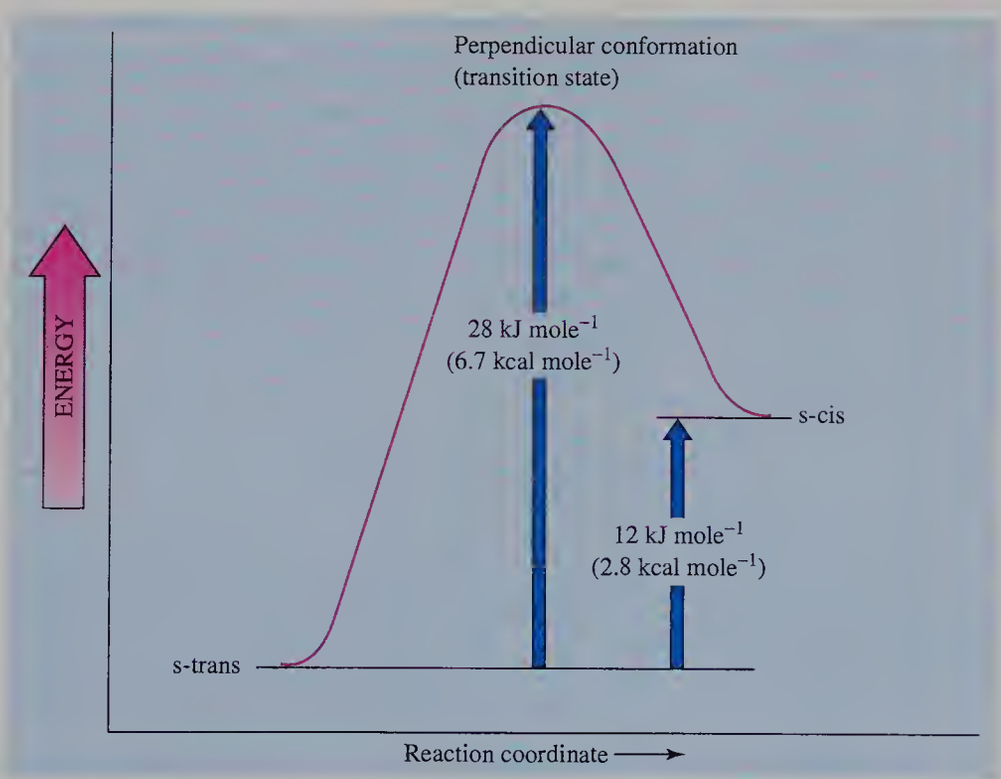


FIGURE 12.6 Rotational Barrier of 1,3-Butadiene
The s-trans conformation has all 2*p* orbitals aligned parallel to one another to form a resonance-stabilized system. The perpendicular conformation at the transition state for rotation has the 2*p* orbitals of the C-2 and C-3 atoms perpendicular to one another. As a result there are two isolated double bonds in the transition state.

Problem 12.8

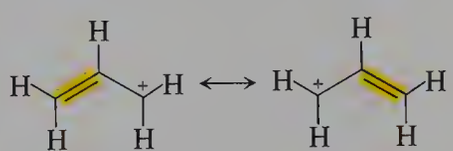
Draw the structure of the planar conformations of (2Z,4Z)-hexadiene and determine whether the equilibrium constant for conversion of the s-trans to s-cis conformation is larger or smaller than the same equilibrium for 1,3-butadiene.

Problem 12.9

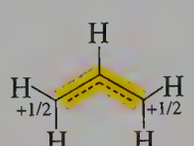
How is the equilibrium constant for the s-trans to s-cis conversion affected by the size of alkyl groups in 2,3-dialkyl-substituted 1,3-butadienes?

12.5 Allylic Systems

We recall that two Lewis structures represent the resonance stabilization of the charge of the allyl carbocation (Section 10.3). The charge is located on the C-1 atom in one resonance form and the C-3 atom in the other. The two resonance forms also have the "double bond" in different places. Thus, we write the two structures to represent delocalization of two electrons over a three-atom system.



A single representation using dashed lines shows the delocalization of the pair of π electrons over the three atoms. The allyl system has a partial positive charge ofa $+\frac{1}{2}$ at each of the terminal carbon atoms.

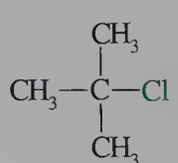


Regardless of the method used to represent it, the allyl carbocation is much more stable than a primary alkyl carbocation. In fact, primary allylic carbocations have about the same stability as secondary carbocations, as shown by the fact that they can form in S_N1 reactions at comparable rates.

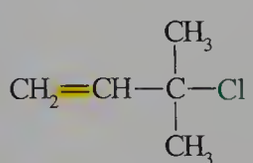
Now let's apply molecular orbital theory to the structure and reactions of allylic systems. In this section we will first discuss allylic carbocations in greater detail. Then we will consider two related resonance-stabilized species: the allylic radical and the allylic carbanion.

Allylic Carbocations

The rate of reaction of 3-chloro-3-methyl-1-butene with solvents such as water or ethanol is about 100 times as fast as the reaction of *tert*-butyl chloride.

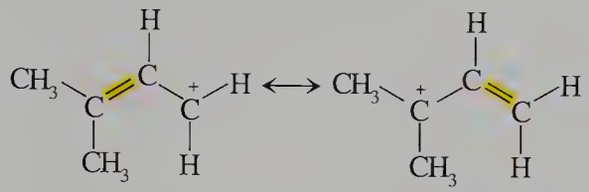


tert-butyl chloride
reactive in S_N1 processes



3-chloro-3-methyl-1-butene
very reactive in S_N1 processes

Both compounds have a tertiary carbon–chlorine bond and react by way of the S_N1 pathway to form tertiary carbocations. However, the carbocation from the unsaturated compound is also allylic. The vinyl group bonded to the positively charged carbon atom releases electrons by resonance to delocalize the positive charge over two atoms.



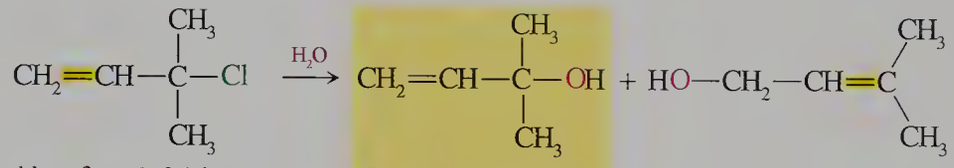
1 2

resonance contributors of 1,1-dimethylallyl carbocation

Because of resonance stabilization, we expect the transition state leading to the allylic carbocation to have a lower energy barrier than the transition state leading to the *tert*-butyl carbocation.

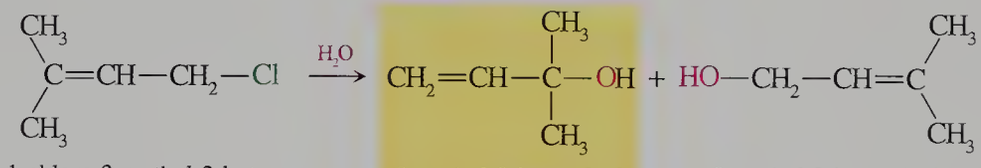
The allyl carbocation itself has its positive charge distributed equally at both terminal carbon atoms because those atoms are equivalently substituted. However, the charge is not equally distributed at two carbon atoms in the substituted allylic carbocation. In structure 1, the positive charge is located at a primary carbon atom, in structure 2 at a tertiary carbon atom. Therefore, charge is not equally distributed at two sites in this allylic carbocation, and the two resonance forms do not contribute equally to the resonance hybrid of the substituted allylic carbocation. Resonance form 2 more closely represents the carbocation, and there is a higher charge at the tertiary carbon atom.

When 3-chloro-3-methyl-1-butene reacts with water, the intermediate carbocation formed in the rate-determining step is captured in a fast second step. Two isomeric substitution products form in unequal amounts in this second step. The tertiary alcohol is the major product.



3-chloro-3-methyl-1-butene — 2-methyl-3-buten-2-ol (85%) — 3-methyl-2-buten-1-ol (15%)

The existence of a resonance-stabilized allylic carbocation formed in the first step of the S_N1 reaction, which subsequently reacts in a faster second step, is also demonstrated by the products of reaction of 1-chloro-3-methyl-2-butene in water.

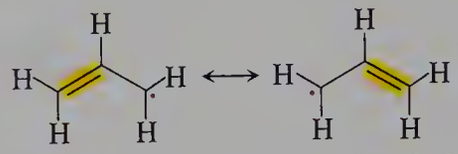


1-chloro-3-methyl-2-butene — 2-methyl-3-buten-2-ol (85%) — 3-methyl-2-buten-1-ol (15%)

Two substitution products result from capture of the allylic carbocation by a nucleophilic water molecule at either of two partially positive sites depicted in the contributing resonance forms. However, remember resonance forms 1 and 2 of the 1,1-dimethylallyl carbocation do not exist. They are not separate species in equilibrium with each other, merely contributing structures to a resonance hybrid. The products formed are not the result of capturing a resonance structure because they have no independent existence.

Allylic Radicals

An allylic radical is resonance stabilized. The unpaired electron is delocalized with an equal probability of being at either of the two terminal carbon atoms. The central carbon atom has no radical character.



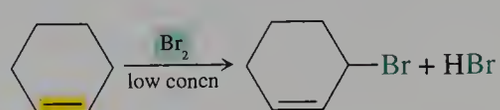
resonance contributors of the allylic radical

The bond dissociation energy of the allyl C—H bond of propene (the C—H bond at C-3), compared to the C—H bond of the primary carbon atom of propane, shows the resonance stabilization of the allylic radical. The 58 kJ mole^{-1} difference between these two bond dissociation energies is a direct measure of the resonance energy of the allylic radical.

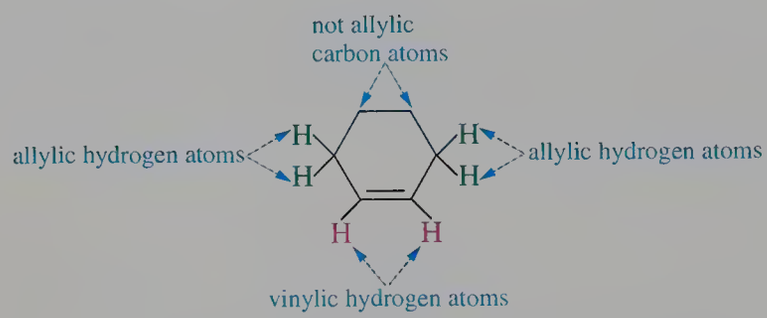
$$CH_2{=}CH{-}CH_2{-}H \longrightarrow CH_2{=}CH{-}CH_2\cdot + H\cdot \qquad \Delta H^\circ = 364 \text{ kJ mole}^{-1}$$

$$CH_3{-}CH_2{-}CH_2{-}H \longrightarrow CH_3{-}CH_2{-}CH_2\cdot + H\cdot \qquad \Delta H^\circ = 422 \text{ kJ mole}^{-1}$$

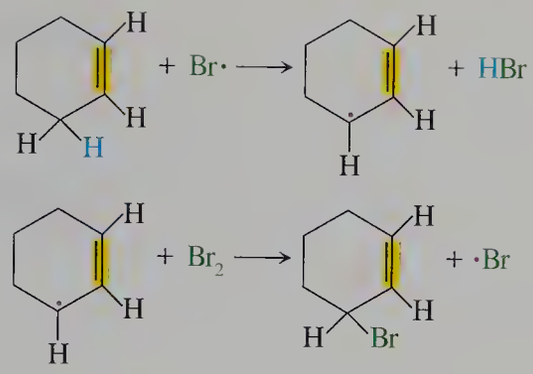
We recall that the C—H bonds of alkanes react with halogens under free radical conditions to give alkyl halides (Section 5.4). The enhanced reactivity of an allylic C—H bond is shown in its reaction with low concentrations of bromine under free radical conditions. Consider the reaction of cyclohexene with bromine when energy is added by a source of light, such as a sunlamp.



Any of the four equivalent allylic hydrogen atoms can react. The vinyl C—H bonds do not react because the C—H bond energy of sp^2-hybridized carbon atoms is larger than the bond energy of sp^3-hybridized carbon atoms. The four C—H bonds not located at allylic sites are less reactive than the allylic C—H bonds. We would expect this result, based on the difference in the bond dissociation energies cited above for propane compared to propene.

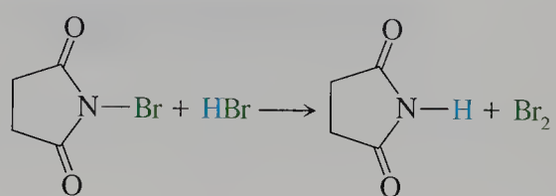


Let's consider the potential complications in the reaction of cyclohexene with bromine. We know that alkenes react with bromine by an electrophilic addition mechanism. Might not this reaction occur in competition with the allylic bromination reaction at low concentrations of bromine? The answer is "no" because the free radical chain reaction is much faster than the addition reaction if the concentration of bromine is low. The free radical chain reaction for reaction of cyclohexene with bromine has the following propagation steps.



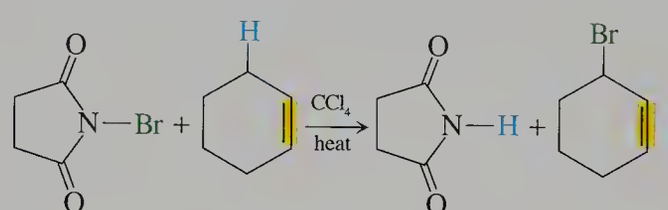
A second competing reaction of cyclohexene is suggested by these propagation steps. Hydrogen bromide continually forms in the reaction. As its concentration increases, might it not add to the double bond in competition with the free radical allylic bromination? The answer is "it could" if it were to accumulate as a reaction product.

We can not only experimentally generate a low concentration of bromine but also prevent the continued production of HBr that would react in an electrophilic addition process. The procedure uses *N*-bromosuccinimide (NBS) as the source of bromine. The initial hydrogen bromide generated in the free radical bromination reacts with NBS to generate bromine. Hence, this reaction simultaneously generates a low concentration of bromine as well as removing HBr formed in the free radical reaction.



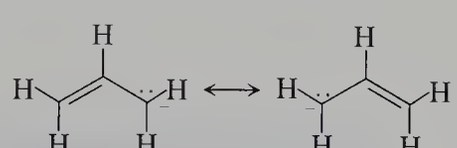
NBS

As a consequence, the net stoichiometry of this reaction shows neither bromine, the active brominating agent, nor the by-product hydrogen bromide.



Allylic Carbanions

Because allylic carbocations and allylic radicals are resonance stabilized, we also expect allylic carbanions to be resonance stabilized.



resonance contributors of the allyl carbanion

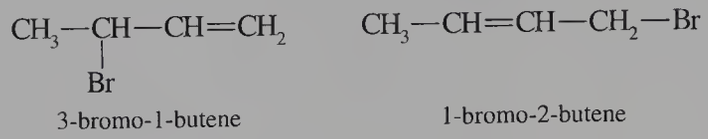
The reactivity of allylic Grignard reagents reveals this stabilization. Although Grignard reagents have considerable carbon–magnesium covalent character, they also behave as carbanions. Grignard reagents may be represented with an ionic carbon–magnesium bond to show their carbanionic character.

$$\overset{\delta^-}{R}—\overset{\delta^+}{MgBr} \quad \text{or} \quad R^- \ ^+MgBr$$

As a result, the ^+MgBr species can move from one carbanion center to another in an allyl anion. Note that this description of the equilibration of two forms of a Grignard reagent is not the same phenomenon as resonance. In resonance, only electrons "move". The allyl Grignard reagent is a mixture of two equilibrium species. In this case, the magnesium atom moves to give structurally equivalent species.

$$CH_2{=}CH{-}CH_2^- \ ^+MgBr \rightleftharpoons BrMg^+ \ ^-CH_2{-}CH{=}CH_2$$

Because of the equilibration of allylic Grignard reagents, isomeric allylic halides react with magnesium to give the same Grignard reagent. For example, both 3-bromo-1-butene or 1-bromo-2-butene react to yield the same mixture of Grignard species.



3-bromo-1-butene 1-bromo-2-butene

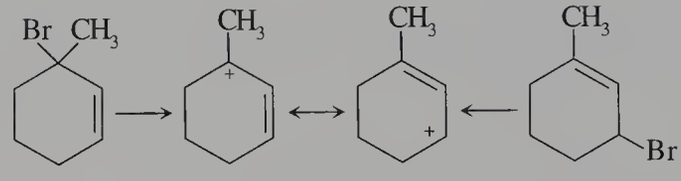
The Grignard reagent made from either compound reacts with water to give a mixture of 1-butene and *cis*- and *trans*-2-butenes.

Problem 12.10

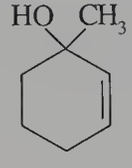
Write the structure of an isomeric compound that will give the same carbocation as 3-bromo-3-methylcyclohexene under S_N1 conditions. Predict the composition of the product mixture from the reaction of either compound in water.

Sample Solution

First write the carbocation obtained by heterolysis of the carbon-bromine bond. Then move an electron pair of a π bond to obtain the isomeric allylic carbocation. Add a bromide ion to that carbocation to obtain the isomeric bromo compound that would give the same resonance-stabilized carbocation.

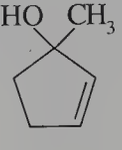


The composition of mixtures of alcohols obtained by hydrolysis given as examples in this section indicated that the more substituted alcohol is obtained as a result of capture of the higher substituted carbocation. Thus, we can predict that the major product should be a tertiary alcohol.



Problem 12.11

What substitution products should form by reaction of the following alcohol with HCl? Which should predominate?

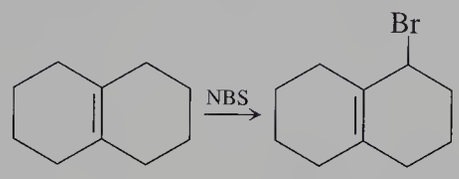


Problem 12.12

Write the structures of all products formed in the allylic bromination of 2-hexene, using one molar equivalent of NBS.

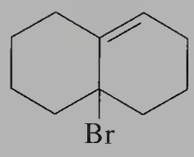
Problem 12.13

Free radical bromination of the following compound using one molar equivalent of NBS gives one allylically substituted bromo compound. Write the structure of a second possible isomeric product and explain why it is not formed.



Sample Solution

A second resonance form can be written for the radical resulting from abstraction of an allylic hydrogen atom. Subsequent reaction of the radical at the tertiary carbon atom would give



The difference in the stabilities of radicals with the degree of substitution is not as pronounced as for carbocations. Thus other structural features such as the stabilization of the double bond are also important in controlling the product formed. The observed product has a tetrasubstituted double bond.

Problem 12.14

Write the structures of the isomeric Grignard reagents formed from 3-methyl-1-bromo-2-butene. Which structure is more stable? Give two reasons for your choice.

12.6 Molecular Orbital Representation of Allyl Systems

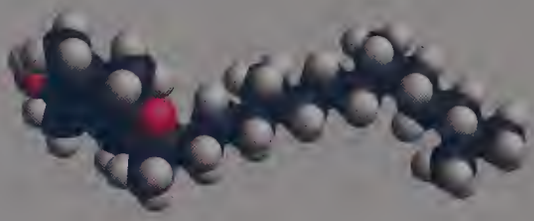
The allyl carbocation, allyl radical, and allyl carbanion all have a π system that results from the overlap of three 2*p* orbitals. The three species differ only in the number of electrons in the resulting molecular orbitals. The cation, radical, and anion have two, three, and four electrons, respectively, in the π system.

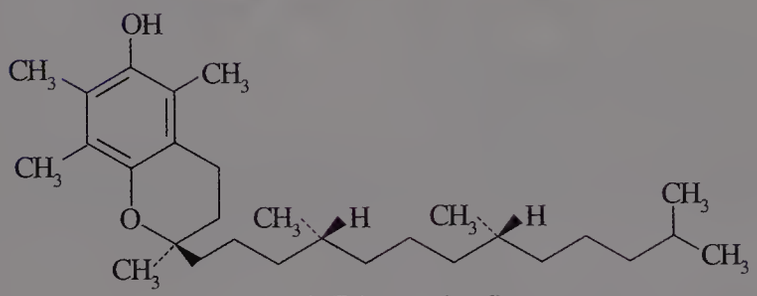
Just as the four 2*p* orbitals of 1,3-butadiene overlap to form four π molecular orbitals, the three 2*p* orbitals of the allyl system overlap to give three π molecular orbitals. We label them π_1, π_2, and π_3 in order of increasing energy. These three orbitals have 0, 1, and 2 vertical nodal planes, respectively. We also expect half of the molecular orbitals to be bonding and half to be antibonding. At this point we see that there is a difference in the model for polyenes and the allyl system. The allyl system has an odd number of molecular orbitals, whereas polyenes have an even number.

The three 2*p* orbitals of the allyl system are shown in Figure 12.7. The lowest energy MO is symmetric and is bonding over all three atoms. The MO labeled π_3 is entirely antibonding and has two vertical nodal planes. It is also symmetric. The antisymmetric π_2 MO seems unusual at first glance. This orbital is neither bonding nor antibonding: It is nonbonding. Because there are three atoms, the single vertical nodal plane must occur at the center carbon atom. Thus, for π_2, the coefficient for the

Allylic Free Radicals and Vitamin E

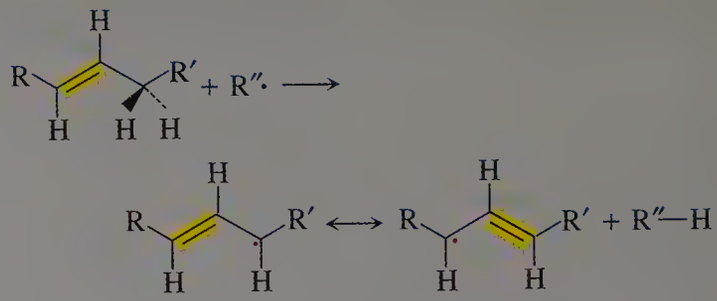
Free radicals are highly reactive species that wreak havoc on cellular molecules. Free radicals, such as the hydroperoxy radical (HOO·), can be generated by metabolism of drugs, as intermediates in enzyme-catalyzed reactions, as well as by other pathways. The *antioxidant* vitamin E, also called α-tocopherol, captures cellular free radicals and renders them harmless.





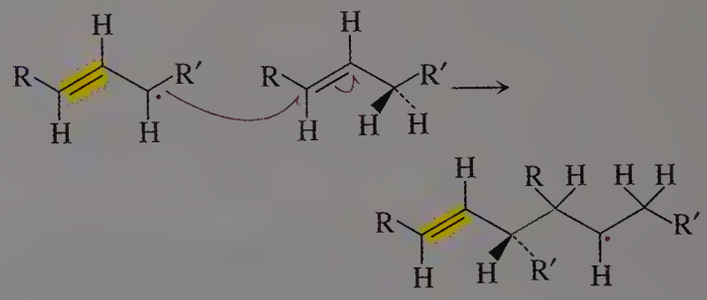
vitamin E (α-tocopherol)

Consider the reaction of a free radical with an unsaturated fatty acid or any other alkene. In the first step, the free radical abstracts an allylic hydrogen atom to give a resonance-stabilized allylic radical.



resonance-stabilized allylic radical

The radical can then react with another unsaturated fatty acid. This reaction is simply the first step in a free radical polymerization. This process destroys lipids in biological membranes, killing cells.



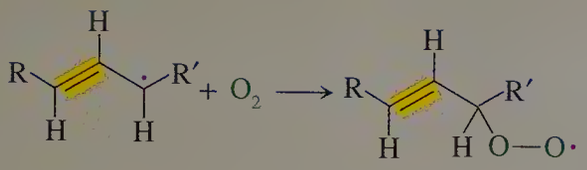
An allylic free radical can also react with oxygen to produce a hydroperoxy radical, an even more reactive intermediate.

contribution of the 2*p* orbital of C-2 is zero. But, you may ask, "Where is the 2*p* orbital of the C-2 atom?" The answer is that none of the 2*p* orbitals are "really" there. We show them to create a picture of the molecular orbital, merely a mathematical combination of the atomic orbitals.

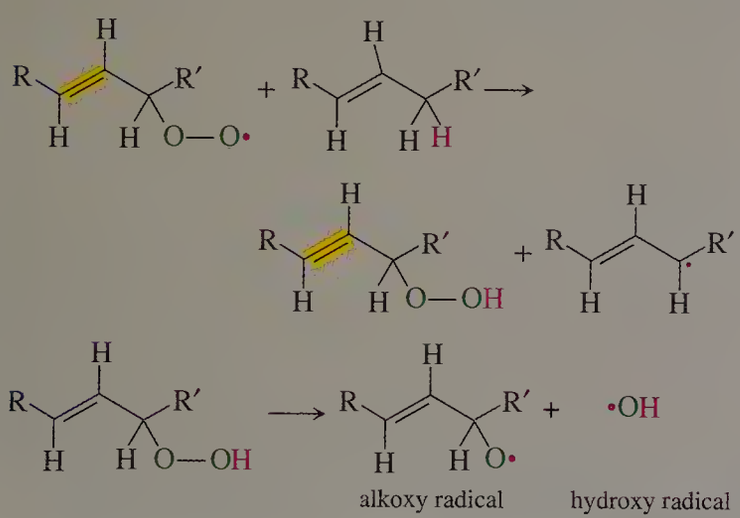
Any electron in the π_2 MO of an allyl system is at the same energy as an electron in a 2*p* atomic orbital. The locations of the electrons in the π orbitals of the carbocation, radical, and carbanion that are not in σ bonds are shown in Figure 12.8.

First, consider the allyl radical. Because it has the same number of π electrons as contributing 2*p* atomic orbitals, the radical has no charge. Two of the π electrons are in the π_1 MO. The third electron of the radical is located in the π_2 MO. A consideration of the contributing atomic orbitals forming this molecular orbital shows the electron is equally shared by the C-1 and C-3 atoms.

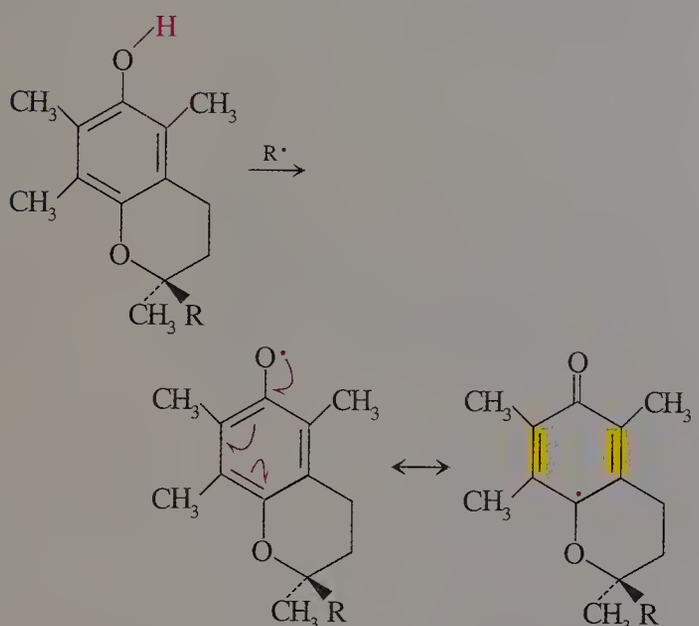
We can determine the charge distribution of both the allyl carbocation and the allyl carbanion using the allyl radical as a reference. A single electron added to the radical to give the anion must be paired with the electron already located in the π_2 MO. The contributing atomic orbitals forming this molecular orbital indicate that the C-1 and C-3 atoms share the electron pair equally. Each atom has a $-\frac{1}{2}$ charge.



Disproportionation of the hydroperoxy radical produces an alkoxy radical and a hydroxyl radical, a very dangerous species in biological systems. Free radicals such as these react with many cellular proteins and nucleic acids, causing extensive cellular damage. Free radicals may also play a significant role in the aging process.



Vitamin E interrupts free radical chain reactions by capturing free radical intermediates. It acts as a scavenger by forming a relatively stable hydroquinone radical. Because the free radical derived from vitamin E is relatively stable, it does not disrupt cellular chemistry.



Many food additives also show antioxidant properties similar to those of vitamin E. These additives, much maligned by persons who object to "unnatural food," not only preserve food by preventing oxidation but also preserve the humans who eat them.

To form the allyl carbocation, one electron can be removed from the π_2 MO. Because only the C-1 and C-3 atoms in the radical have electron density, the positive charge generated by loss of an electron is distributed on both atoms. Each atom has a $+\frac{1}{2}$ charge.

Problem 12.15

Consider the π_3 MO for the pentadienyl radical. How many vertical nodal planes does it have? Noting that the unpaired electron must be in π_3, determine which atoms have radical character.

$$CH_2{=}CH{-}CH{=}CH_2{-}CH_2\cdot$$

Problem 12.16

The ionization energies of the carbon-chlorine bond for (*E*)-1-chloro-2-butene and 3-chloro-2-methyl-1-propene in the gas phase are 672 and 706 kJ mole^{-1}, respectively. Using molecular orbital concepts, explain this order based on the stability of the carbocations.

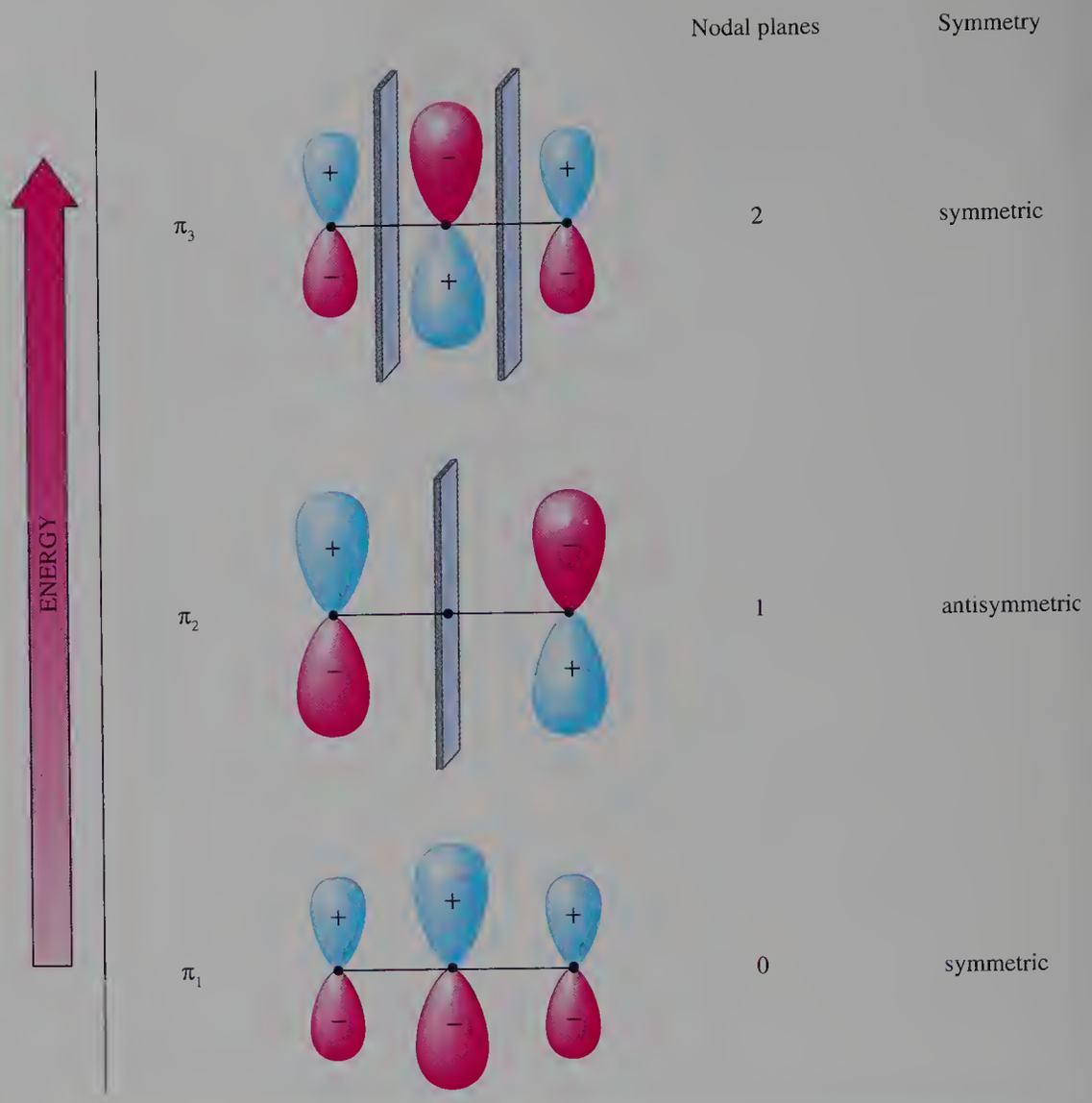


FIGURE 12.7 Molecular Orbitals of Allyl Systems
The sizes of the 2*p* atomic orbitals represent the degree to which the orbitals contribute to the molecular orbitals in the allyl system. The constructive overlap of all three 2*p* orbitals in the lowest energy molecular orbital is bonding over the whole system. The nonbonding molecular orbital has a nodal plane at the center carbon atom.

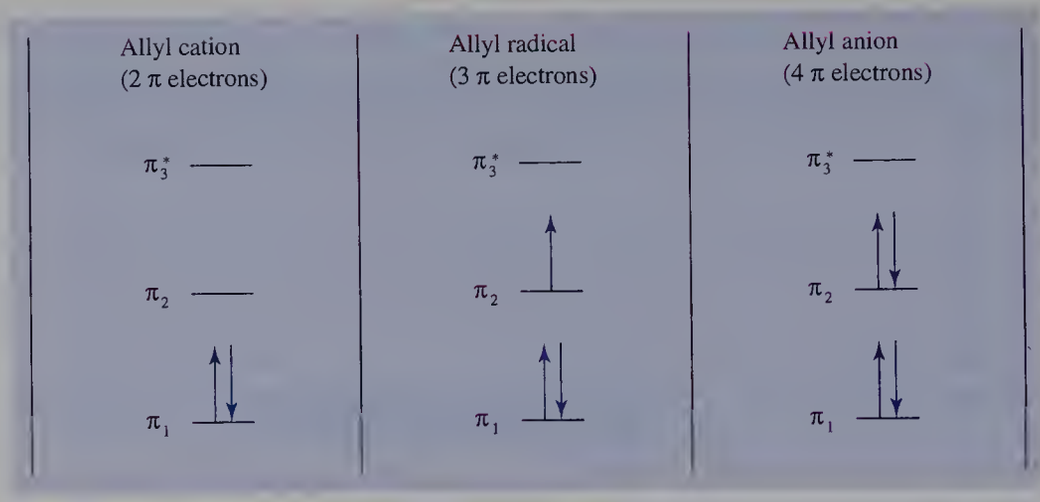


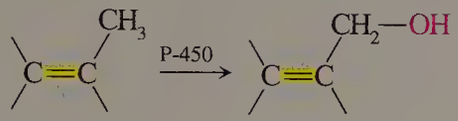
FIGURE 12.8 Electronic Configuration of Allyl Intermediates
The electrons of the π system are located in the lowest available orbitals.

Sample Solution

Both compounds give allylic carbocations. One of the resonance contributors for the carbocation from (*E*)-1-chloro-2-butene has the positive charge at a secondary carbon atom. In terms of molecular orbital theory, the methyl group is at the "end" of an allyl system where it affects the stability of the π_2 molecular orbital. The two resonance contributors for the carbocation from 3-chloro-2-methyl-1-propene are both primary. In terms of molecular orbital theory, the methyl group is bonded to the "center" carbon of an allyl system. There is a node at the C-2 atom of the π_2 molecular orbital, and the methyl group cannot stabilize the carbocation.

Allylic Oxidation and the Metabolism of Marijuana

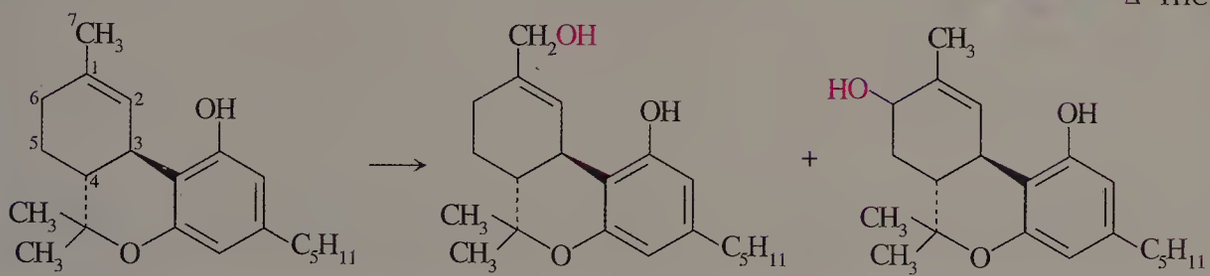
The detoxification of some compounds by the enzyme cytochrome P-450 occurs by the oxidation of allylic sites. An example of such an allylic oxidation is the first step in the degradation of one of the psychoactive ingredients in marijuana. Although the nature of all steps is not well known, an allyl radical is a likely intermediate.



(an allyl alcohol)

Marijuana contains Δ^1-tetrahydrocannabinol (Δ^1-THC), which has three allylic centers. The C-3 and C-6 centers are secondary and the C-7 is primary. Allylic oxidation does not occur at the C-3 atom because of steric hindrance caused by the geminal dimethyl groups. Of the other two possible sites, the C-7 product predominates over the C-6 product even though the C-7 atom is primary. However, the difference in the stabilities of radicals is not as large as the difference in the stabilities of carbocations. Thus, other factors such as steric hindrance could play a role in the regioselectivity of this reaction. The C-7 methyl group is sterically more accessible than the secondary C-6 site. Interestingly, the C-7 product is even more psychoactive than Δ^1-THC.

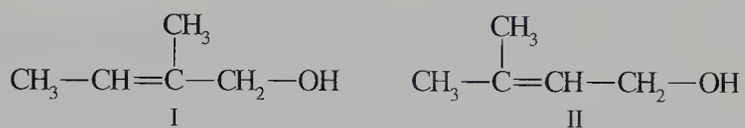
Δ^1-THC



Δ^1-THC | 7-hydroxy-Δ^1-THC | 6-hydroxy-Δ^1-THC

Problem 12.17

Based on molecular orbital theory, predict which of the following primary alcohols should react faster with HBr in a S_N1 reaction.

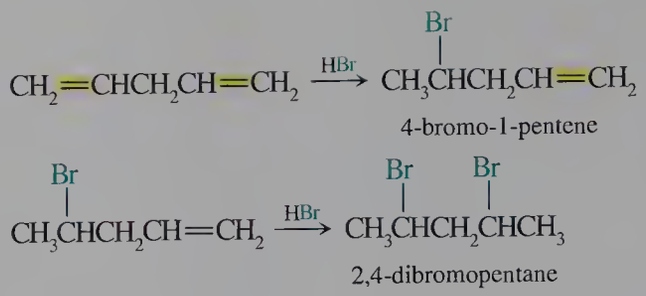


12.7 Electrophilic Conjugate Addition Reactions

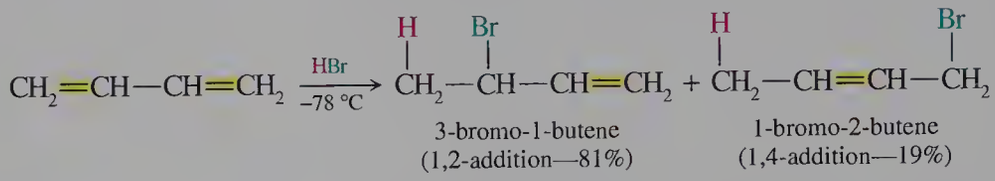
Our discussion of conjugated alkadienes at the beginning of this chapter was limited to their physical properties and the role of molecular orbital theory in describing their structure. Next, we focused on the stability of allylic intermediates and their reactivity. We will use this accumulated knowledge to interpret the reactions of conjugated dienes with electrophiles that generate allylic intermediates.

1,2- and 1,4-Addition Reactions

Addition of electrophilic reagents to nonconjugated alkadienes can occur at one or both double bonds. The products are those predicted by Markovnikov's rule. Both products result from a **1,2-addition** reaction.

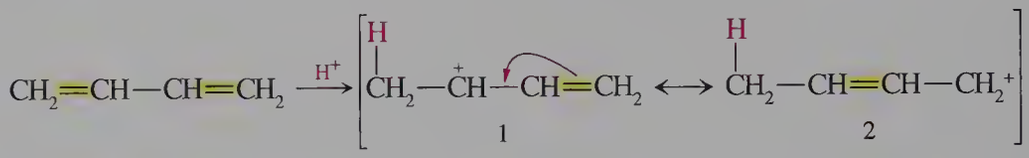


The addition of HBr to a conjugated diene differs strikingly. Two products result when one molar equivalent of HBr reacts at a low temperature.

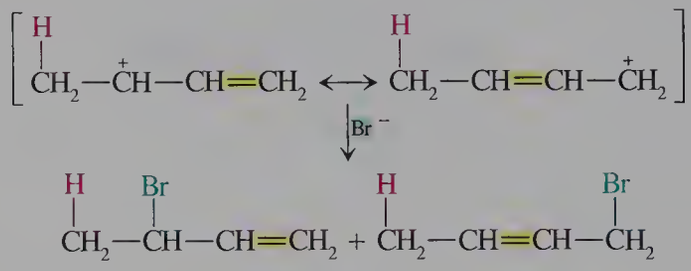


The 3-bromo-1-butene results from direct addition to a double bond. This product follows Markovnikov's rule. The 1-bromo-2-butene is an unusual product, which results from addition of HBr to the C-1 and C-4 atoms. This product results from a **1,4-addition reaction**. Note that the double bond in the product lies between the C-2 and C-3 atoms.

Now let's consider the origin of the two addition products by examining the intermediate formed in the electrophilic addition of a proton to the conjugated diene.



The carbocation intermediate is an allylic-type ion, represented by two contributing resonance structures. In the next step in the addition reaction, the nucleophilic bromide ion can bond to the secondary carbon atom (resonance form 1) to give the 1,2-addition product. However, if the bromide ion bonds to the primary carbon atom (resonance form 2), the 1,4-addition product results.



Kinetic Control of Addition Reactions

When HBr adds to 1,3-butadiene at −78 °C, the major reaction product is the one that forms at the faster rate. We say that the process is under **kinetic control**. Kinetically controlled reactions account for the observed products in most organic reactions. The product that forms in the larger amount results from the reaction with the lowest energy barrier leading to the transition state for the rate-determining step. In the addition of HBr, the carbocation forms in the rate-determining step, but it still must react with a nucleophile and pass through a second transition state of lower energy (Figure 12.9).

Because of the predominance of a 1,2-addition product over one from 1,4-addition, we conclude that the energy barrier for combination of the carbocation with bromide ion at the C-2 atom is lower than for combination at the C-4 atom. Because the transition state energy is closer to that of the carbocation than the product, the

structure of the transition state resembles the carbocation. Resonance form 1 is the more important contributor to the allylic carbocation. Thus, the energy barrier is lower for the transition state for combination of a nucleophile at the C-4 atom.

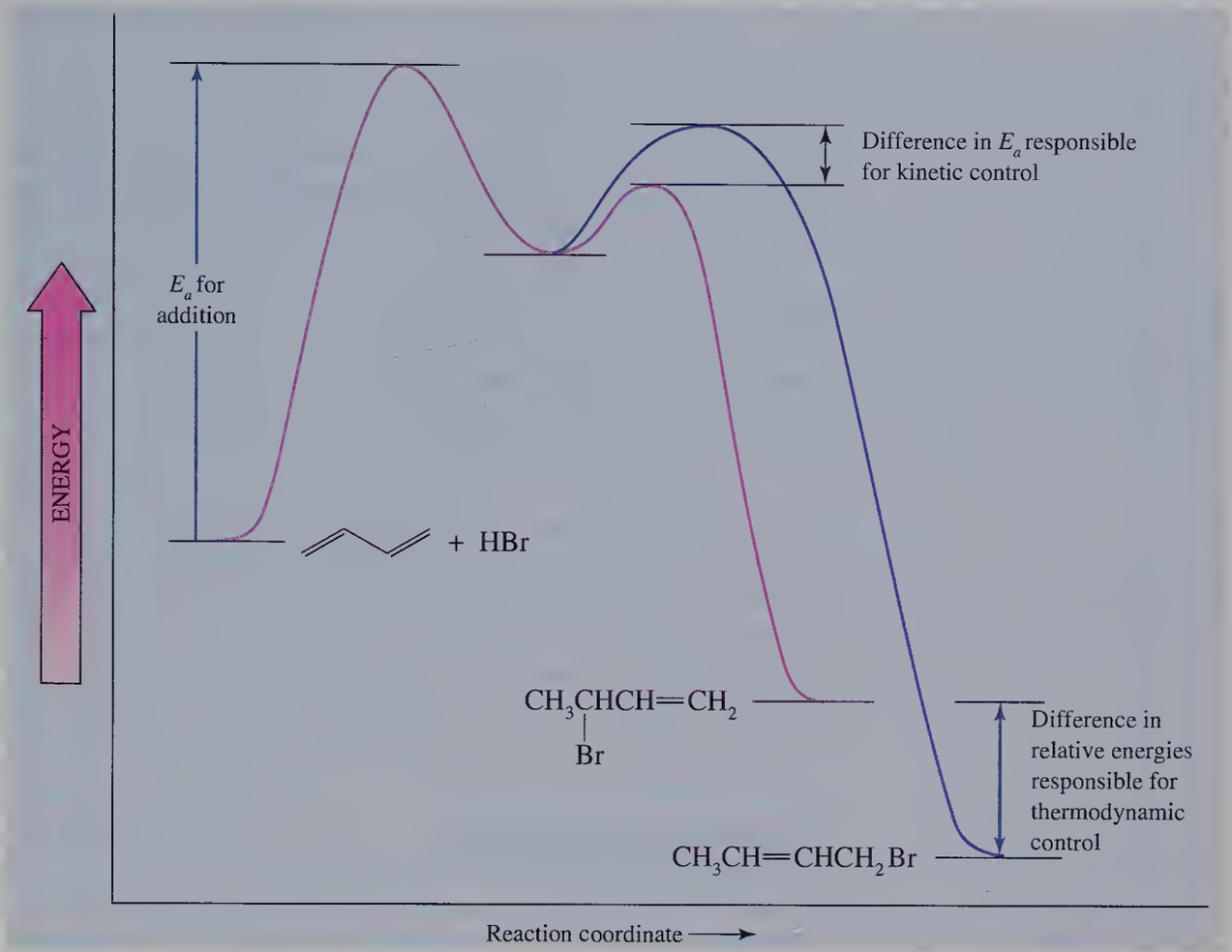
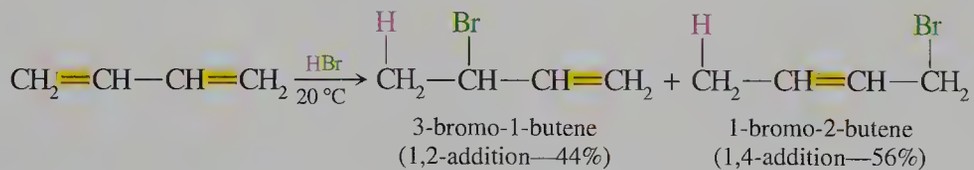


FIGURE 12.9 Reaction Coordinate Diagram for 1,2- and 1,4- Addition
The transition state energy for 1,2-addition of HBr to 1,3-butadiene is lower than 1,4-addition. This difference in energy is responsible for kinetic control of the addition reaction. The 1,4-addition product is of lower energy than the 1,2-addition product. This difference is responsible for thermodynamic control of the addition product.

Thermodynamic Control of Addition Reactions

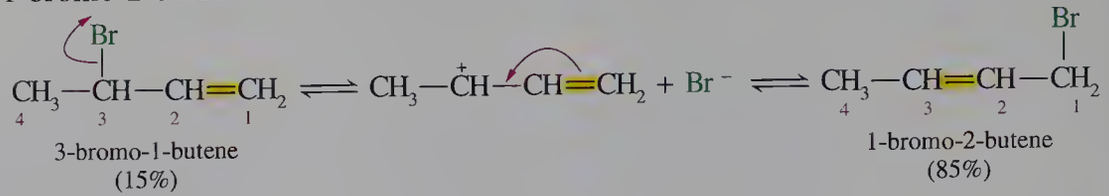
In some reactions, products can equilibrate with each other. In such cases, the product composition reflects the relative stabilities of the products, not their relative rates of formation. Reactions in which the products equilibrate are said to be under **thermodynamic control**.

When the electrophilic addition reaction of HBr to 1,3-butadiene is carried out at 20 °C, the product mixture markedly differs from the product mixture of a reaction carried out at −78 °C. The major product results from the 1,4-addition reaction.



Why does the ratio of products depend on temperature? The answer is provided by a third experimental fact. At higher temperatures, the two products can interconvert

by a common allylic carbocation. In a separate experiment, when either of the two compounds is heated at 45 °C, an equilibrium mixture with a ratio of 85:15 of 1-bromo-2-butene to 3-bromo-1-butene forms.



3-bromo-1-butene (15%)

1-bromo-2-butene (85%)

Even though 3-bromo-1-butene, the product of 1,2-addition, still forms faster in the electrophilic addition reaction, it equilibrates to form the more stable 1-bromo-2-butene. As a result, it may appear that the 1,4-addition product forms faster, but it does not.

Why is 1-bromo-2-butene favored at equilibrium over 3-bromo-1-butene? It is no longer a question of the location of a charge in the transition state. The position of the chemical equilibrium reflects thermodynamic stability, and we know that the disubstituted double bond of 1-bromo-2-butene is more stable than the terminal, monosubstituted double bond in 3-bromo-1-butene. At a higher temperature, the reaction is under thermodynamic control. The more stable product predominates.

Now let's account again for the effect of temperature on the composition of the product mixture. Figure 12.9 indicates the relative energies of the two transition states leading to 1,2- and 1,4-addition products and the relative energies of these two products. At a low temperature, the individual products do not have sufficient energy to ionize and form the carbocation intermediate. This makes the reaction irreversible, and the product mixture reflects kinetic control governed by the relative energies of the transition states. At a higher temperature, the products do ionize and form the allylic carbocation intermediate. The less stable 3-bromo-1-butene then converts to the more stable 1-bromo-2-butene.

Problem 12.18

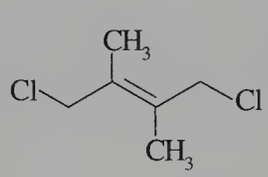
When bromine adds to a conjugated diene, a carbocation forms, not a bromonium ion. Explain why. One molar equivalent of bromine adds to 1,3-butadiene to give a mixture of two products. What are their structures?

Problem 12.19

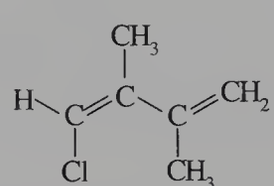
Reaction of 2-methyl-1,3-butadiene with chlorine in water gives a chlorine-containing tertiary alcohol. Draw its structure. Does 1,2- or 1,4-addition occur? What is the electrophile in the reaction?

Problem 12.20

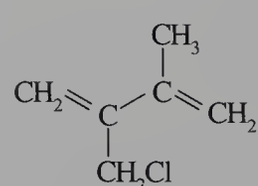
Reaction of 2,3-dimethyl-1,3-butadiene with chlorine gives a mixture with the indicated composition. Explain the origin of each of the products.



(45%)



(1%)



(54%)

12.8 Cumulated Dienes

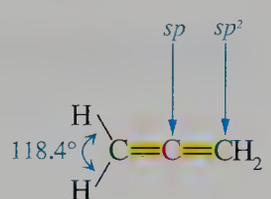
Cumulated dienes have one carbon atom between two carbon–carbon double bonds. Cumulated dienes are also called **allenes** after the common name of the simplest member of the series, $CH_2{=}C{=}CH_2$. The two double bonds of allenes are closer together than conjugated double bonds because there is no intervening single bond. We might naively think that "closer is better" and predict that allenes are even more stable than conjugated dienes. The fallacy of this generalization is shown by the heat of hydrogenation data—our traditional way of characterizing the stability of a substance compared to a saturated reference compound. The total heat of hydrogenation of 1,2-pentadiene is 292 kJ mole^{-1}.

$$CH_2{=}C{=}CH{-}CH_2{-}CH_3 \xrightarrow[Pt]{H_2} CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_3 \quad \Delta H^\circ = -292 \text{ kJ mole}^{-1}$$

The total heats of hydrogenation of 1,3-pentadiene and 1,4-pentadiene in forming pentane are 225 and 252 kJ mole^{-1}, respectively. Thus, the cumulated double bonds of 1,2-pentadiene are not only less stable than those of a conjugated diene, but even less stable than two isolated double bonds.

Structure of Allene

The carbon–carbon double bond distance in allene is 131 pm, slightly shorter than the 134 pm carbon–carbon double bond distance of 1-propene.



The terminal carbon atoms are sp^2 hybridized, and each provides one $2p$ orbital to form a double bond with the central carbon atom. The central carbon atom must provide two $2p$ orbitals, and thus must be sp hybridized. Each of the sp hybrid orbitals forms a σ bond to a terminal carbon atom. The two $2p$ atomic orbitals of the central carbon atom must be mutually perpendicular, and as a consequence so must the individual double bonds (Figure 12.10). The plane of one CH_2 unit stands perpendicular to the plane of the other CH_2 unit. This precludes resonance interaction between the two π systems.

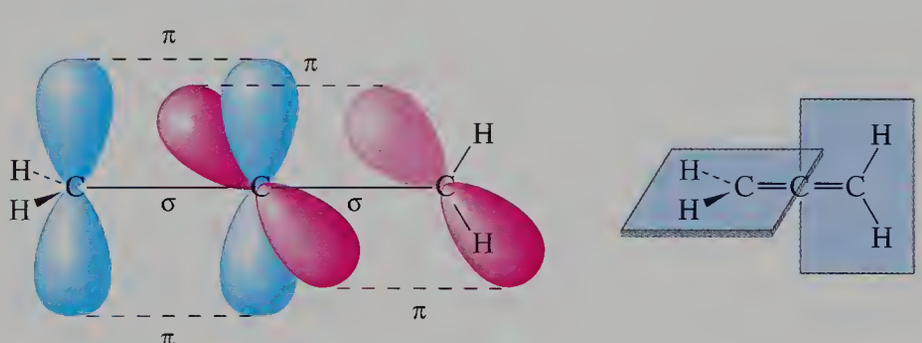
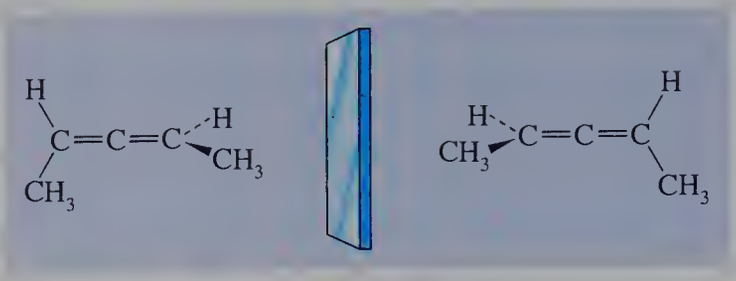


FIGURE 12.10 Structure of Allene
The two π bonds of allene are perpendicular to each other. The plane of one CH_2 unit is perpendicular to the plane of the other CH_2 unit.

Let's consider the geometric arrangement of atoms bonded to sp^2-hybridized carbon atoms of allenes. The two groups bonded to one atom lie in a plane perpendicular to the two groups bonded to the other atom. Hence, the mirror image

2,3-pentadienes are not superimposable on each other (Figure 12.11). There are two enantiomeric compounds represented by this name. What is so interesting about these enantiomers? Well, there is no chiral carbon atom! Although all chiral substances studied to this point have one or more chiral carbon atoms, the existence of enantiomers does not depend on this requirement. The only requirement for chirality is that two isomers exist as nonsuperimposable mirror images.

FIGURE 12.11 Chirality in Allenes



Problem 12.21

What is the expected C—H bond length in allene?

Problem 12.22

Can 2-methyl-2,3-pentadiene exist as a set of enantiomers?

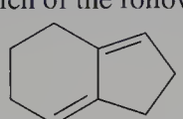
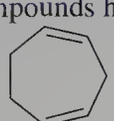
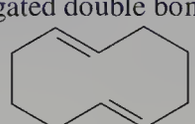
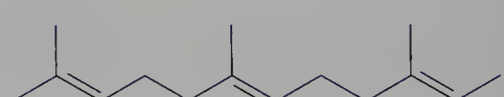
Problem 12.23

Reaction of 3-methyl-1,2-butadiene with chlorine under free radical conditions yields 2-chloro-3-methyl-1,3-butadiene. Write a mechanism for formation of the product.

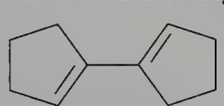
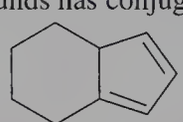
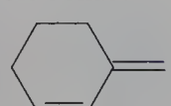
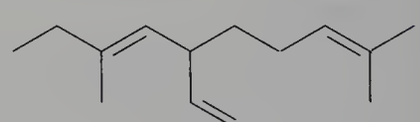
EXERCISES

Classes of Polyenes

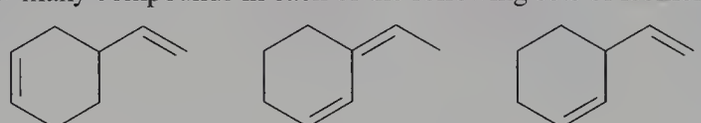
12.1 Which of the following compounds has conjugated double bonds?

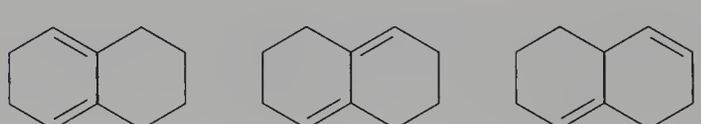
(a)  (b)  (c)  (d) 

12.2 Which of the following compounds has conjugated double bonds?

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

12.3 How many compounds in each of the following sets of isomeric compounds contain conjugated double bonds?

(a) 

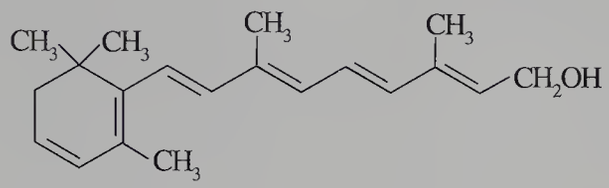
(b) 

12.4 Classify the double bonds in each of the following compounds.

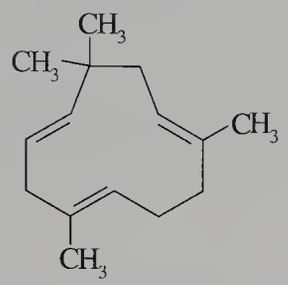
(a) mycomycin, an antibiotic

$$H{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CO_2H$$

(b) vitamin A_2, contained in freshwater fish



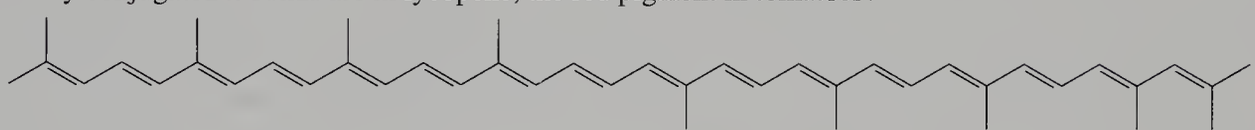
(c) humulene, a compound found in hops



12.5 Cyanodecapentayne has been identified in intergalactic space by radio astronomers. How many conjugated π bonds are in this compound?

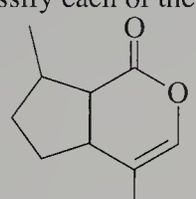
$$H{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}N$$

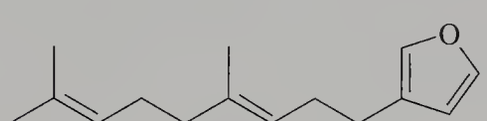
12.6 How many conjugated π bonds are in lycopene, the red pigment in tomatoes?

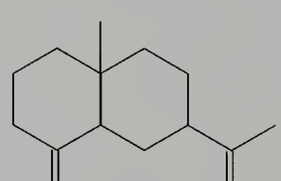


Terpenes

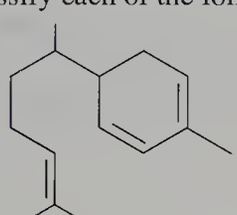
12.7 Classify each of the following terpenes and divide it into isoprene units.

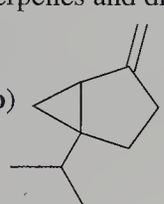
(a) 

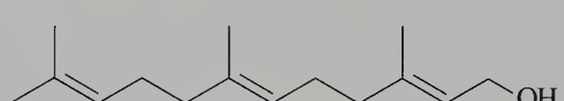
(b) 

(c) 

12.8 Classify each of the following terpenes and divide it into isoprene units.

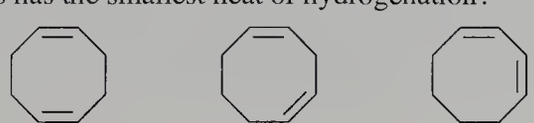
(a) 

(b) 

(c) 

Stability of Polyenes

12.9 Which of the following octadienes has the smallest heat of hydrogenation?



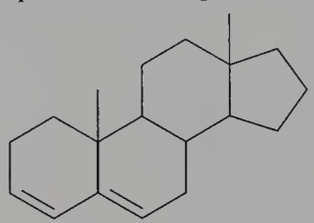
I II III

12.10 Estimate the heat of hydrogenation of each of the following isomers when forming hexane.

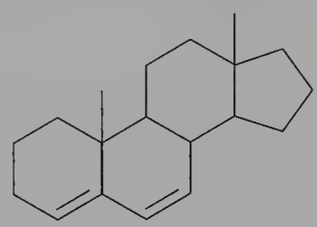
(a) (*E*)-1,3-hexadiene **(b)** (2*E*,4*E*)-hexadiene **(c)** (*E*)-1,4-hexadiene **(d)** 1,5-hexadiene

12.11 In acid solution, 1,4-cyclohexadiene isomerizes to a mixture containing 1,3-cyclohexadiene. Write a mechanism to account for this rearrangement. Which of the two isomers should form the major component of the equilibrium mixture?

12.12 Compare the relative stabilities of the following two dienes. If no competing reactions occur, indicate how the two compounds could be equilibrated using an acid catalyst.



I



II

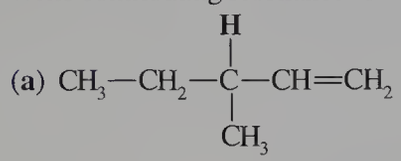
Molecular Orbitals of Polyenes

12.13 Which of the bonding molecular orbitals of 1,3,5,7-octatetraene resembles the Lewis structure for this compound?

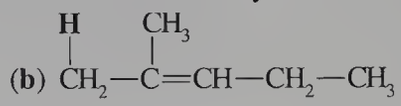
12.14 Determine the symmetry of each molecular orbital of 1,3-butadiene and suggest another guideline that could be added to your list of ways to write sequences of molecular orbitals.

Allylic Systems

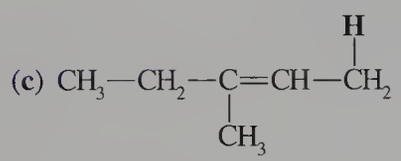
12.15 Write contributing resonance forms for the radical formed by abstraction of the bold hydrogen atom in each structure.



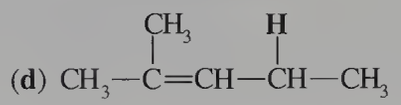
(a)



(b)

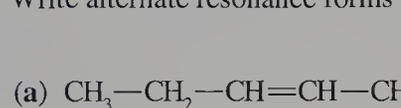


(c)

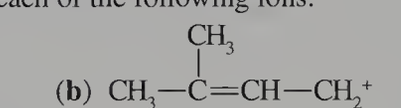


(d)

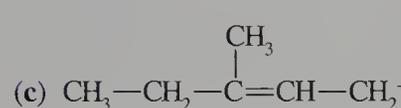
12.16 Write alternate resonance forms for each of the following ions.



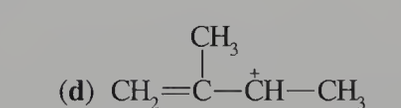
(a)



(b)



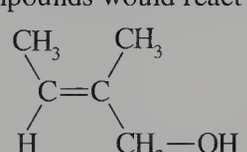
(c)



(d)

12.17 The rate of reaction of 1-chloro-3-methyl-2-butene in ethanol to give substitution products is about 6×10^3 times as fast as the rate for allyl chloride. Explain why.

12.18 Which of the following two compounds would react faster with HCl to produce an alkyl halide?



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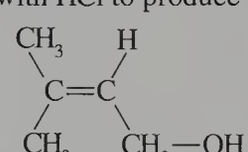
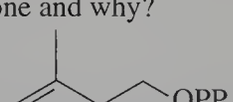
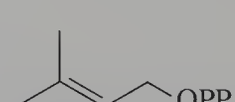


II

12.19 3-Isopentenyl pyrophosphate and 2-isopentenyl pyrophosphate are intermediates in the biosynthesis of terpenes. The pyrophosphate ion is a good leaving group. One of the two compounds reacts more readily to form a carbocation than the other. Which one and why?



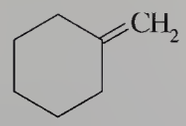
3-isopentenyl pyrophosphate



2-isopentenyl pyrophosphate

12.20 Write the structure of the major substitution product expected from the reaction of 1-methyl-3-cyclohexen-1-ol and HBr.

12.21 Write the structures of the compounds expected for the allylic bromination of methylenecyclohexane using one molar equivalent of NBS.



methylenecyclohexane

12.22 The reaction of NBS with 1-octene gives the following products in the indicated yields. Account for each of these products using accepted mechanisms. Explain why the indicated yields are "expected".

(*E*)-1-bromo-2-octene 44% (*Z*)-1-bromo-2-octene 39% 3-bromo-1-octene 17%

12.23 Alkenes can be allylically chlorinated using *tert*-butyl hypochlorite, $(CH_3)_3CO—Cl$, because the compound undergoes homolytic cleavage to give the *tert*-butoxy radical and a chlorine atom. Reaction of (*E*)-4,4-dimethyl-2-pentene with this compound gives two C_5H_9Cl products in the ratio 93:7. What are the structures of these two products?

12.24 Which compound should undergo allylic bromination at the faster rate, 1,3-pentadiene or 1,4-pentadiene? How would the composition of the product mixtures compare?

12.25 The C—Br bond dissociation energies of the following two compounds are essentially equal. Explain why the allylic compound does not have a lower bond dissociation energy.

I II

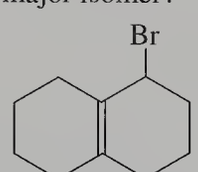
12.26 Which of the carbon–carbon bonds of 1,5-hexadiene has the smallest bond dissociation energy? Why?

12.27 The Grignard reagent of 3-bromo-1-butene is prepared and then reacted with D_2O. Write the products formed, indicating the location of the deuterium atom.

12.28 Write the structures of all species present in the Grignard reagent prepared from 1-bromo-3-methyl-2-butene.

12.29 The Grignard reagent of 3-chloro-4,4-dimethyl-1-pentene is prepared and then reacted with D_2O. Predict the major product formed in the reaction.

12.30 The Grignard reagent of the following bicyclic compound is prepared and then reacted with D_2O. Draw the structures of the two possible products. Which is the major isomer?



Molecular Orbitals of Allylic Systems

12.31 The highest energy π electrons of the pentadienyl anion are found in the π_3 molecular orbital. Write a representation of this orbital and predict the location of the negative charge for the ion.

$$CH_2{=}CH{-}CH{=}CH{-}CH_2^-$$

pentadienyl anion

12.32 Reaction of the pentadienyl cation with a nucleophile occurs by interaction with an empty molecular orbital. Which orbital? On the basis of this analysis, predict the carbon atoms at which the nucleophile will bond. Is this prediction consistent with the products predicted by writing conventional Lewis resonance forms for the cation?

$$CH_2{=}CH{-}CH{=}CH{-}CH_2^+$$

pentadienyl cation

Conjugate Addition Reactions

12.33 Only one product forms in the addition of one molar equivalent of HBr to 1,3-cyclohexadiene. Explain why.

12.34 Write the structure of the products formed in the addition of one molar equivalent of DBr to 1,3-cyclohexadiene, indicating the location of the deuterium.

12.35 Explain why the extent of 1,2- versus 1,4-addition cannot be determined for the reaction of 1,3-pentadiene with one molar equivalent of HCl.

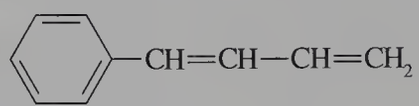
12.36 Write the structures of the products of the addition of one molar equivalent of DCl to 1,3-pentadiene. Considering these products, can you determine the amounts of 1,2- and 1,4-additions?

12.37 1,3,5-Hexatriene reacts with one molar equivalent of bromine to give only 1,2- and 1,6-addition products. Write the structures of these products. Why does no 1,4-addition product result?

12.38 Reaction of 1,3-butadiene with one molar equivalent of bromine at −15 °C gives a 60:40 mixture of two products. At 60 °C, the product ratio is 10:90. Write the structures of the two products. Explain why different product ratios are observed at the two temperatures.

12.39 Reaction of 2,3-dimethyl-1,3-butadiene with one molar equivalent of HBr gives only one product. Write its structure and explain why this product is favored.

12.40 Reaction of 1-phenyl-1,3-butadiene with one molar equivalent of Cl_2 gives only one product. Write its structure and explain why this product is favored.



1-phenyl-1,3-butadiene

12.41 Write the structures of the products from the reaction of 1,3-butadiene with an aqueous bromine solution.

12.42 A single chloro alcohol forms in the reaction of 2-methyl-1,3-butadiene with an aqueous chlorine solution. Write its structure and explain why this product is favored.

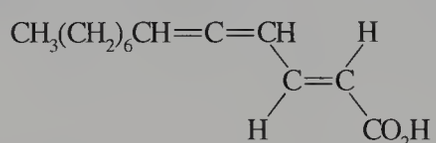
Allenes

12.43 Explain why the carbon–carbon double bond of allene is shorter than the carbon–carbon double bond of propene.

12.44 Are the two alkyl groups bonded to the allene carbon atoms in 2,2,6,6-tetramethyl-3,4-heptadiene expected to sterically interfere with each other? Contrast the environment of these groups with the alkyl groups in *cis*-2,2,5,5-tetramethyl-3-hexene.

12.45 Mycomycin (Exercise 12.4) is optically active. Explain why.

12.46 Can the sex attractant of the male dried-bean beetle exist as an optically active substance?



12.47 Which of the following compounds can exist as pairs of enantiomers?

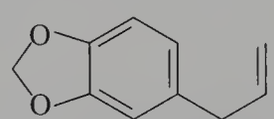
(a) 1,3-difluoro-1,2-propadiene **(b)** 1-bromo-1,2-butadiene

(c) 2,3-dichloro-2,3-pentadiene **(d)** 1,2-dichloro-3-methyl-1,2-butadiene

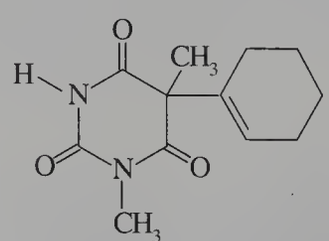
12.48 Can 2,3,4-hexatriene exist as a pair of enantiomers?

Allylic Oxidations

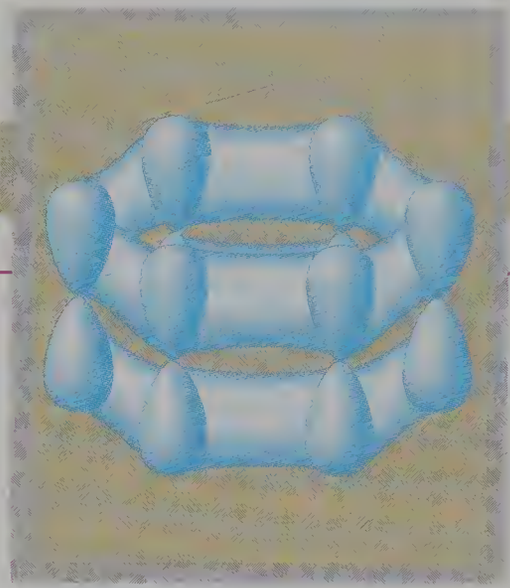
12.49 Write the structures of two possible allylic oxidation products of safrole, a carcinogenic compound.



12.50 Write the structures of two possible allylic oxidation products of the barbiturate hexobarbital.



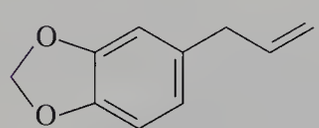
13



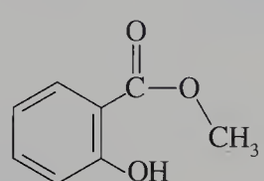
Arenes and Aromaticity

13.1 Aromatic Compounds

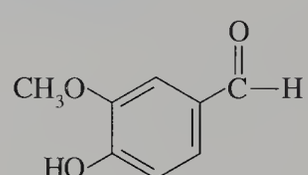
Early chemists used the term "aromatic" to describe substances with an aroma. Many of these fragrant compounds, it turned out, contain a benzene ring bonded to one or more substituents. Oil of sassafras, oil of wintergreen, and vanillin are examples.



safrole
(oil of sassafras)

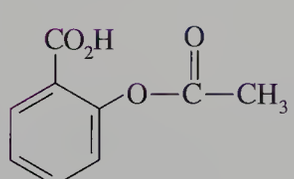


methyl salicylate
(oil of wintergreen)

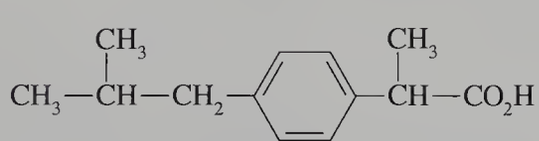


vanillin
(vanilla)

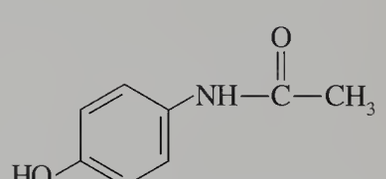
The term aromatic as used by chemists now includes all compounds with at least one benzene ring, most of which are not fragrant. For example, some aromatic compounds are solids with little or no odor. Solid aromatic compounds include the pain relievers, or analgesics, aspirin, ibuprofen, and acetaminophen and the antibiotics chloramphenicol and protosil.



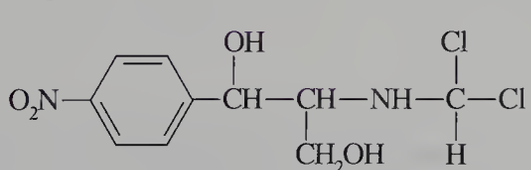
aspirin



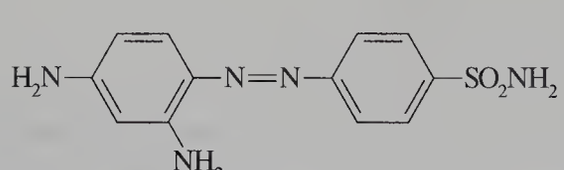
ibuprofen



acetaminophen

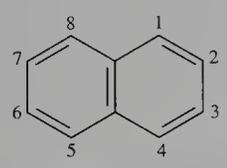


chloramphenicol

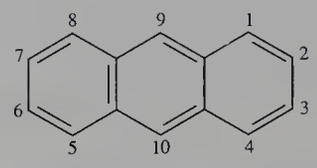


protosil

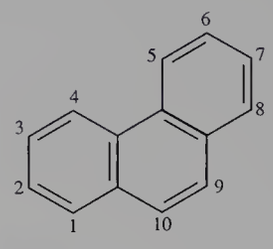
Substituted benzene compounds belong to a class of conjugated compounds called **arenes**. Examples include benzene, naphthalene, anthracene, and phenanthrene. The common structural feature of arenes is a monocyclic or polycyclic system of π electrons that results in a special stability called **aromaticity**. As a result, aromatic compounds are less reactive in electrophilic addition reactions than we would expect based on the reactivity of polyenes.



naphthalene



anthracene



phenanthrene

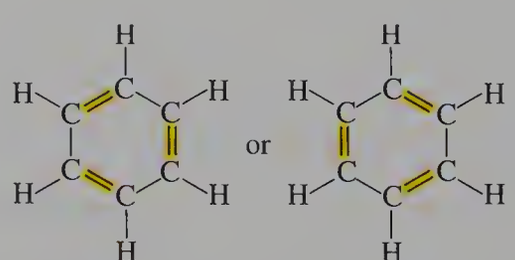
13.2 Aromaticity

Benzene, often represented by a hexagon containing three double bonds, is highly unsaturated. However, benzene does not undergo an addition reaction with bromine as we would expect if benzene were a "triene". Furthermore, benzene does not undergo addition reactions with HBr, cannot be hydrated, and does not react with the powerful oxidizing agent potassium permanganate.

The low reactivity of benzene contradicts what we know about unsaturated compounds. Benzene does not react with most reactants that attack π bonds to form addition products. That is, it does not behave like "1,3,5-cyclohexatriene". Benzene does react with bromine to give a substitution product in which a bromine atom replaces a hydrogen atom, but the reaction requires iron(III) bromide as a catalyst. Only one compound, C_6H_5Br, forms.

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

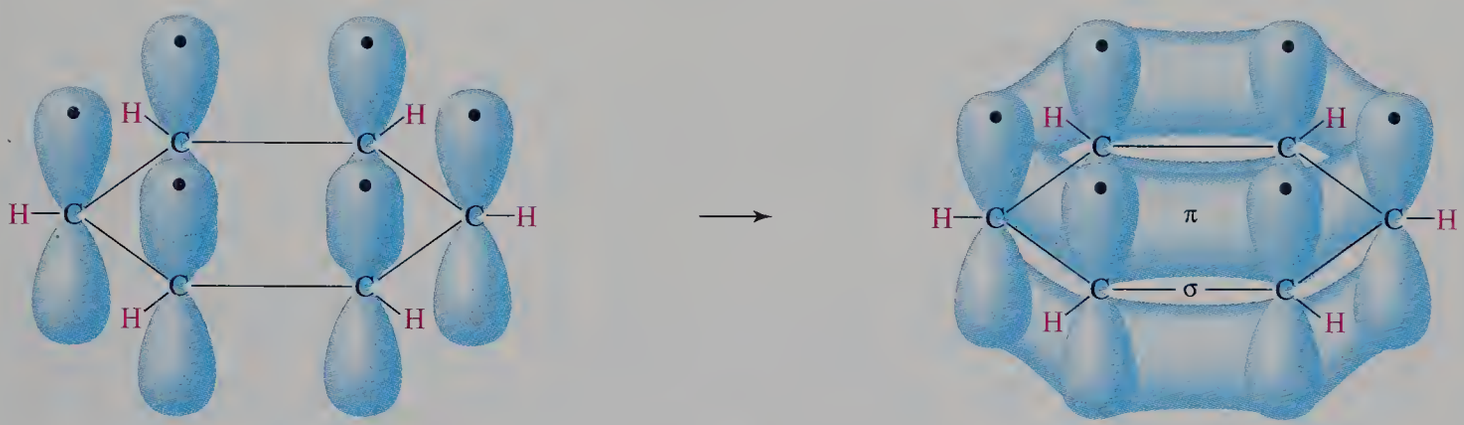
In 1865, a German chemist, F. August Kekulé, suggested that benzene has a single ring of six carbon atoms linked by alternating single and double bonds, now called a Kekulé structure. He further proposed that the single bonds rapidly become double, as the adjacent double bonds become single. Kekulé based his structure on two facts: A single monosubstituted brominated product forms, and three isomeric dibromobenzenes exist.

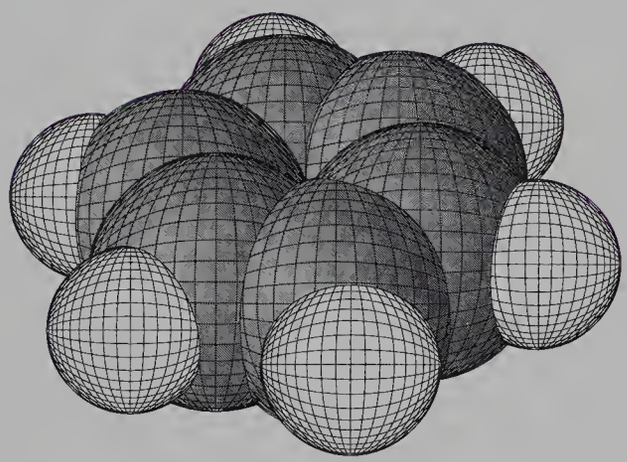


Kekulé proposed that the rapid oscillation of single and double bonds somehow made benzene resist addition reactions. He reasoned that the rapid oscillation of single and double bonds around the ring makes all six carbon atoms, and therefore all six hydrogen atoms, equivalent.

Resonance Theory and Benzene

Kekulé's proposal was nearly correct. Modern measurements show that benzene is a planar molecule in which all carbon–carbon bonds are equivalent. The carbon–carbon bond length, 140 pm, lies between those of a single bond, 154 pm, and a double bond, 133 pm. The carbon–carbon–carbon bond angles of the ring are all 120°. Each carbon atom in benzene is sp^2 hybridized. The carbon atoms link by σ bonds in which the carbon atom shares one electron in each of its σ bonds. Two σ bonds link adjacent carbon atoms. The third links to a hydrogen atom. Each sp^2-hybridized carbon atom has an electron in a $2p$ orbital perpendicular to the plane of the benzene ring (Figure 13.1). The six $2p$ orbitals of benzene overlap to share electrons in a six-π-electron system that extends over the entire ring. These electrons are located both above and below the plane of the ring. The delocalization of the electrons over all carbon atoms of benzene accounts for its unique chemical stability.



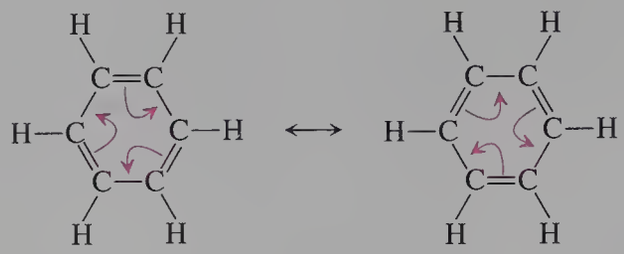


Space-filling model

FIGURE 13.1 Bonding in the Benzene Ring
The lines between carbon atoms represent the σ bonds of the benzene ring. In addition, each carbon atom has one p orbital that contributes one electron to the π system. Overlap of the six $2p$ orbitals that are maintained mutually parallel results in a delocalized system that distributes the electrons over the entire carbon framework.

Two resonance structures—Kekulé structures that differ only in the positions shown for double bonds—depict the structure of benzene. Because the two resonance structures are otherwise identical, they contribute equally to the resonance hybrid of benzene. Kekulé structures are not "real", but the benzene molecule can be viewed

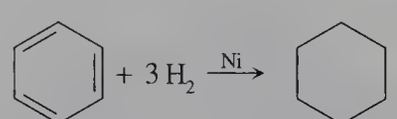
as a resonance hybrid of these two structures. We indicate the relationship between the contributing structures by a double-headed arrow.



The structure of benzene is usually represented in chemical equations as one of the two possible Kekulé structures. Each corner of the hexagon represents a carbon atom with one attached hydrogen atom, often not shown.

Resonance Energy

The stability of benzene compared to the hypothetical 1,3,5-cyclohexatriene is called the **resonance energy** of benzene. We determine the resonance energy by measuring the heat of hydrogenation of benzene and comparing that value to heats of hydrogenation of alkenes. Hydrogenating benzene is more difficult than hydrogenating alkenes or acyclic polyenes. This lack of reactivity is yet another example of the unusual stability of benzene. Conversion of benzene to cyclohexane requires a catalyst such as nickel, 100 atm pressure of hydrogen gas, and a temperature of 200°C. The ΔH°_{rxn} for the complete hydrogenation of benzene is –208 kJ mole^{-1} (–49.8 kcal mole^{-1}). This quantity is often expressed as a positive quantity called the heat of hydrogenation, which for benzene is 208 kJ mole^{-1}.

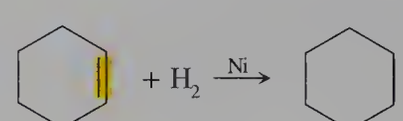


benzene cyclohexane

$\Delta H^\circ = -208$ kJ mole^{-1}

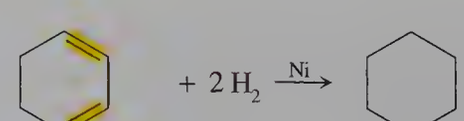
To calculate the resonance energy of benzene based on its heat of hydrogenation, we first estimate the heat of hydrogenation without resonance. We recall that the heats of hydrogenation of alkenes (Section 6.11) are about 125 kJ mole^{-1} (30 kcal mole^{-1}). Without resonance, we would expect the heat of hydrogenation of benzene to be three times that of a double bond. The experimental value for the resonance-stabilized molecule is much less.

The heat of hydrogenation of "1,3,5-cyclohexatriene" can be approximated using cyclohexene, 120 kJ mole^{-1} (28.6 kcal mole^{-1}), and 1,3-cyclohexadiene, 231 kJ mole^{-1} (55.4 kcal mole^{-1}), as model compounds.



cyclohexene cyclohexane

$\Delta H^\circ = -120$ kJ mole^{-1}



1,3-cyclohexadiene cyclohexane

$\Delta H^\circ = -231$ kJ mole^{-1}

We recall that conjugated dienes are resonance stabilized. This stabilization is reflected in the heat of hydrogenation of 1,3-cyclohexadiene, which is slightly less than twice the heat of hydrogenation of cyclohexene. The resonance energy—the added stability due to conjugation—of 1,3-cyclohexadiene is only 9 kJ mole^{-1}.

$$\text{resonance energy} = 2(120 \text{ kJ mole}^{-1}) - (231 \text{ kJ mole}^{-1}) = 9 \text{ kJ mole}^{-1}$$

Similarly, we can calculate the resonance energy of benzene based on the predicted heat of hydrogenation of the hypothetical 1,3,5-cyclohexatriene. Without any interaction between the three double bonds, we would predict a heat of hydrogenation equal to three times the heat of hydrogenation of cyclohexene. Rather than 360 kJ mole^{-1}, only 208 kJ mole^{-1} is released. We conclude that benzene is more stable than 1,3,5-cyclohexatriene by 152 kJ mole^{-1} (36 kcal mole^{-1}).

$$\text{resonance energy} = 3(120 \text{ kJ mole}^{-1}) - (208 \text{ kJ mole}^{-1}) = 152 \text{ kJ mole}^{-1}$$

Figure 13.2 illustrates the "extra stability" or resonance energy of benzene based on heat of hydrogenation data. Other methods for calculating the resonance energy of arenes such as benzene compare an experimental value for the arene with an expected value based on structures that do not exist. Thus, any stated resonance energy is approximate. Nevertheless, we are safe in the conclusion that arenes have large res-

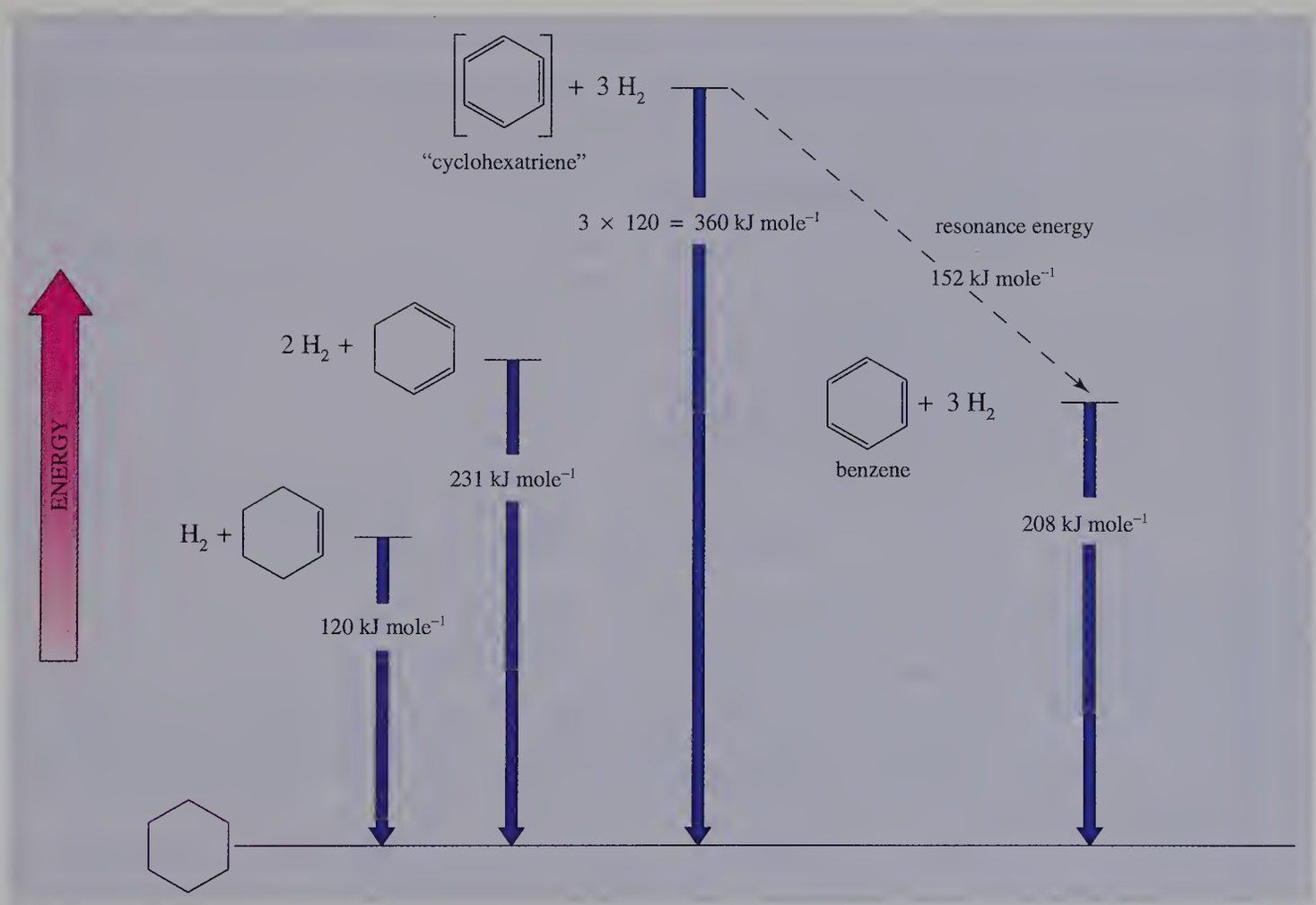
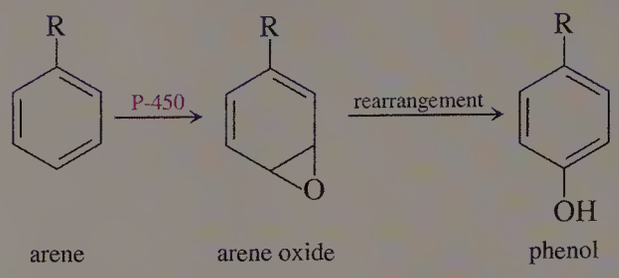


FIGURE 13.2 Heats of Hydrogenation and Resonance Energy
The relative energies of cyclohexene, 1,3-cyclohexadiene, "1,3,5-cyclohexatriene," and benzene and their heats of hydrogenation to form cyclohexane are given in kJ mole^{-1}.

Metabolism of Benzene

Benzene is remarkably unreactive even under extreme reaction conditions. We might therefore expect benzene to remain inert in cells, where conditions never exceed pH 7 and 37 °C, and it is. Most human cells cannot metabolize benzene. It accumulates in the liver, where specialized cells can metabolize it, often producing poisonous phenols. The enzyme cytochrome P-450 oxidizes benzene and other aromatic compounds. The reaction produces a three-membered heterocyclic ring intermediate called an epoxide. The epoxide intermediates, called **arene oxides**, then rearrange to phenols.

All arene oxide intermediates are very reactive, and undergo several types of reactions besides the rearrangement reaction to form phenols. Arene oxides react with proteins, RNA, and DNA. As a consequence, serious cellular disruptions can occur, causing diseases such as leukemia. We will discuss these processes in Section 17.10, with the chemistry of epoxides.



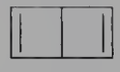
onance energies. The resonance energy of 152 kJ mole^{-1} for benzene is significantly larger than the resonance energy of conjugated polyenes such as 1,3-cyclohexadiene.

Problem 13.1

Three isomeric dibromobenzenes result from substitution of hydrogen by bromine. Write the structures of the isomers. How many isomeric dibromo compounds would form by replacing hydrogen atoms with bromine in "1,3,5-cyclohexatriene", a structure with alternating single and double bonds?

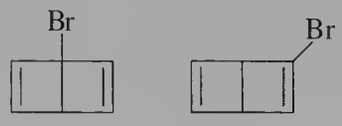
Problem 13.2

Consider the following structure as a possible representation of benzene. Consider the substitution of a hydrogen atom by bromine. How many isomeric monobromo derivatives are possible? How many isomeric dibromo derivatives are possible?



Sample Solution

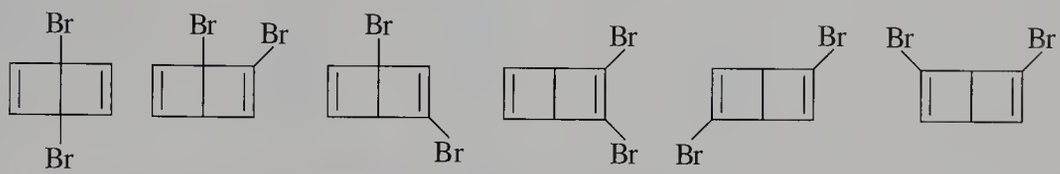
There are two sets of equivalent hydrogen atoms: those located at the two equivalent tertiary carbon atoms and those located at the four equivalent unsaturated carbon atoms. Thus, two monobromo derivatives result from replacing a hydrogen atom at either of these two sites.



The dibromo derivatives fall into three classes based on the types of hydrogen atoms replaced. The bromine attoms may be present as

1. Two tertiary bromines.
2 One tertiary bromine and one vinyl bromine.
3. Two vinyl bromines.

There is only one possible isomer containing two tertiary bromines. However, there are two isomers containing one tertiary bromine and one vinyl bromine. There are three isomers containing two vinyl bromine atoms.



Problem 13.3

The $\Delta H°$ for the complete hydrogenation of (*Z*)-1,3,5-hexatriene to give hexane is –337 kJ mole^{-1}. Using this value, calculate the resonance energy of the triene.

13.3 The Hückel Rule

What is responsible for the unusual stability and unique reactivity of benzene? To be considered aromatic, a molecule must first be cyclic and planar. Second, the ring must contain only sp^2-hybridized atoms that can form a delocalized system of electrons in π orbitals. (There can be no interruption by sp^3-hybridized atoms.) Third, the number of *p* electrons in the delocalized π system must equal $4n + 2$, where *n* is an integer. (As we will see shortly, n is not necessarily the number of carbon atoms in the ring, nor the number of p orbitals in a ring.) The "$4n + 2$ rule" was proposed by Erich Hückel and is known as the **Hückel rule**. The Hückel rule predicts that cyclic π systems having 2 ($n = 0$), 6 ($n = 1$), 10 ($n = 2$), and 14 ($n = 3$) electrons will be aromatic.

Benzene meets the criteria for aromaticity, with six π electrons distributed over a six-atom system. The following section will present other examples for various 6, 10, and 14 π electron systems. We will also see that aromatic compounds with $4n + 2$ π electrons need not have $4n + 2$ carbon atoms. Furthermore, aromatic compounds can have atoms other than carbon in the ring.

Nonaromatic Cyclic Polyenes

Now let's consider cyclic conjugated polyenes that do not satisfy the Hückel rule and are not aromatic. Two examples are cyclobutadiene and cyclooctatetraene. Both are cyclic polyenes with alternating single and double bonds that are not aromatic.

cyclobutadiene cyclooctatetraene

Cyclobutadiene is extremely unstable and has been isolated only at very low temperature. Its fleeting existence also has been inferred from the products of its reactions. The four π electrons of cyclobutadiene do not satisfy the Hückel rule. Cyclooctatetraene has eight π electrons, a number that also does not satisfy Hückel's rule: There

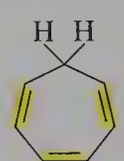
is no integer n for which $4n + 2 = 8$. Cyclooctatetraene is a stable molecule, but reacts like an alkene. For example, it undergoes addition reactions with bromine and is easily hydrogenated. Also, cyclooctatetraene is not planar. It exists in a "tub" conformation, so its $2p$ orbitals cannot overlap to form a continuous π system. Cyclooctatetraene does not exhibit the general characteristics of aromatic compounds.

tub conformation
of cyclooctatetraene

Aromatic Ions

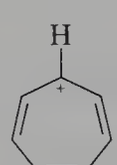
An aromatic ion has $4n + 2\,\pi$ electrons in a ring with a p orbital on each atom. As noted above, this definition does not mean that the number of p orbitals must equal $4n + 2$. Carbocyclic compounds are electrically neutral when the number of π electrons equals the number of atoms in the ring. When the number of electrons in a π system is less than the number of carbon atoms, the substance is a cation. When the number of electrons is greater than the number of carbon atoms, the substance is an anion.

Let's consider 1,3,5-cycloheptatriene, a conjugated triene that does not have the special stability associated with aromatic compounds. An sp^3-hybridized carbon atom connects the "ends" of the triene system. Thus, although conjugated, the π system is not continuous around the ring, and delocalization of electrons over all atoms is not possible. The triene is easily hydrogenated. It is also rapidly attacked by electrophilic reagents.



1,3,5-cycloheptatriene

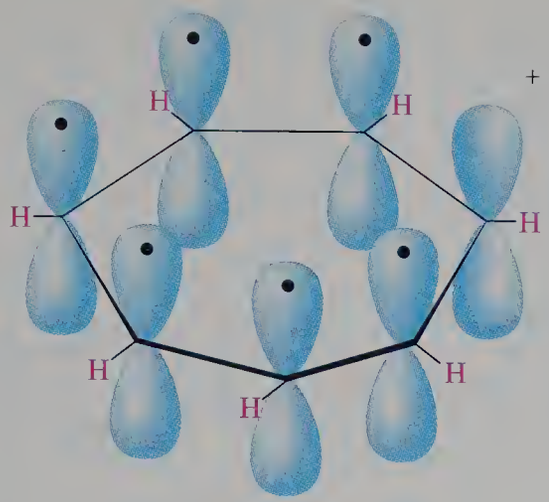
When 1,3,5-cycloheptatriene is treated with a strong Lewis acid, it loses a hydride ion to form the cycloheptatrienyl cation.



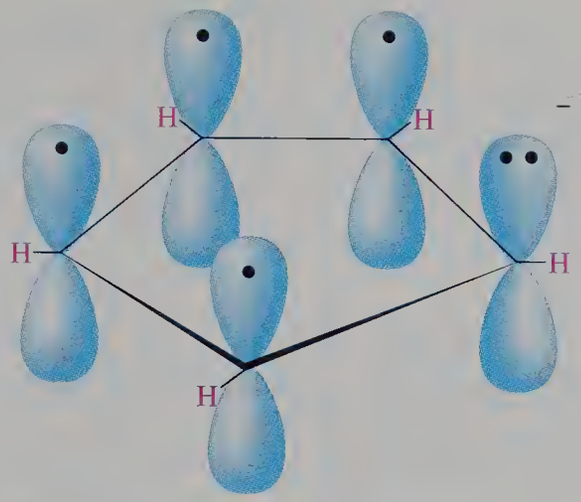
cycloheptatrienyl cation

This cation has a $2p$ orbital on each carbon atom and six π electrons (Figure 13.3). Each carbon atom is sp^2 hybridized. More than one Lewis structure can represent the cycloheptatrienyl cation, so it is resonance stabilized. Resonance forms depict the distribution of the positive charge over all carbon atoms.

resonance structures of cycloheptatrienyl cation



cycloheptatrienyl carbocation

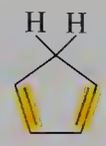


cyclopentadienyl anion

FIGURE 13.3 Orbitals and Electrons in Aromatic Ions
Each carbon atom of the cyloheptatrienyl carbocation and the cyclopentadienyl anion has a 2*p* orbital. One of the orbitals is deficient by an electron in the cation, and one of the orbitals has two electrons in the anion. In total each ion has six π electrons.

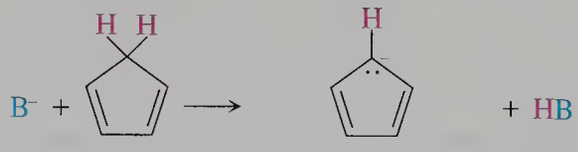
Because the cycloheptatrienyl cation, or tropylium ion, has six π electrons, it meets the Hückel criteria for aromaticity. Although we won't discuss the chemistry of this ion, it is more stable than a simple secondary carbocation. Moreover, all its carbon atoms are structurally equivalent, and all its carbon–carbon bonds are of equal length.

Next, let's consider 1,3-cyclopentadiene. An sp^3-hybridized carbon atom connects the "ends" of this diene. Thus, the π system is not closed, and delocalization of electrons over all atoms is not possible. The diene is not aromatic.



1,3-cyclopentadiene

Reaction of 1,3-cyclopentadiene with a base yields the cyclopentadienyl anion.



cyclopentadienyl anion

The cyclopentadienyl anion has a 2*p* orbital on each carbon atom and six π electrons (Figure 13.3). Thus, it is aromatic. Each carbon atom is sp^2 hybridized, including the one with the negative charge shown in the single Lewis structure. Like the tropylium ion, the cyclic anion is resonance stabilized, so we can write alternative resonance forms that distribute the negative charge over all atoms.

The enhanced acidity of 1,3-cyclopentadiene (pK_a = 16), comparable to water, shows the special stability of the cyclopentadienyl anion. Thus, 1,3-cyclopentadiene is far more acidic than other simple alkanes and alkenes. The low pK_a of 1,3-

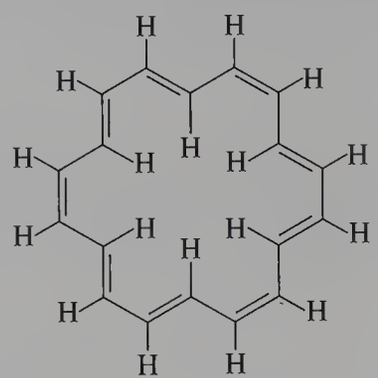
cyclopentadiene is a striking contrast to the high pK_a of 1,3,5-cycloheptatriene.

1,3,5-cycloheptatriene cycloheptatrienyl anion

The cycloheptatrienyl anion has several resonance structures, so the negative charge can be delocalized over all seven carbon atoms. However, since the anion contains eight π electrons, it is not aromatic. As a result, cycloheptatriene is 10^{-20} times less acidic than cyclopentadiene.

Problem 13.4

Annulenes are large monocyclic, completely conjugated compounds. A prefix within brackets indicates the number of carbon atoms in the ring. Based on the Hückel rule, is [18]-annulene aromatic?



[18]annulene

Problem 13.5

Write the resonance structures of the cyclopentadienyl anion to show how the negative charge can be delocalized over five carbon atoms.

Problem 13.6

Consider the loss of a hydride ion from 1,3-cyclopentadiene to form the cyclopentadienyl carbocation. Is the ion aromatic?

13.4 Molecular Orbitals and the 4n + 2 Rule

When we discussed molecular orbitals (Section 12.3), we noted that the number of molecular orbitals equals the number of atomic orbitals from which the molecular orbitals derive and that molecular orbitals result from linear combinations of atomic orbitals. When Erich Hückel calculated the molecular orbitals resulting from the linear combination of atomic orbitals in a conjugated cyclic system, he found a pattern of electron configuration that formed the basis for his $4n + 2$ rule. It turns out that neutral aromatic compounds always have one lowest energy bonding molecular orbital and one highest energy antibonding molecular orbital. The remaining molecular orbitals occur in degenerate pairs (same energy). Half of the degenerate pairs are bonding molecular orbitals, and half are antibonding molecular orbitals. With elec-

trons occupying this pattern of molecular orbitals, two electrons (one pair) fill the lowest energy molecular orbital and four electrons (two pairs) fill the successive energy levels, each of which consists of two degenerate orbitals. If the electrons fill all the bonding molecular orbitals, with none left over, the molecule is a neutral aromatic compound. The filled π orbitals form a "closed" shell that is in some ways analogous to the closed shell of the rare gases.

Benzene

Figure 13.4 shows the distribution of molecular orbitals for benzene. Two π electrons of benzene fill π_1, the lowest energy bonding molecular orbital. The remaining four electrons occupy the degenerate π_2 and π_3 molecular orbitals.

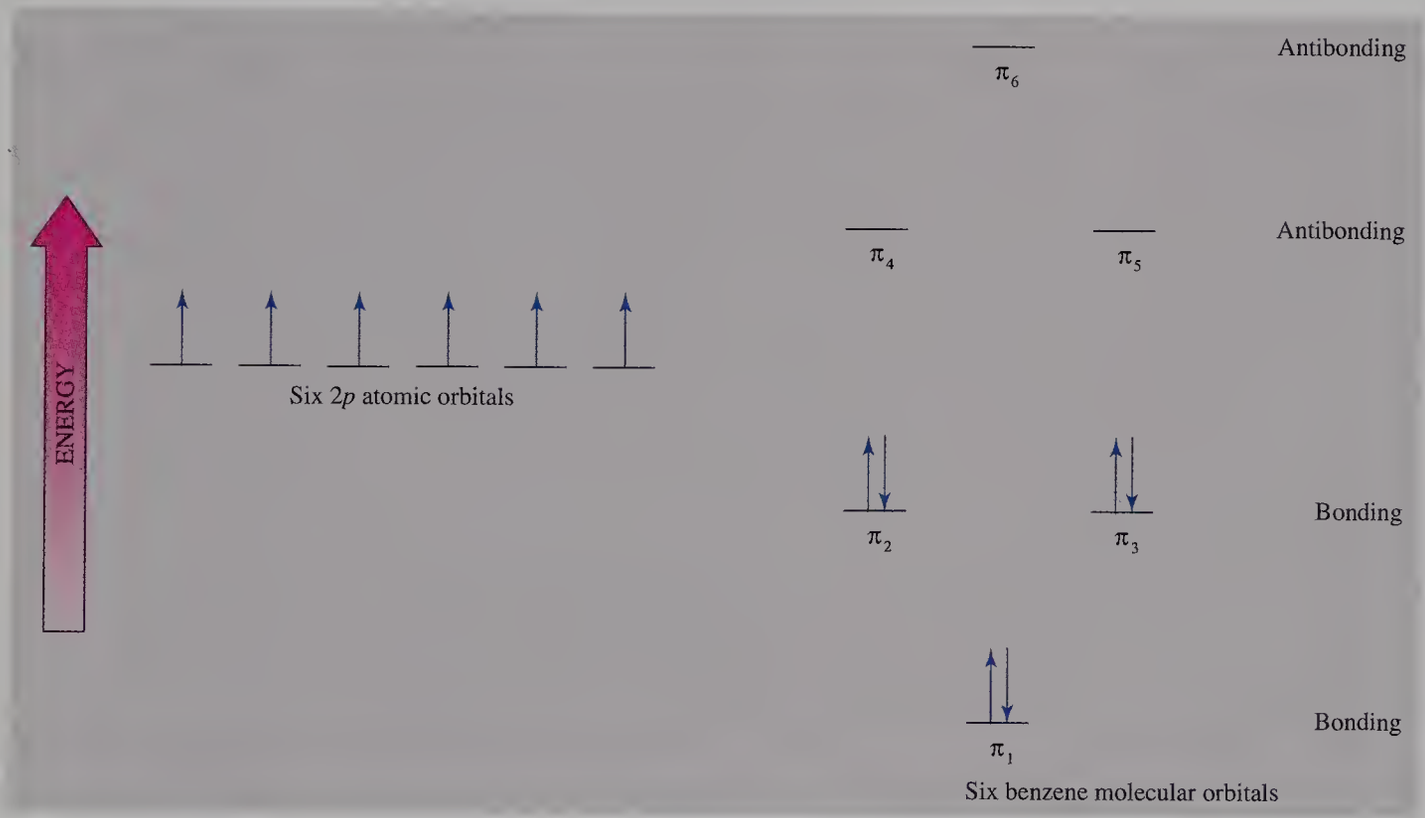


FIGURE 13.4 The Six Orbitals of Benzene
Three of the molecular orbitals are of lower energy than isolated 2*p* orbitals. These bonding molecular orbitals are fully occupied in benzene.

The six π electrons of benzene occupy bonding molecular orbitals whose total energy is less than the energy of the individual electrons in six 2*p* orbitals. It also turns out that the total energy of this arrangement of six π electrons in three molecular orbitals is less than that of six electrons occupying three independent π bonding orbitals of unconjugated double bonds. This energy difference is the resonance energy.

Cyclobutadiene and Cyclooctatetraene

We recall that cyclobutadiene and cyclooctatetraene are not aromatic. Each contains $4n$ electrons rather than $4n + 2$ electrons. That is, there are four electrons ($n = 1$) in

cyclobutadiene and eight electrons ($n = 2$) in cyclooctatetraene. If the molecules were to adopt a planar regular polygon structure, the predicted arrangement of the four π orbitals for cyclobutadiene and eight for cyclooctatetraene shown in Figure 13.5 would result. Notice that the distribution of degenerate orbitals for the $4n$ π electron system is different from that for the $4n + 2$ π system. For any system of $4n$ orbitals in a cyclic conjugated molecule, there is always a set of degenerate **nonbonding** molecular orbitals. They are nonbonding because their energies are the same as those of the original $2p$ orbitals. Therefore, any electrons occupying nonbonding molecular orbitals do not stabilize the molecule.

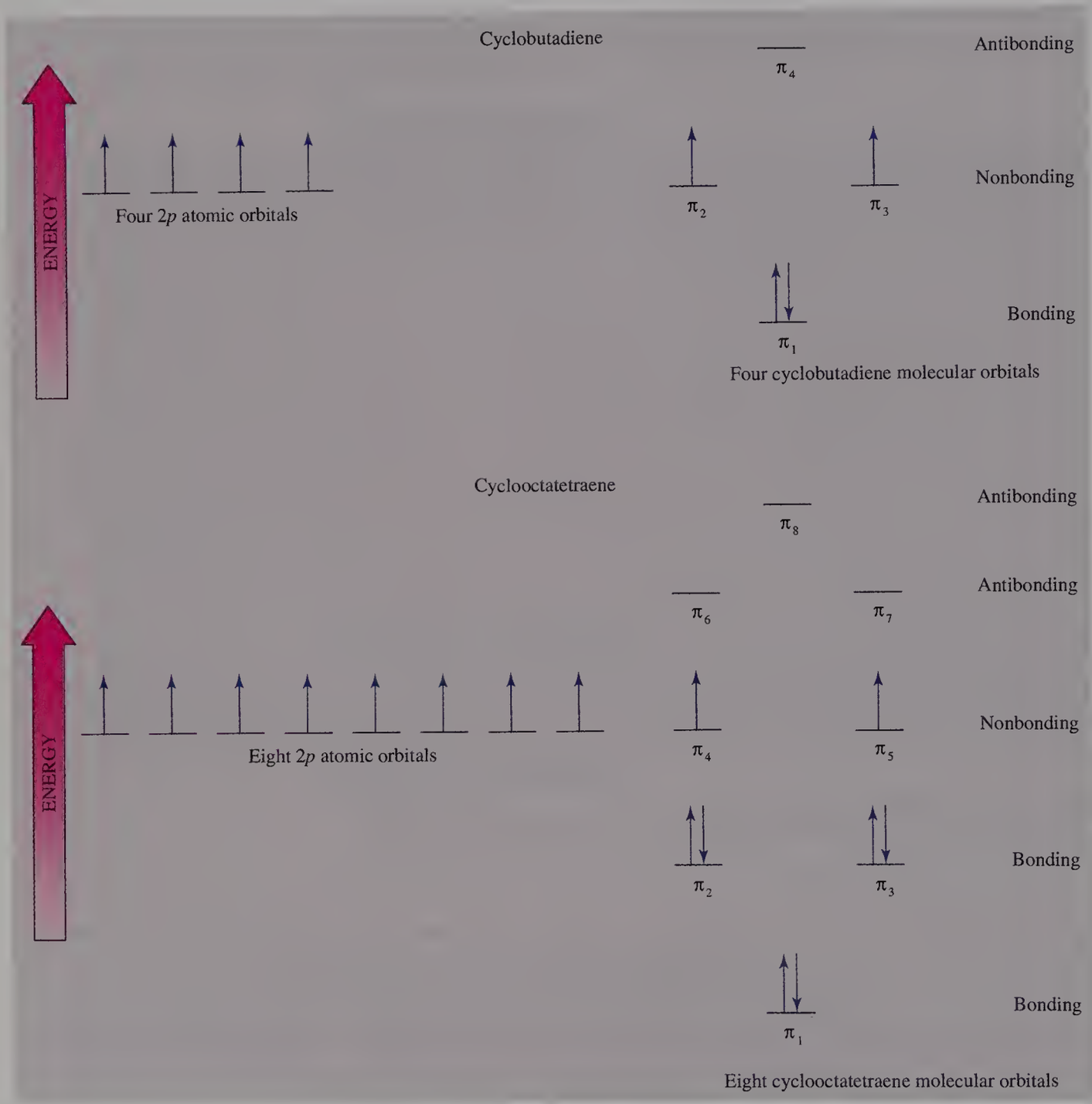


FIGURE 13.5 Molecular Orbitals of Cyclobutadiene and Cyclooctatetrane

The molecular orbitals shown assume that both molecules are planar and that the $2p$ atomic orbitals combine to form molecular orbitals.

Let's consider what molecular orbitals the electrons would occupy if cyclobutadiene had a square, planar geometry. According to Hund's rule, electrons half-fill degenerate orbitals before filling any of them. Thus, after two electrons occupy π_1, the remaining two electrons occupy the degenerate π_2 and π_3 molecular orbitals, one in each orbital. A square, planar cyclobutadiene molecule would have two unpaired electrons, and therefore it would be a diradical. Furthermore, those two electrons would occupy orbitals that do not stabilize the molecule.

Let's apply the same analysis to cyclooctatetrene. If it were a planar molecule, six of its eight π electrons would be in bonding molecular orbitals. Two electrons would be unpaired in two nonbonding molecular orbitals, and the molecule would be a diradical.

Neither cyclobutadiene nor cyclooctatetraene behaves as a diradical. The hypothesized planar species are of higher energy than the actual structures. Cyclobutadiene is a rectangular molecule with two pairs of π electrons in two localized double bonds. Cyclooctatetraene exists with four isolated double bonds in a "tub" conformation.

Aromatic Ions

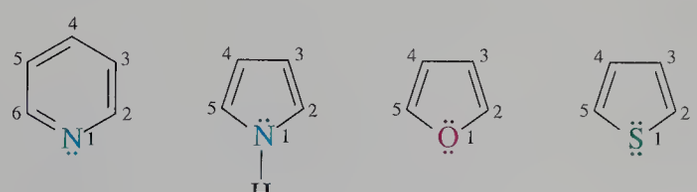
Finally, let's consider the molecular orbitals of the cyclopentadienyl anion and cycloheptatrienyl cation. Although each of these ions has six π electrons, as does benzene, they do not have six molecular orbitals. Each ion has an odd number of molecular orbitals, so the arrangement of molecular orbitals differs somewhat from the arrangement of benzene. Each has a single lowest energy bonding molecular orbital, but there is no corresponding single highest energy antibonding molecular orbital. However, all remaining molecular orbitals exist as degenerate pairs (Figure 13.6). When electrons fill these degenerate pairs, all electrons are paired in both the cyclopentadienyl anion and cycloheptatrienyl cation. The electrons occupy bonding molecular orbitals, so the ions have a net stabilization similar to that of benzene.

Problem 13.7

Consider the electronic structure of the carbocation that would result from the loss of a hydride ion from 1,3-cyclopentadiene. How many electrons are in the π system? Are they all paired?

13.5 Heterocyclic Aromatic Compounds

Cyclic compounds that have one or more atoms other than carbon within the ring are called **heterocyclic compounds**. Those that have $4n + 2\,\pi$ electrons are **heterocyclic aromatic compounds.** Nitrogen and oxygen are the most commonly encountered heteroatoms in naturally occurring heterocyclic compounds. Sulfur-containing compounds also exist. The structures of a few commonly encountered heterocyclic aromatic compounds are



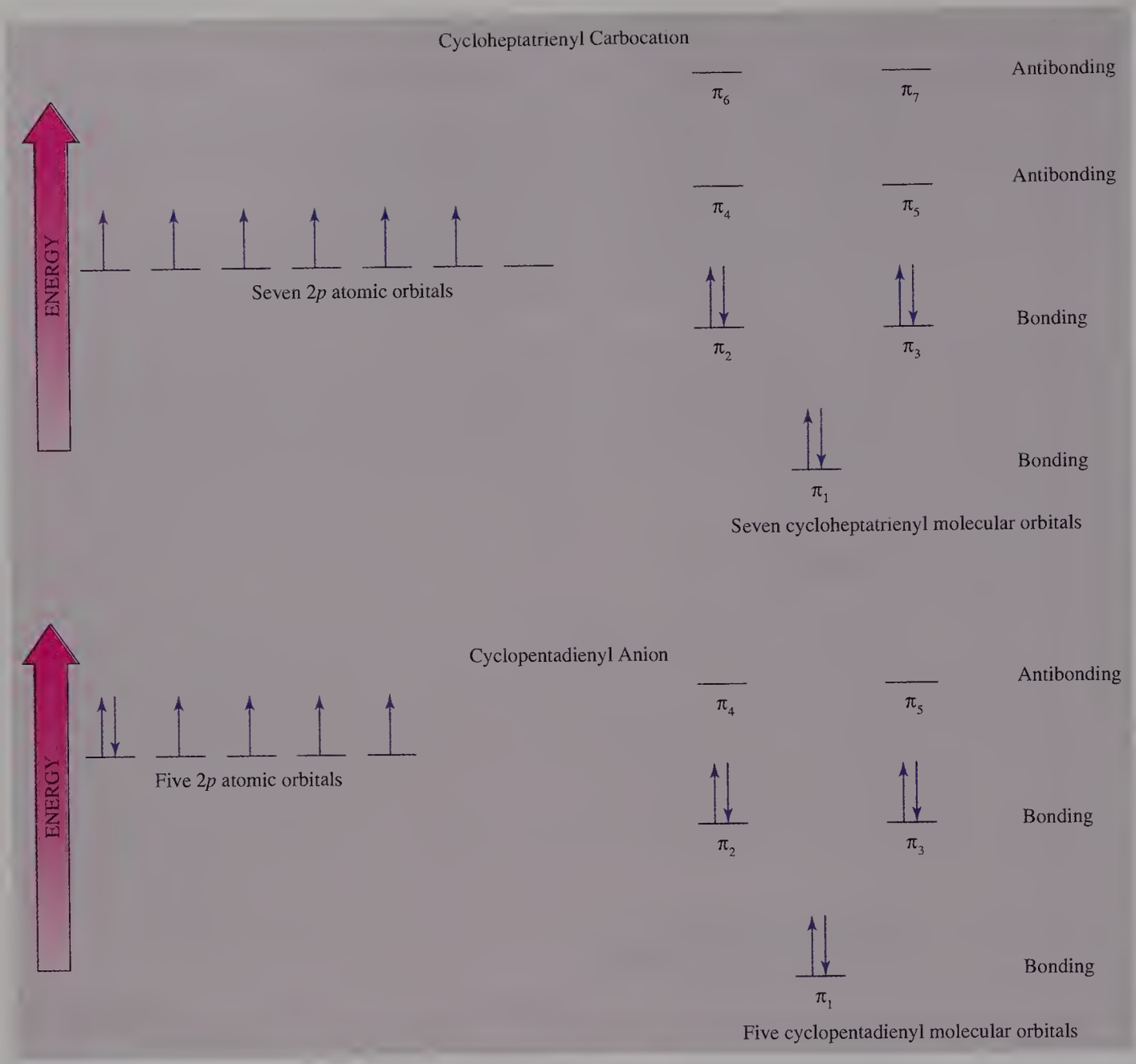


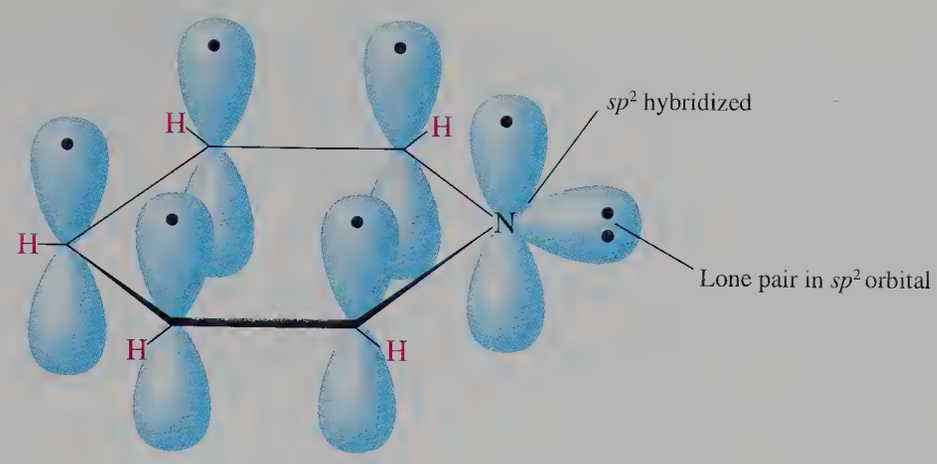
FIGURE 13.6 Molecular Orbitals of Cycloheptatrienyl Carbocation and Cyclopentadienyl Anion

Pyridine resembles benzene: It is planar; each of its ring atoms, including the nitrogen atom, is sp^2 hybridized; and each ring atom contributes one electron in a p orbital to an aromatic system of six π electrons. The sp^2-hybridized nitrogen atom has five valence electrons, one of which contributes to the aromatic sextet. The remaining four valence electrons of nitrogen occupy the three sp^2 orbitals. Two valence electrons form σ bonds to two carbon atoms, and two valence electrons remain as a lone pair in an sp^2 orbital. The lone pair projects out from the plane of the ring in the same direction as the carbon–hydrogen bonding electrons of benzene (Figure 13.7a). This lone pair allows pyridine to act as a base.

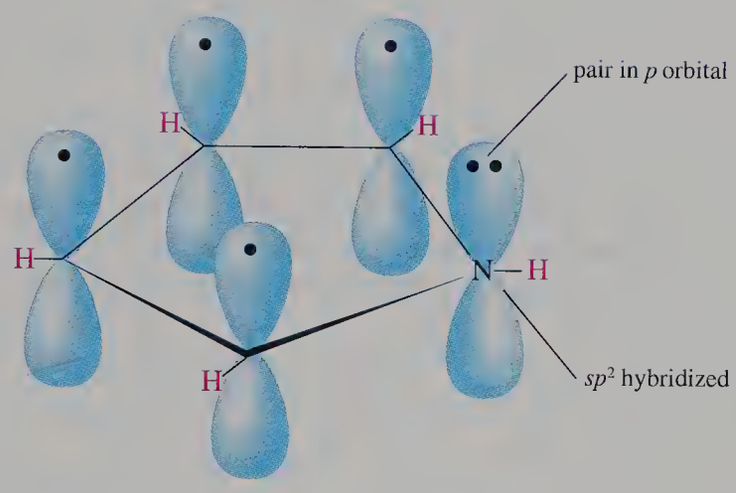
Pyrrole also contains an sp^2-hybridized nitrogen atom. However, in pyrrole the electrons are distributed differently than in pyridine. The pyrrole nitrogen atom contributes one electron to each of the three sp^2 orbitals. Two of them form σ bonds to carbon atoms, and the third forms a bond with the hydrogen atom (Figure 13.7b). The nitrogen atom's remaining two valence electrons occupy a $2p$ orbital. These two

FIGURE 13.7 Bonding in Heterocyclic Aromatic Hydrocarbons

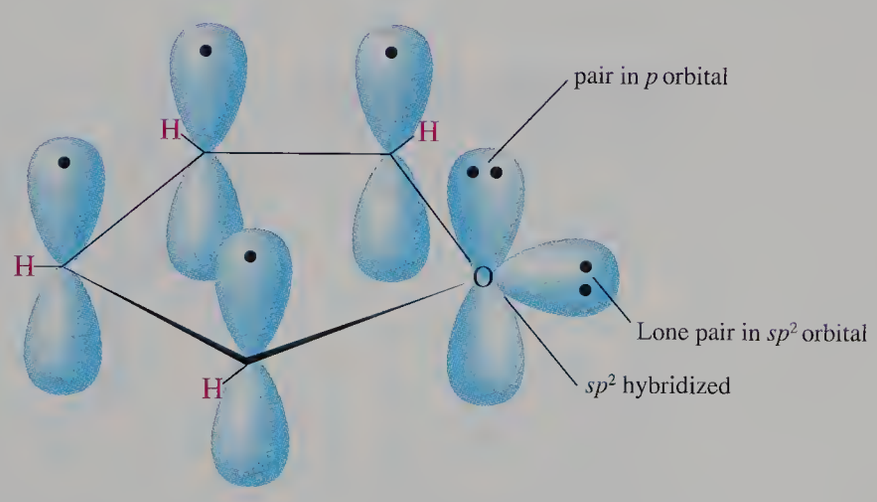
(a) In pyridine two electrons of the nitrogen atom are located in an sp^2 hybrid orbital directed outward from the plane. These electrons are not involved in resonance with the π electrons. (b) In pyrrole two electrons of the nitrogen atom are located in a p orbital that is part of the π system. The other three electrons of nitrogen are in sp^2 hybrid orbitals which form three σ bonds - two with carbon atoms and one with a hydrogen atom. (c) In furan two electrons of the oxygen atom are located in a *p* orbital that is part of a π system. The other four electrons of oxygen are in sp^2 hybrid orbitals. Two of the electrons form σ bonds with carbon atoms. The remaining two electrons are located in an sp^2 hybrid orbital directed outward from the plane of the ring.



(a)



(b)



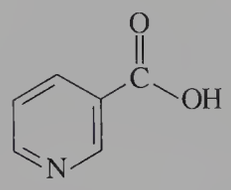
(c)

electrons plus the four electrons in the 2*p* orbitals of the four carbon atoms provide a six-electron π system. Therefore, pyrrole is aromatic. It is isoelectronic with the cyclopentadienyl anion.

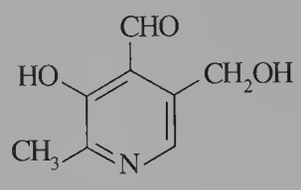
Furan and thiophene are similar to pyrrole. Furan has an sp^2-hybridized oxygen atom and thiophene has an sp^2-hybridized sulfur atom. Let's just focus on furan.

Oxygen has six valence electrons. Two of them are in a $2p$ orbital and, along with the four π electrons of four carbon atoms in the ring, provide a six-electron π system. The remaining four valence electrons of oxygen occupy three sp^2 orbitals. Two of the orbitals have one electron each, and these form σ bonds to two carbon atoms. The remaining sp^2 orbital has two electrons. As in pyridine, this lone pair of electrons has the same relationship to the ring as the carbon–hydrogen bonding electrons of benzene (Figure 13.7c).

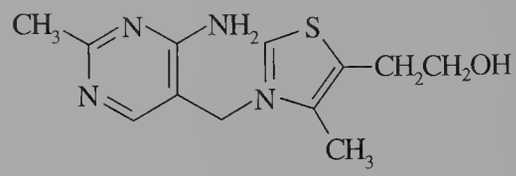
Many naturally occurring, biologically important compounds—such as vitamins B_1, B_3, and B_6—have one or more aromatic heterocyclic rings of five or six atoms. Vitamin B_1 has two rings with heteroatoms.



niacin (B_3)

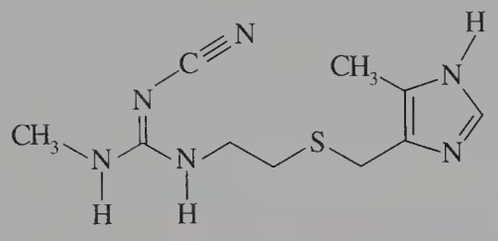


pyridoxine (B_6)

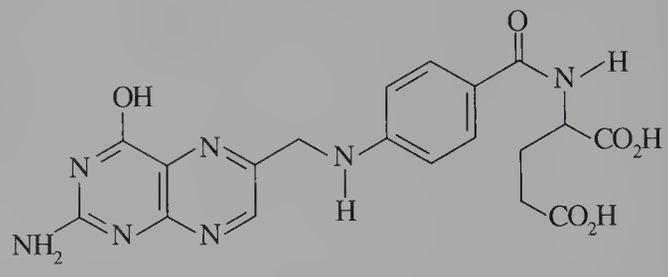


thiamine (B_1)

Heterocyclic rings are present in many pharmaceutical compounds. For example, Tagamet (generic name cimetidine), an antiulcer drug, contains a heterocyclic aromatic ring with two nitrogen atoms. Methotrexate, a chemotherapeutic agent used to treat some kinds of cancer, contains four nitrogen atoms in a ring resembling naphthalene.



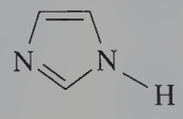
cimetidine



methotrexate

Problem 13.8

The heterocyclic ring in the drug cimetidine is imidazole. Neither of the nitrogen atoms is depicted with the pair of electrons required for an octet. Locate the valence electrons of each nitrogen atom.



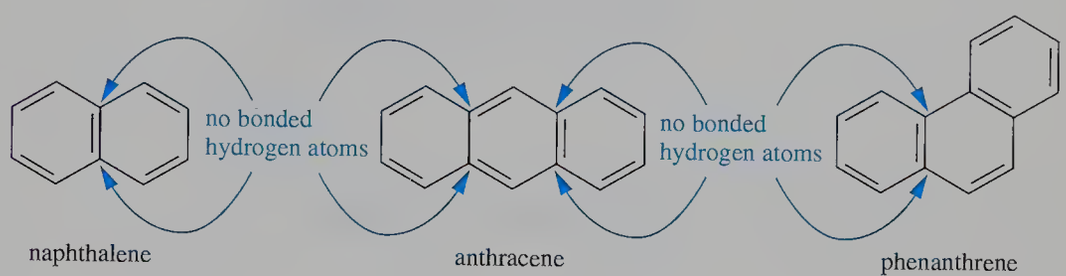
Sample Solution

The nitrogen atom on the right of the structure is bonded to a hydrogen atom and resembles the nitrogen atom of pyrrole. Three σ bonds are shown. Each has one valence electron contributed from the nitrogen atom. Thus, the remaining two valence electrons of nitrogen are located in a $2p$ orbital. These two electrons, along with the four electrons of the two π bonds shown in the imidazole structure, account for six electrons of an aromatic system.

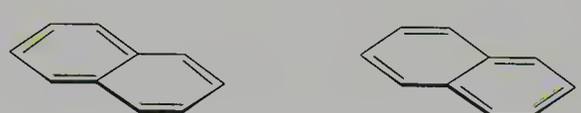
The nitrogen atom on the left has one single and one double bond as shown. This nitrogen atom resembles the nitrogen atom of pyridine. Two of its electrons are used to form two σ bonds; one electron is contributed to the π bond with a carbon atom. The remaining two electrons are in an sp^2 hybrid orbital projecting out from the plane of the ring.

13.6 Polycyclic Aromatic Compounds

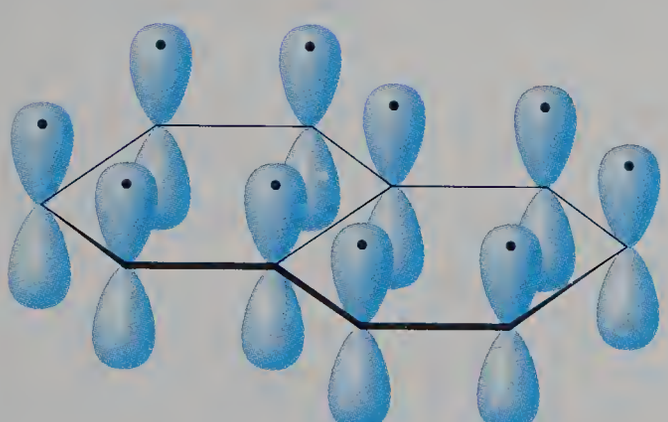
The concept of aromaticity can be extended to "fused" compounds containing two or more rings, so called because two carbon atoms are common to two rings. Compounds of this type, called **polycyclic aromatic hydrocarbons**, have a *p* orbital on every carbon atom. Examples of polycyclic aromatic hydrocarbons include anthracene and phenanthrene. All carbon atoms in naphthalene, anthracene, and phenanthrene are sp^2 hybridized. All atoms in the rings, as well as those directly attached to the rings, are coplanar. Naphthalene, with two fused rings, is the simplest polycyclic aromatic molecule. Note that all the carbon atoms except those at the points of fusion have a bond to a hydrogen atom.



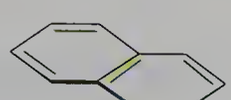
Naphthalene, which has 10 π electrons, satisfies the Hückel rule for aromaticity. Figure 13.8 shows naphthalene's 2*p* orbitals. The various *p* orbitals can overlap around the periphery of the molecule and across the two carbon atoms at the fusion site. Naphthalene has three resonance forms. Unlike benzene, they are not all equivalent. The most stable resonance form has two Kekulé representations of benzene rings. In this form, both rings share the double bond at the points of fusion. The other two resonance forms contain only one Kekulé benzene ring; they are of equal energy. In general, the contribution of a resonance form to the resonance hybrid for a polycyclic aromatic hydrocarbon is proportional to the number of Kekulé benzene rings in the structure.



Less stable resonance forms



2*p* orbitals

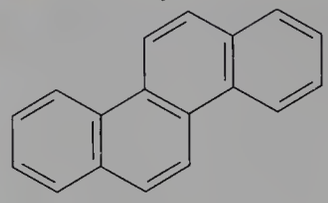


Most stable resonance form

FIGURE 13.8 Orbital Picture of Naphthalene and Resonance Forms
The ten π electrons of naphthalene are delocalized over both rings. Three resonance forms can be written using localized double bonds.

Problem 13.9

Determine the number of π electrons in chrysene. Is the compound aromatic?



chrysene

Problem 13.10

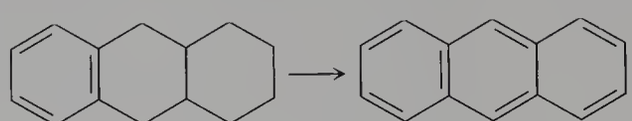
The heat of hydrogenation of naphthalene to form *trans*-decalin, a saturated bicyclic hydrocarbon, is 332 kJ $mole^{-1}$. Using the heat of hydrogenation of cyclohexene as a reference value, calculate the resonance energy of naphthalene.

Problem 13.11

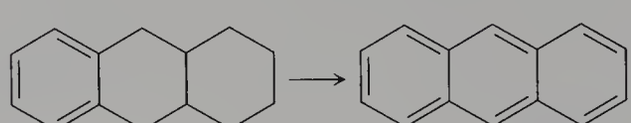
Draw the four resonance forms of anthracene and determine which one(s) make the greatest contribution to the structure.

Sample Solution

Start with the two possible Kekulé structures for the ring at the left. Then place alternating single and double bonds in the other two rings based on the initial restricted location of the double bonds in the ring at the left. Two structures result. Neither structure has a "benzene" ring in the ring at the right.

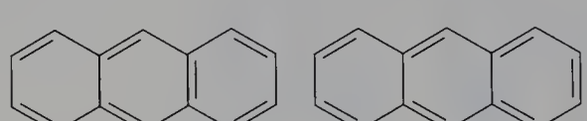


I



II

Two additional structures can be written using the same technique starting with the ring at the right. These forms can also be obtained by rotating the original two structures by 180°.



III IV

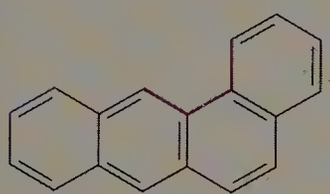
Structures I and III each have two "benzene" rings because the double bond at the fused carbon atoms is shared by the center ring and one terminal ring. These structures contribute to a greater degree than structures II and IV, which have only one "benzene" ring.

Problem 13.12

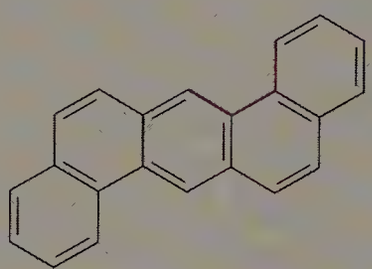
Draw the five contributing resonance forms of phenanthrene. Based on these structures, explain why the C-9 to C-10 bond behaves more like a double bond than the other bonds in the molecule.

Carcinogenic Aromatic Compounds

Fused polycyclic aromatic hydrocarbons that contain four or more rings with a bay region are carcinogenic. Their structures resemble phenanthrene. Three of the most potent carcinogens are 1,2-benzanthracene, 1,2,5,6-dibenzanthracene, and 3,4-benzpyrene. The bay area is outlined in each structure.



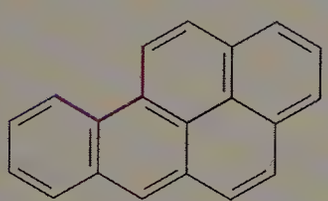
1,2-benzanthracene

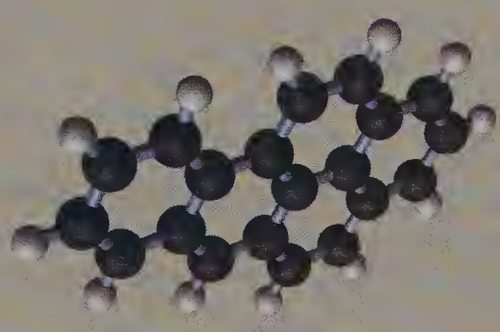


1,2,5,6-dibenzanthracene

Small amounts of these angular fused-ring aromatic hydrocarbons cause cancer in about a month when applied to the skin of a mouse. These compounds are present in the effluent from coal-burning power plants and in automobile exhaust. They are also present in tobacco smoke and in meat cooked over charcoal. The incidence of lung cancer among smokers and inhabitants of large urban areas may partly result from inhaling these airborne compounds in minute amounts over time.

It was once common for chimney sweeps in England to develop cancer. While they worked, the chimney sweeps became covered with chimney soot, and inhaled sooty dust that contained angular, fused, aromatic hydrocarbons.

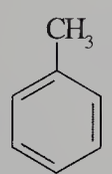




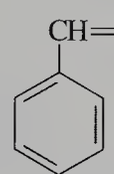
3,4-benzpyrene

13.7 Nomenclature of Benzene Compounds

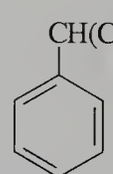
Like the other classes of compounds we have discussed, benzene compounds have both common, nonsystematic, names and IUPAC names. Common names often stem from the sources of the compounds, and they have been used for so long that they have become accepted by IUPAC. One example is toluene, which used to be obtained from the South American gum tree, *Toluifera balsamum*. A few others are also shown.



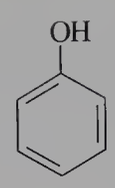
methylbenzene
(toluene)



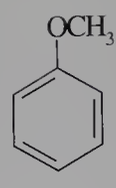
vinylbenzene
(styrene)



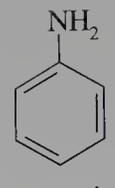
isopropylbenzene
(cumene)



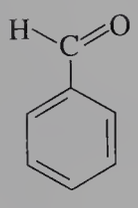
benzenol
(phenol)



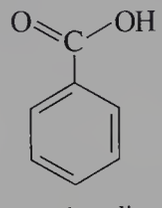
methoxybenzene
(anisole)



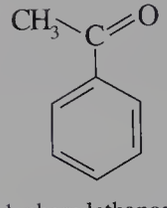
benzenamine
(aniline)



benzenecarboxaldehyde
(benzaldehyde)

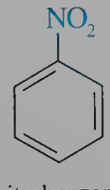


benzenecarboxylic acid
(benzoic acid)

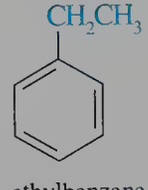


1-phenylethanone
(acetophenone)

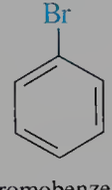
The IUPAC system of naming substituted aromatic hydrocarbons uses the names of the substituents as prefixes to benzene. Examples include



nitrobenzene

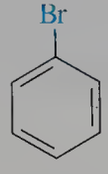


ethylbenzene

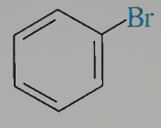


bromobenzene

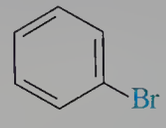
All compounds shown in this section have the substituent shown at a "12 o'clock" position. However, the six positions on the benzene ring are equivalent, and you should be able to recognize a compound, such as bromobenzene, no matter where the bromine atom is written.



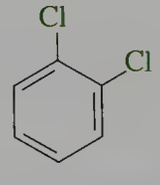
is the same as



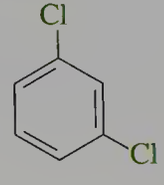
is the same as



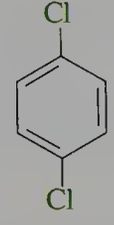
Disubstituted compounds result from replacing two hydrogen atoms of the benzene ring by other groups. Two substituents can occur in a benzene ring in three different ways to give three different isomers. These isomers are designated ortho, meta, and para, usually abbreviated as the prefixes *o*-, *m*-, and *p*-, respectively.



o-dichlorobenzene
1,2-dichlorobenzene



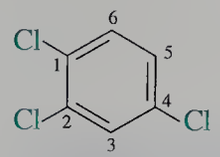
m-dichlorobenzene
1,3-dichlorobenzene



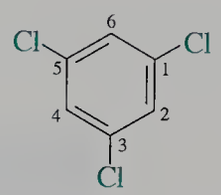
p-dichlorobenzene
1,4-dichlorobenzene

The ortho isomer has two groups on adjacent carbon atoms—that is, in a 1,2 relationship. In the meta and para isomers, the two groups are in a 1,3 and a 1,4 re-

lationship, respectively. The IUPAC name of a disubstituted aromatic compound is obtained by numbering the benzene ring to give the lowest possible numbers to the carbon atoms bearing the substituents. When three or more substituents are present, the ring carbon atoms must be numbered.

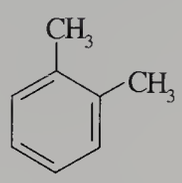


1,2,4-trichlorobenzene

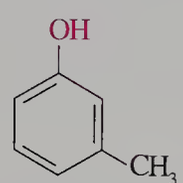


1,3,5-trichlorobenzene

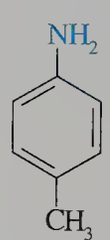
Many disubstituted compounds have common names. Examples include the xylenes, cresols, and toluidines, all of which can be ortho, meta, or para isomers.



o-xylene

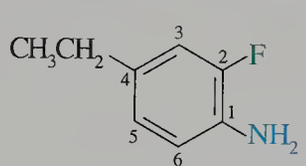


m-cresol

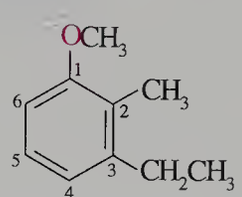


p-toluidine

Many derivatives of benzene are named with the common name of the monosubstituted aromatic compound as the parent. The position of the substituent of the "parent" is automatically designated 1, but the number is not used in the name. The remaining substituents are prefixed in alphabetical order to the parent name, along with numbers indicating their locations.

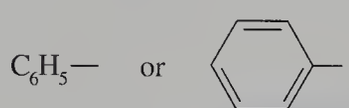


4-ethyl-2-fluoroaniline

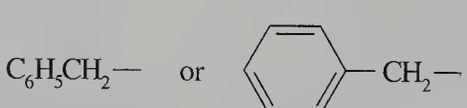


3-ethyl-2-methylanisole

An aromatic ring residue attached to a larger parent structure is called an **aryl group**. It is indicated Ar (not to be confused with argon), just as the symbol R is used for an alkyl group. Two groups whose names unfortunately do not make much sense are the phenyl (fen'-nil) and benzyl groups. We might reasonably expect that the aryl group derived from benzene (C_6H_5—) would be named benzyl. Alas, it is a phenyl group. A benzyl group, derived from toluene, has the formula $C_6H_5CH_2$—.

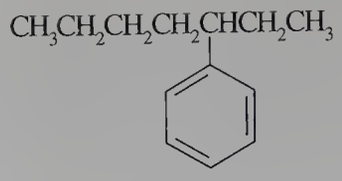


phenyl group



benzyl group

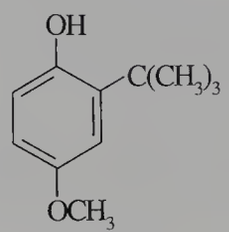
If alkyl groups containing fewer than six carbon atoms are bonded to a benzene ring, the compound is named as an alkyl-substituted benzene. For more complex molecules, the term phenyl designates the aryl group on the parent chain of carbon atoms, as in 3-phenylheptane.



3-phenylheptane

Problem 13.13

Indicate how a name could be derived for the following trisubstituted compound, used as an antioxidant in some food products.

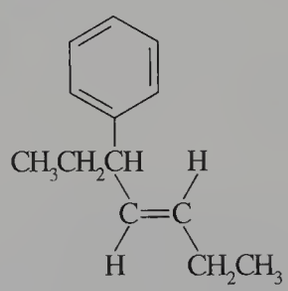


Sample Solution

Either the —OH or the —OCH_3 group could provide the parent name, which would be phenol or anisole, respectively. Let's assume that the compound is a substituted anisole. When we assign the number 1 to the carbon atom bearing the —OCH_3 group at the "6 o'clock" position, we must number the ring in a counterclockwise direction. A *tert*-butyl group is located at the 3 position and a hydroxyl group at the 4 position, so the compound is 3-*tert*-butyl-4-hydroxyanisole.

Problem 13.14

What is the name of the following compound?



Sample Solution

The compound is an alkene with an aromatic ring as a substituent. First, we determine that the chain has seven carbon atoms. Next, we number the chain from right to left so that the double bond is assigned to the C-3 atom. The phenyl group is then located on the C-5 atom. Also, we note that the compound is the *E* isomer. The complete name is (*E*)-5-phenyl-3-heptene.

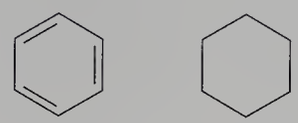
Problem 13.15

Write the structure of each of the following compounds.

(a) 2,4,6-trinitrophenol
(b) 3,5-dibromoaniline
(c) 2,4-dinitrotoluene
(d) *p*-methylbenzoic acid
(e) *m*-chloroanisole
(f) *o*-methylacetophenone

13.8 Physical Properties of Substituted Benzene Compounds

Like other classes of hydrocarbons, benzene and other aromatic hydrocarbons are nonpolar. Consequently, the boiling points of substituted benzene compounds are similar to those of cycloalkanes and alkanes of similar molecular weight.



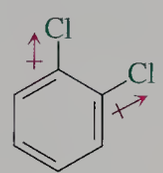
bp 80.1 °C

bp 80.7 °C

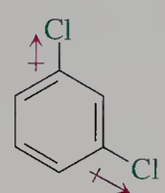
$CH_3(CH_2)_4CH_3$

bp 69 °C

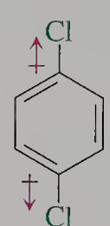
If a benzene ring has a polar substituent, the compound has a dipole moment, and the boiling point increases. For example, the boiling points of the isomeric dichlorobenzenes increase as their dipole moments increase. *p*-Dichlorobenzene has a zero dipole moment and the lowest boiling point of the three isomers. *o*-Dichlorobenzene has the largest dipole moment because the two C—Cl bond moments most strongly reinforce each other and the highest boiling point of the three isomers. The meta isomer has an intermediate dipole moment and an intermediate boiling point.



o-dichlorobenzene
bp 181 °C

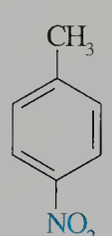


m-dichlorobenzene
bp 173 °C

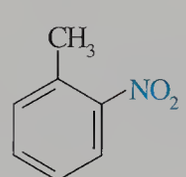


p-dichlorobenzene
bp 170 °C

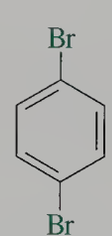
Aromatic compounds are planar. Hence, they tend to be more symmetrical than other classes of hydrocarbons, and the flat molecules can pack more efficiently in the solid state. Therefore, aromatic compounds have higher melting points than nonaromatic compounds of comparable molecular weight. The symmetry of a benzene derivative depends on the substitution pattern, which in turn affects the efficiency of packing. For example, the para isomers pack better into crystals and therefore have higher melting points than the ortho and meta isomers, as shown in the following examples.



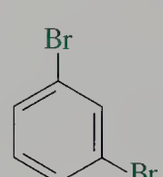
p-nitrotoluene
mp 54.5 °C



o-nitrotoluene
mp –9.6 °C



p-dibromobenzene
mp 87.3 °C



m-dibromobenzene
mp –7 °C

The isomers with the highest melting points tend to crystallize most easily. Therefore, recrystallization can usually separate the para isomer from the ortho and meta isomers.

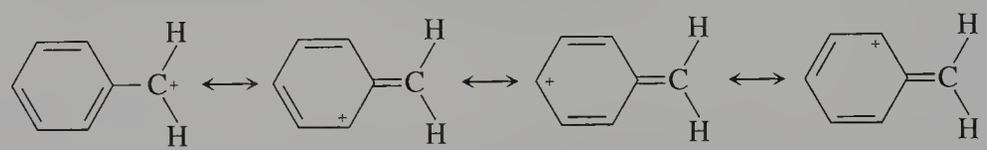
Like other hydrocarbons, aromatic compounds are soluble in solvents such as hexane, diethyl ether, and carbon tetrachloride. As a class, aromatic compounds are not soluble in water, but some polar functional groups such as those present in phenol and benzoic acid make some substituted benzene compounds moderately soluble in water.

13.9 Reactions of Side Chains

A group of carbon atoms bonded to an aromatic ring constitutes a **side chain**. Side-chain sp^3-hybridized carbon atoms separated from the aromatic ring by two or more σ bonds behave independently of the aromatic ring. However, carbon atoms directly bonded to the aromatic ring, known as **benzyl carbon atoms**, are influenced by the ring. If the side chain undergoes a reaction in which the benzyl carbon atom becomes a carbocation or a free radical, the intermediate is resonance stabilized.

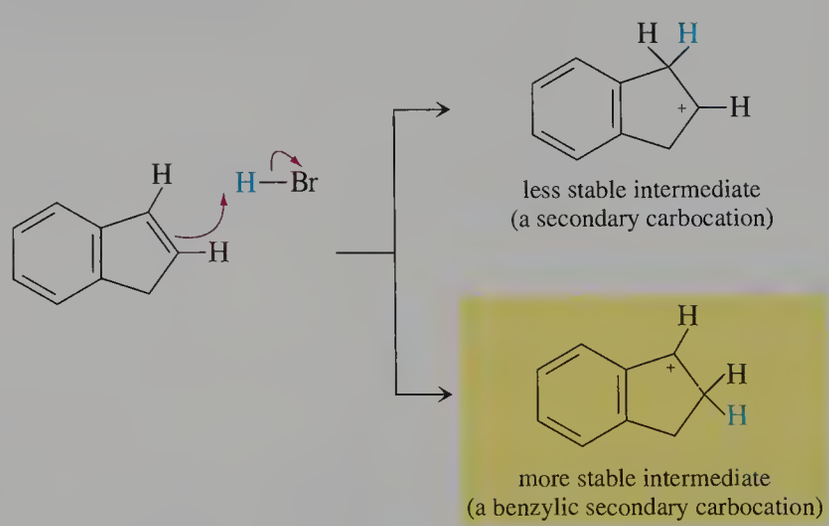
Carbocations

Any reaction that forms a carbocation at the benzyl carbon atom is especially favored. A carbocation in which the positively charged carbon atom is directly attached to a benzene ring is a **benzylic carbocation**. We recall that the formula of a benzyl group is $C_6H_5CH_2$—, so the benzyl carbocation has the formula $C_6H_5CH_2^+$. The benzyl carbocation is resonance-stabilized in the same manner as the allyl carbocation we discussed in Chapter 12. The positive charge at the benzyl carbon atom is delocalized on the ring carbon atoms that are ortho and para to it.

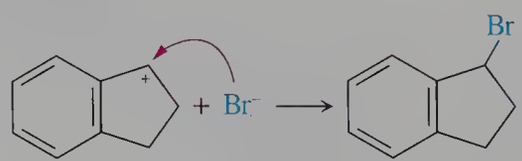


resonance forms of benzyl carbocation

Let's consider the addition reaction of HBr to indene, which has a double bond conjugated with the benzene ring. Electrophilic attack of H^+ at the carbon atom two atoms away from the ring gives a stable benzyl carbocation. Attack at the carbon atom directly attached to the ring would produce a much less stable secondary carbocation.



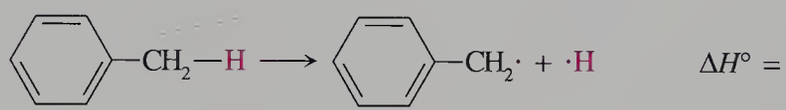
The reaction gives only the product derived from the more stable benzylic carbocation, which then reacts with the bromide ion.



A benzylic radical is resonance stabilized in the same manner as an allylic radical. This stability is reflected in the dissociation energies of the allylic C—H bond of propene and the benzylic C—H bond of toluene, compared to that of the primary C—H bond of propane. Thus, the C—H bond dissociation energies of both propene and toluene are significantly smaller than the bond dissociation energy of the primary C—H bond of propane.

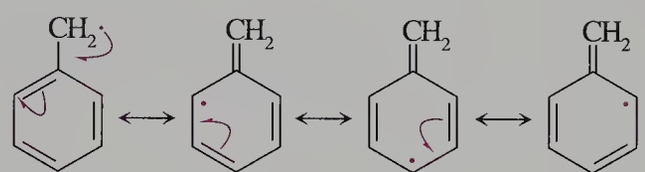
$$CH_3—CH_2—CH_2—H \longrightarrow CH_3—CH_2—CH_2\cdot + \cdot H \qquad \Delta H° = 422 \text{ kJ mole}^{-1}$$

$$CH_2{=}CH—CH_2—H \longrightarrow CH_2{=}CH—CH_2\cdot + \cdot H \qquad \Delta H° = 368 \text{ kJ mole}^{-1}$$

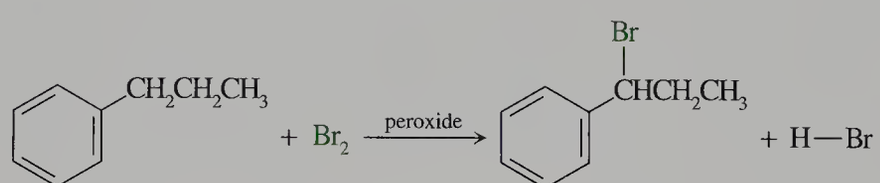


$\Delta H° = 356 \text{ kJ mole}^{-1}$

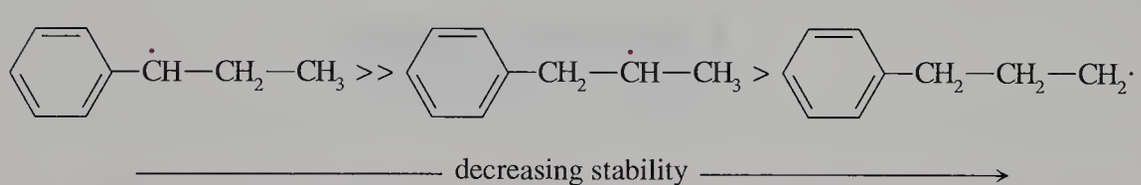
The C—H bond dissociation energy of the methyl hydrogen atom of toluene to form the benzyl radical is smaller than the bond dissociation energy of propane because the unpaired electron is delocalized on the ring carbon atoms that are ortho and para to it.



The stability of the benzyl radical is reflected in the regioselectivity of the free radical halogenation of the side chain of aromatic compounds. For example, the bromination of propylbenzene gives (1-bromopropyl)benzene.



The reaction occurs with formation of a secondary benzylic radical that is more stable than the secondary radical resulting from homolysis of the C-2 to H bond. The primary radical from homolysis of the C-3 to H bond is the least stable.

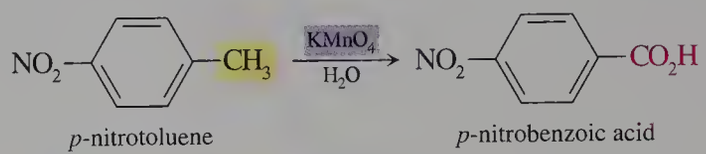


Problem 13.16

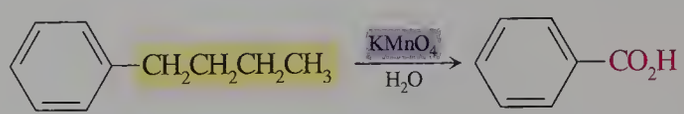
Predict the product of the addition of HBr to 1-phenyl-1-propene in the absence of peroxides. Do the same for a reaction in the presence of peroxides.

13.10 Oxidation of Side Chains

Although the aromatic ring affects the reactivity of the side chain, the ring itself is quite unreactive toward many reagents and remains intact. Oxidation of the side-chain alkyl groups of alkylbenzenes illustrates the special stability of the aromatic ring. We recall that potassium permanganate (Section 7.9) reacts with the π bonds of an alkene under conditions where the σ bonds of the saturated parts of the molecule do not react. Potassium permanganate does not oxidize the benzene ring, even though it is "unsaturated." However, under vigorous conditions, the alkyl side chain is totally oxidized to produce a carboxylic acid at the site of the alkyl group. When two or more alkyl groups are present on a ring, they are all oxidized. The benzene ring, however, remains unscathed!

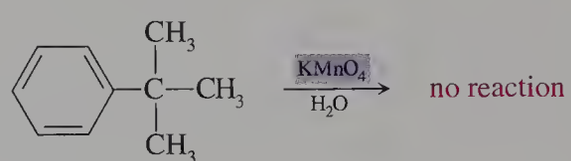


p-nitrotoluene — *p*-nitrobenzoic acid

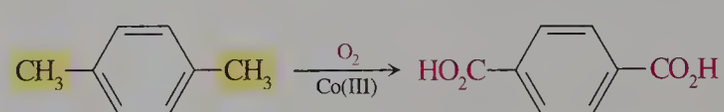


butylbenzene — benzoic acid

Potassium permanganate does not, however, oxidize tertiary alkyl substituents, because they lack the benzylic hydrogen atom required to initiate the oxidation process.



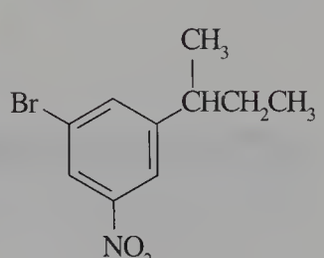
Permanganate is not the only strong oxidizing agent that will oxidize an alkyl group on a benzene ring. For example, the oxidation of *p*-xylene to prepare terephthalic acid, used in production of polyester fibers such as Dacron, is an important industrial process. Air serves as the oxidizing agent in a reaction catalyzed by cobalt(III) salts.



p-xylene — terephthalic acid

Problem 13.17

What is the product formed by the oxidation of the following compound by potassium permanganate?

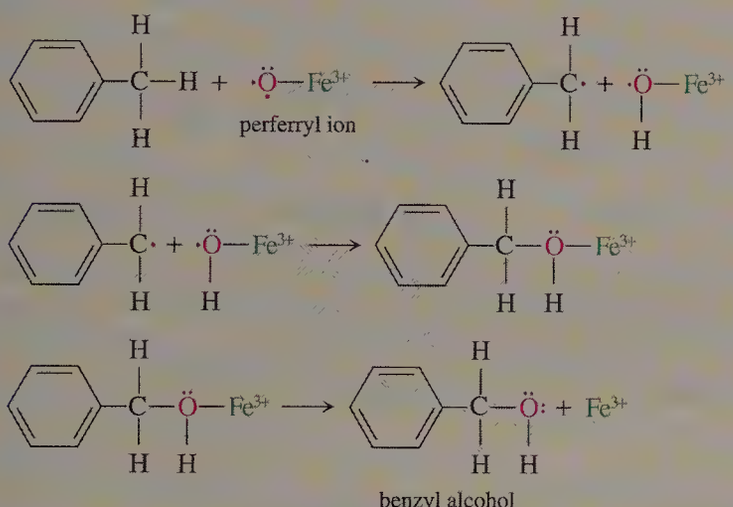


Oxidation of Aromatic Side Chains by Cytochrome P-450

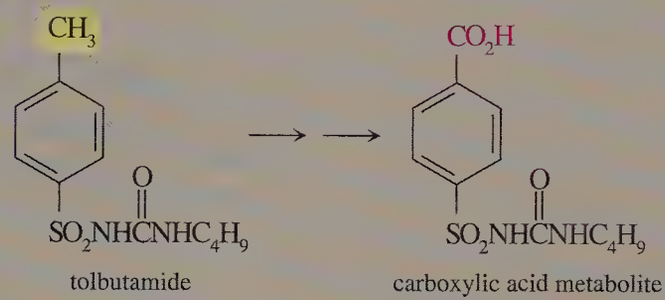
At one time benzene was widely used as a solvent in the chemical industry and in many commercial products. However, it is no longer used for these purposes because its metabolic products can cause leukemia. Benzene has been replaced by toluene, which does not yield toxic by-products. The oxidation of side chains in alkylbenzenes, such as toluene's methyl group, occurs in the liver, catalyzed by the enzyme cytochrome P-450.

Oxidation of a methyl group bonded to an aromatic ring occurs to give a primary alcohol called a benzyl alcohol, Ar—CH_2OH, which the body subsequently eliminates.

The cytochrome P-450 enzymes contain a heme group. At the heart of the heme lies an Fe(III), which combines with O_2 at the active site to give a perferryl ion (FeO^{3+}). This species is a radical, but its precise electronic structure is still open to question. The oxygen atom in the perferryl ion extracts a hydrogen atom from the methyl group of toluene to give a benzyl radical that combines with the OH group bonded to the iron atom of heme to give benzyl alcohol.



A benzyl alcohol derived from the oxidation of methyl-substituted aromatic compounds can also be oxidized further in metabolic reactions to produce aromatic aldehydes, Ar—CHO, and finally carboxylic acids, Ar—CO_2H. These acids dissolve more easily in water than the original methyl-substituted compound, and therefore the body can excrete them. The oral hypoglycemic drug tolbutamide (Orinase) is oxidized in the liver in several steps to the corresponding carboxylic acid.



Sample Solution

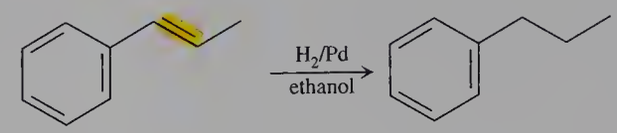
Potassium permanganate oxidizes the side chain of substituted aromatic compounds completely and forms a carboxylic acid. The *sec*-butyl group is oxidized and a —CO_2H group results. The product of the reaction is 3-bromo-5-nitrobenzoic acid.

Problem 13.18

Oxidation of a compound with molecular formula $C_{10}H_{14}$ by potassium permanganate yields terephthalic acid. Write the structures of all possible isomers that would give this product.

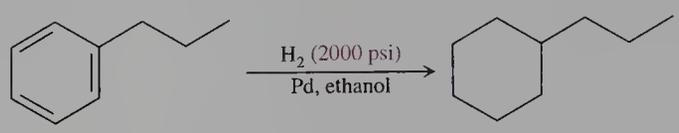
13.11 Reduction of Aromatic Compounds

Aromatic rings are not as easily hydrogenated as alkenes. Thus, at atmospheric pressure and room temperature, a carbon–carbon double bond can be reduced without affecting an aromatic ring. For example, (*E*)-1-phenyl-1-propene is reduced to propylbenzene in the presence of a palladium catalyst.



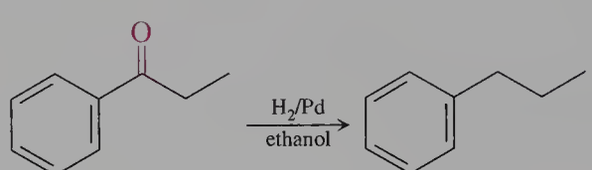
(*E*)-1-phenyl-1-propene propylbenzene

The aromatic ring of the product is reduced only under pressures of hydrogen gas as high as 2000 psi.



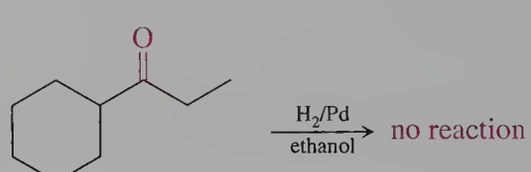
propylbenzene propylcyclohexane

A carbonyl group may be reduced to a methylene group if it is directly bonded to an aromatic ring. For example, 1-phenyl-1-propanone (propiophenone) is converted to propylbenzene by hydrogen gas at atmospheric pressure in the presence of a palladium catalyst.



1-phenyl-1-propanone propylbenzene

The carbonyl group of 1-cyclohexyl-1-propanone is not reduced under the same conditions. The aromatic ring, which activates the carbonyl carbon atom, is necessary for reduction.



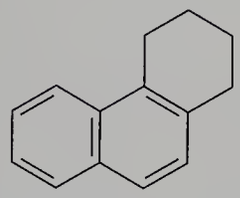
1-cyclohexyl-1-propanone

Problem 13.19

Reduction of any of three isomeric compounds with molecular formula C_9H_{10} using hydrogen gas and a palladium catalyst at atmospheric pressure yields propylbenzene. Write their structures. Arrange them in order of their heats of hydrogenation.

Problem 13.20

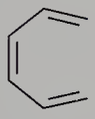
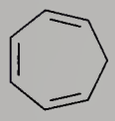
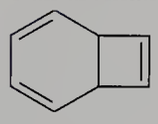
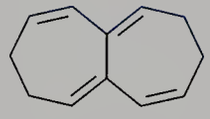
Reduction of a compound with molecular formula $C_{14}H_{12}O$ using hydrogen gas and a palladium catalyst at atmospheric pressure yields the following compound. Write the structure of two possible isomeric compounds that would give this result.



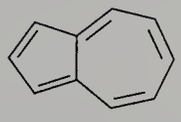
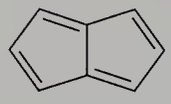
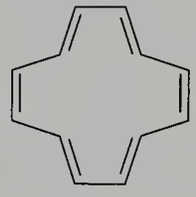
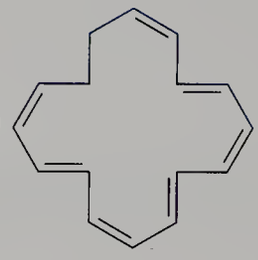
EXERCISES

Aromaticity

13.1 Determine whether each of the following is an aromatic compound.

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

13.2 Determine whether each of the following is an aromatic compound.

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

Heats of Hydrogenation

13.3 The heat of hydrogenation of 1,4-cyclohexadiene to form cyclohexane is 240 kJ mole^{-1} (57.4 kcal mole^{-1}). Calculate the heat of hydrogenation of 1,4-cyclohexadiene to form cyclohexene.

13.4 The heats of hydrogenation of benzene and 1,3-cyclohexadiene to form cyclohexane are 208 and 231 kJ mole^{-1}, respectively. Calculate the heat of hydrogenation of benzene to form 1,3-cyclohexadiene.

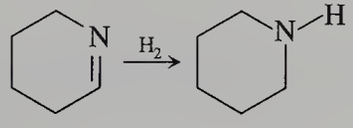
Resonance Energy

13.5 The resonance energy of anthracene is 351 kJ mole^{-1} (84 kcal mole^{-1}). Predict the heat of hydrogenation of anthracene in forming the saturated tricyclic compound with molecular formula $C_{14}H_{24}$.

13.6 The heats of formation of anthracene and phenanthrene are 231 and 206 kJ mole^{-1}, respectively. Which compound has the higher resonance energy?

13.7 The heats of formation of furan and tetrahydrofuran (C_4H_8O) are −35.1 and −184 kJ mole^{-1}, respectively. The heat of hydrogenation of cyclopentene is 110 kJ mole^{-1}. Calculate the resonance energy of furan.

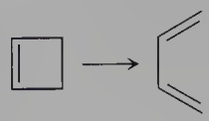
13.8 The heats of formation of pyridine and the saturated heterocycle piperidine ($C_5H_{11}N$) are +144 and −49.4 kJ mole^{-1}, respectively. The $\Delta H°$ of the following reaction is −87.6 kJ mole^{-1}. Calculate the resonance energy of pyridine.

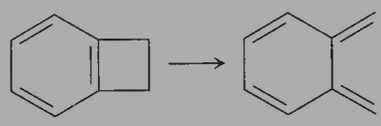


piperidine

13.9 The heat of combustion of benzene is -3300 kJ mole^{-1}. If benzene were not resonance stabilized, what would be the heat of combustion?

13.10 Explain why the $\Delta H°$ values of these two related isomerization reactions differ.

(1)  $\Delta H° = -42$ kJ mole^{-1}

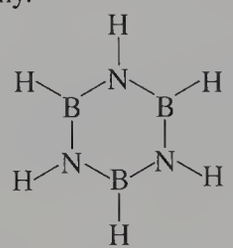
(2)  $\Delta H° = +42$ kJ mole^{-1}

13.11 The heat of hydrogenation of biphenyl ($C_6H_5—C_6H_5$) in forming cyclohexylcyclohexane is approximately 415 kJ mole–1 (100 kcal mole^{-1}). What does this value indicate about the degree of conjugation between the two benzene rings? Suggest a reason that supports your answer based on steric effects.

13.12 Would the heat of hydrogenation of 1-phenylcyclobutene in forming phenylcyclobutane be larger or smaller than the heat of hydrogenation of a trisubstituted alkene? Discuss two structural features that affect the values.

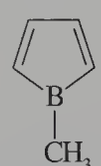
Hückel Rule

13.13 Borazole is an aromatic compound. Explain why.

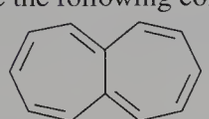
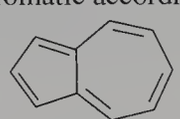
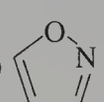
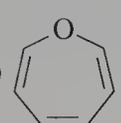


borazole

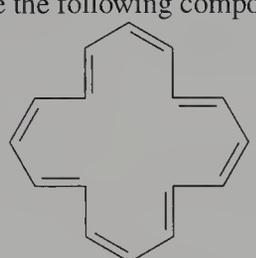
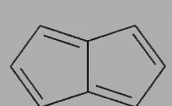
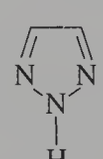
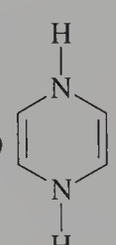
13.14 Is the following compound aromatic? Explain your answer.



13.15 Are the following compounds aromatic according to the Hückel rule?

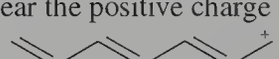
(a)  (b)  (c)  (d) 

13.16 Are the following compounds aromatic according to the Hückel rule?

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

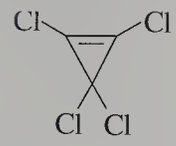
Aromatic Ions

13.17 Write the resonance forms of the following ion. How many carbon atoms bear the positive charge? Compare this answer to the number of carbon atoms that bear the positive charge in the cycloheptatrienyl ion.



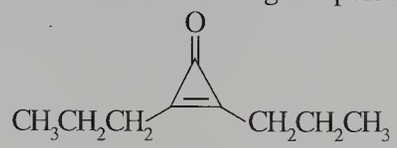
13.18 3-Iodo-1,5-pentadiene reacts rapidly with methanol to give a mixture of methoxypentadienes. Explain why 5-iodo-1,3-cyclopentadiene is unreactive under the same conditions.

13.19 1,2,3,3-Tetrachlorocyclopropene reacts with one mole of $SbCl_5$ to give the $C_3Cl_3^+$ ion. Draw the structure of the ion and explain why it forms.



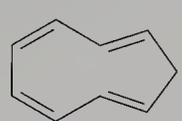
1,2,3,3-tetrachlorocyclopropene

13.20 The dipole moment of dipropylcyclopropenone is 5 D. This value is significantly higher than that of acetone, which is 3 D. Write a resonance form that accounts for the larger dipole moment of the cyclic ketone.



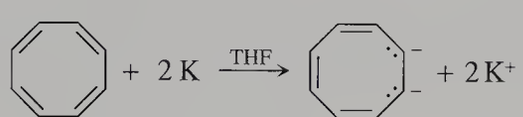
dipropylcyclopropenone

13.21 What reaction of 1,3,5,7-cyclononatetraene could lead to an aromatic ion?

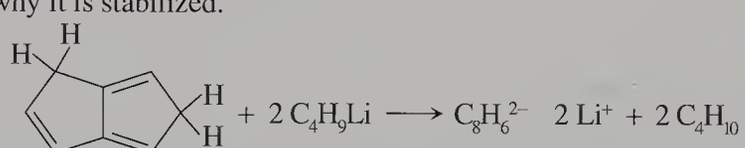


1,3,5,7-cyclononatetraene

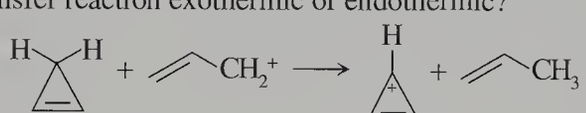
13.22 Cyclooctatetraene is reduced by potassium to give a stable dianion. Explain why. Draw a more stable alternate resonance form.



13.23 The following hydrocarbon reacts with two moles of butyllithium to form the stable ion $C_8H_6^{2-}$. Draw the structure of this ion. Explain why it is stabilized.



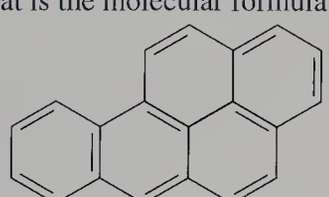
13.24 Is the following hydride ion transfer reaction exothermic or endothermic?



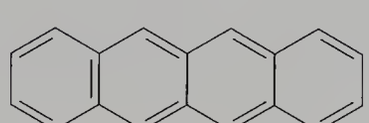
Polycyclic Aromatic Compounds

13.25 What is the molecular formula of each of the following compounds?

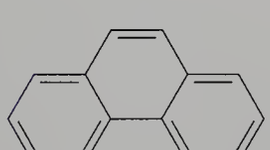
(a)



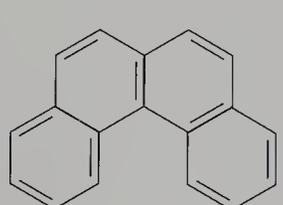
(b)



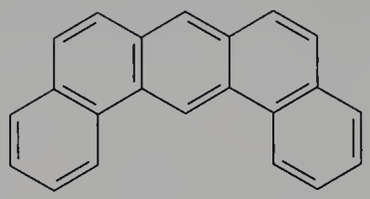
(c)

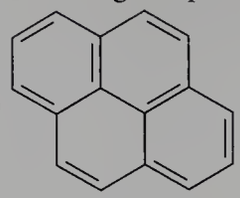


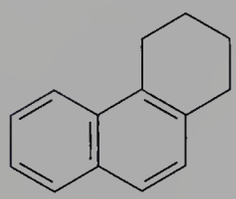
(d)

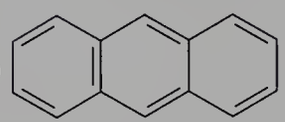


13.26 What is the molecular formula of each of the following compounds?

(a) 

(b) 

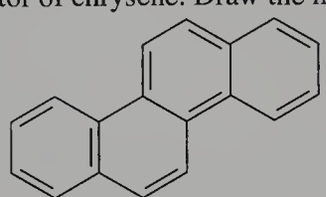
(c) 

(d) 

13.27 Two isomeric bromonaphthalenes exist. Draw their structures.

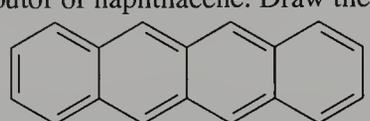
13.28 Three isomeric bromoanthracenes exist. Draw their structures.

13.29 Consider the following resonance contributor of chrysene. Draw the most stable resonance contributor.



chrysene

13.30 Consider the following resonance contributor of naphthacene. Draw the most stable resonance contributor.



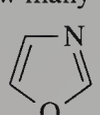
naphthacene

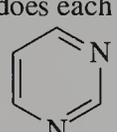
Heterocyclic Aromatic Compounds

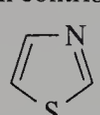
13.31 There are three isomeric diazines ($C_4N_2H_4$) that resemble benzene but have two nitrogen atoms in place of carbon atoms in the ring. Draw their structures. Which of the isomers should have no dipole moment?

13.32 There are three isomeric triazines ($C_3N_3H_3$) that resemble benzene but have three nitrogen atoms in place of carbon atoms in the ring. Draw their structures. Which of the isomers should have no dipole moment?

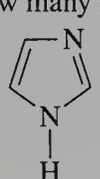
13.33 How many electrons does each heteroatom contribute to the π system in each of the following compounds?

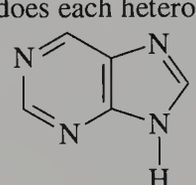
(a) 

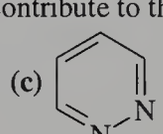
(b) 

(c) 

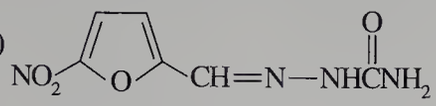
13.34 How many electrons does each heteroatom contribute to the π system in each of the following compounds?

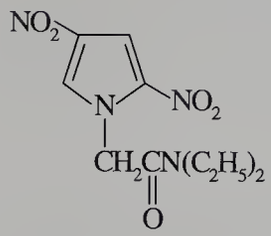
(a) 

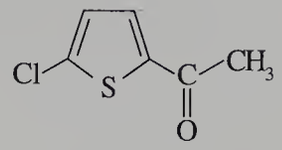
(b) 

(c) 

13.35 Identify the heterocyclic ring structure contained in each of the following compounds, which have been investigated as possible male contraceptives.

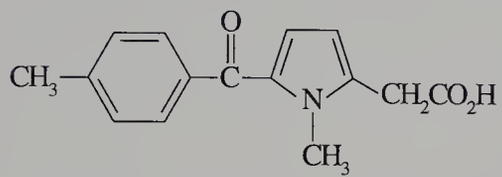
(a) 

(b) 

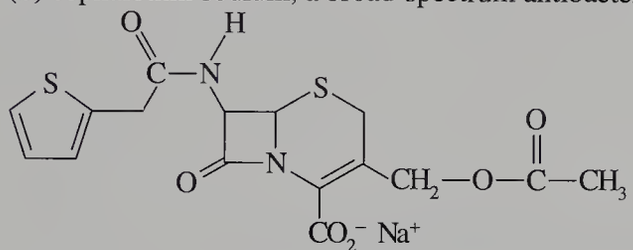
(c) 

13.36 Identify the aromatic heterocyclic ring structure contained in each of the following compounds.

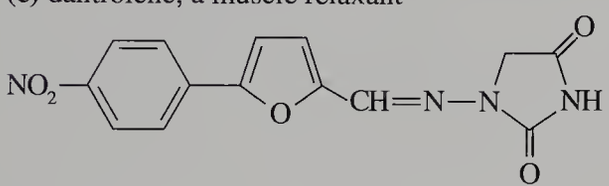
(a) tolmetin, a drug used to lower blood sugar levels



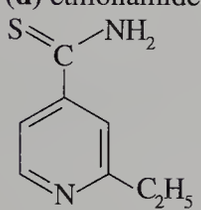
(b) cephalothin sodium, a broad-spectrum antibacterial



(c) dantrolene, a muscle relaxant



(d) ethionamide, an antitubercular agent



Properties of Aromatic Compounds

13.37 There are three isomeric trichlorobenzenes. One compound is nonpolar. Which one?

13.38 There are three isomeric tetrachlorobenzenes. One compound is nonpolar. Which one?

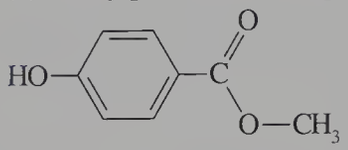
13.39 The boiling points of benzyl alcohol and anisole are 205 and 154°C, respectively. Explain this difference.

13.40 The boiling points of the ortho, meta, and para-chlorophenols are 175, 214, and 220°C, respectively. Considering the phenomenon of hydrogen bonding, explain why the ortho isomer has a significantly lower boiling point than the other isomers.

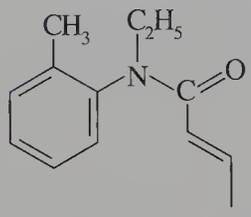
Nomenclature of Aromatic Compounds

13.41 Identify each of the following as an ortho-, meta-, or para-substituted compound.

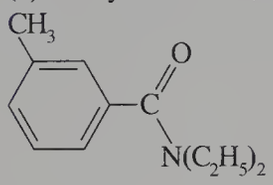
(a) methylparaben, a food preservative used to protect food against molds



(b) crotamiton, used in creams for topical treatment of scabies

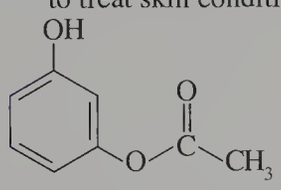


(c) diethyltoluamide, an insect repellent

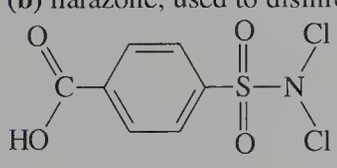


13.42 Identify each of the following as an ortho-, meta-, or para-substituted compound.

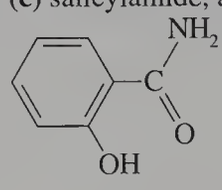
(a) resorcinol monoacetate, a germicide used to treat skin conditions



(b) halazone, used to disinfect water

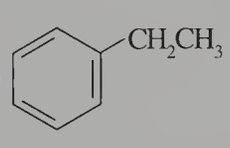


(c) salicylamide, an analgesic

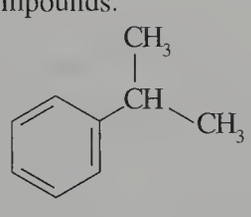


13.43 Name each of the following compounds.

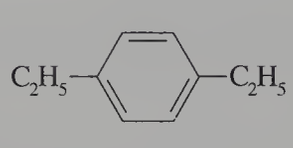
(a)



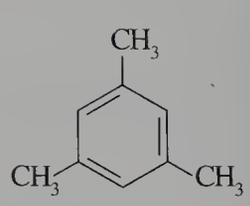
(b)



(c)

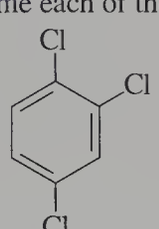


(d)

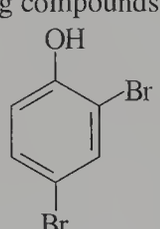


13.44 Name each of the following compounds.

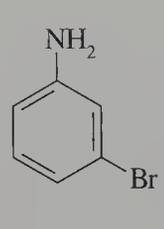
(a)



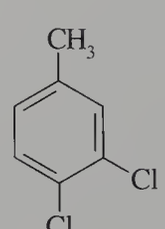
(b)



(c)

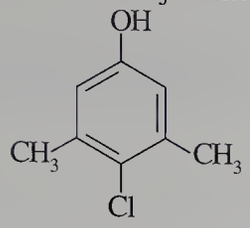


(d)

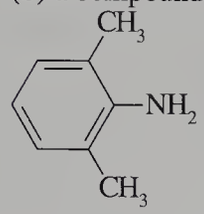


13.45 Name each of the following compounds.

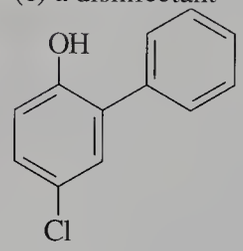
(a) an antiseptic agent used to treat athlete's foot and jock itch



(b) a compound used to make a local anesthetic



(c) a disinfectant



13.46 Draw the structure of each of the following compounds.

(a) 5-isopropyl-2-methylphenol, found in oil of marjoram

(b) 2-isopropyl-5-methylphenol, found in oil of thyme

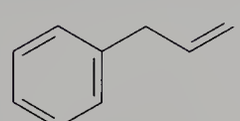
(c) 2-hydroxybenzyl alcohol, found in the bark of the willow tree

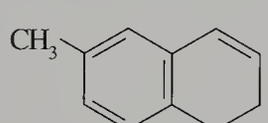
13.47 Draw the structure of 3,4,6-trichloro-2-nitrophenol, a lampricide used to control sea lampreys in the Great Lakes.

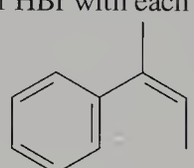
13.48 *N*,*N*-Dipropyl-2,6-dinitro-4-trifluoromethylaniline is the IUPAC name for Treflan, a herbicide. Draw its structure. (The prefix *N* signifies the location of a substituent replacing hydrogen on a nitrogen atom.)

Reactions of Side Chains

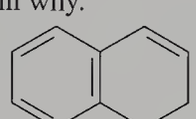
13.49 Write the structure of the addition product formed in the reaction of HBr with each of the following compounds.

(a) 

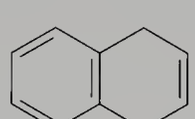
(b) 

(c) 

13.50 Compare the structures of the addition products of HBr with each of the following two compounds. Are they identical or do they differ? Explain why.

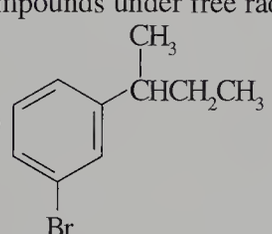


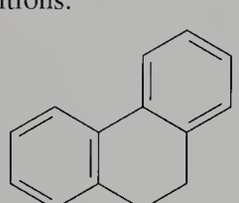
1,2-dihydronaphthalene
I

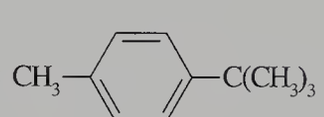


1,4-dihydronaphthalene
II

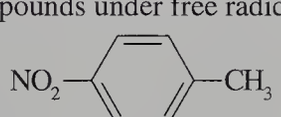
13.51 Draw the structure of the product formed in the reaction of one mole of Br_2 with each of the following compounds under free radical conditions.

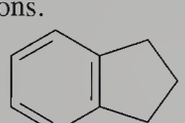
(a) 

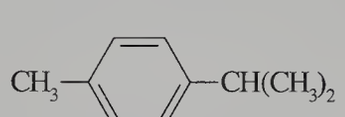
(b) 

(c) 

13.52 Draw the structure of the product formed in the reaction of one mole of Br_2 with each of the following compounds under free radical conditions.

(a) 

(b) 

(c) 

Oxidation of Aromatic Compounds

13.53 Draw the structure of the product formed in the reaction of each of the compounds in Exercise 13.49 using excess $KMnO_4$.

13.54 Draw the structure of the product formed in the reaction of each of the compounds in Exercise 13.50 using excess $KMnO_4$.

Reduction of Aromatic Compounds

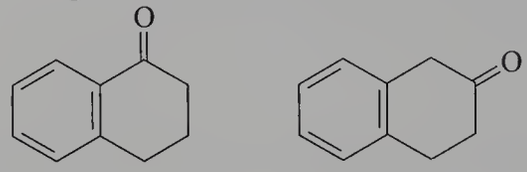
13.55 Draw the structure of the product formed in the reaction of each of the compounds in Exercise 13.49 with hydrogen gas at atmospheric pressure in the presence of palladium catalyst.

13.56 The heat of hydrogenation of one of the compounds in Exercise 13.50 is 101 kJ $mole^{-1}$; the value for the other is 113 kJ $mole^{-1}$. Match an appropriate heat of hydrogenation with each compound.

13.57 Hydrogenation of *p*-xylene with hydrogen gas at high pressure in the presence of platinum yields a mixture of isomeric C_8H_{16} compounds. Explain why.

13.58 What product results from the complete hydrogenation of naphthalene at high pressure in the presence of platinum?

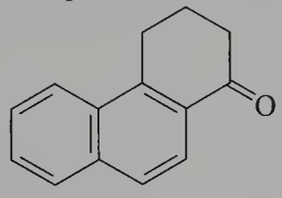
13.59 Compare the reactivity of the following two compounds with hydrogen gas in the presence of palladium catalyst under conditions where the aromatic ring is not reduced.



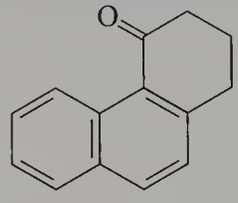
I II

13.60 Draw the structure of the compound formed from each of the following compounds in a reaction with hydrogen gas in the presence of palladium catalyst under conditions where the aromatic ring is not reduced.

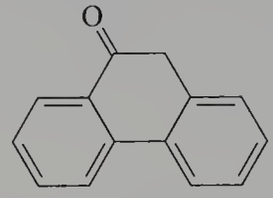
(a)



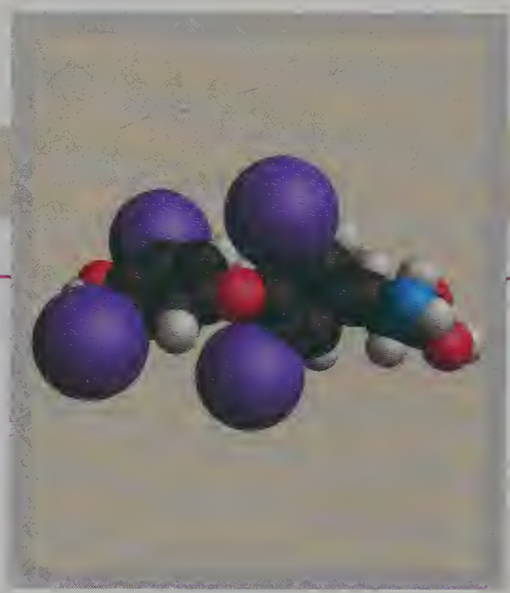
(b)



(c)



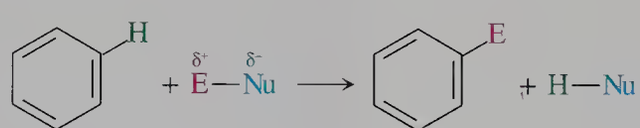
14



Electrophilic Aromatic Substitution

14.1 Reactivity of Aromatic Rings

Aromatic rings do not undergo the electrophilic addition reactions we discussed in Chapter 7 for alkenes. Instead, they react with electrophiles—only in the presence of a catalyst—to give a substitution product. In these reactions an electrophile (E^+) substitutes for H^+. The general process is shown below.

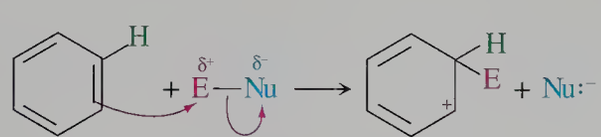


Many electrophiles can substitute for hydrogen on an aromatic ring. A halogen atom, usually chlorine or bromine, adds to the ring through a **halogenation** reaction. The nitro group ($—NO_2$) and the sulfonic acid group ($—SO_3H$) become substituents through **nitration** and **sulfonation** reactions. **Alkylation** and **acylation** reactions introduce alkyl groups (—R) and acyl groups (—COR), respectively. These reactions all occur by the same general reaction mechanism.

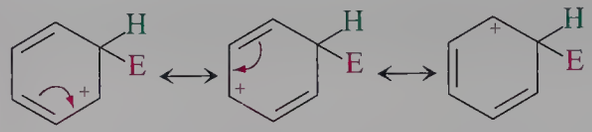
Mechanism of Electrophilic Aromatic Substitution

The first step of electrophilic aromatic substitution resembles the addition of electrophiles to alkenes. The electrophile accepts a pair of electrons from the aromatic ring. However, because this electron pair forms part of a delocalized aromatic sextet, aromatic compounds are significantly less reactive than alkenes. They are so much less reactive that a Lewis acid, such as $FeBr_3$ in bromination or $AlCl_3$ in alkylation, is required as a catalyst to generate an electrophile sufficiently reactive to attack the aromatic ring.

An electrophile adds to the aromatic ring and produces a carbocation intermediate in the first step of electrophilic aromatic substitution, which is most often the rate-determining step.



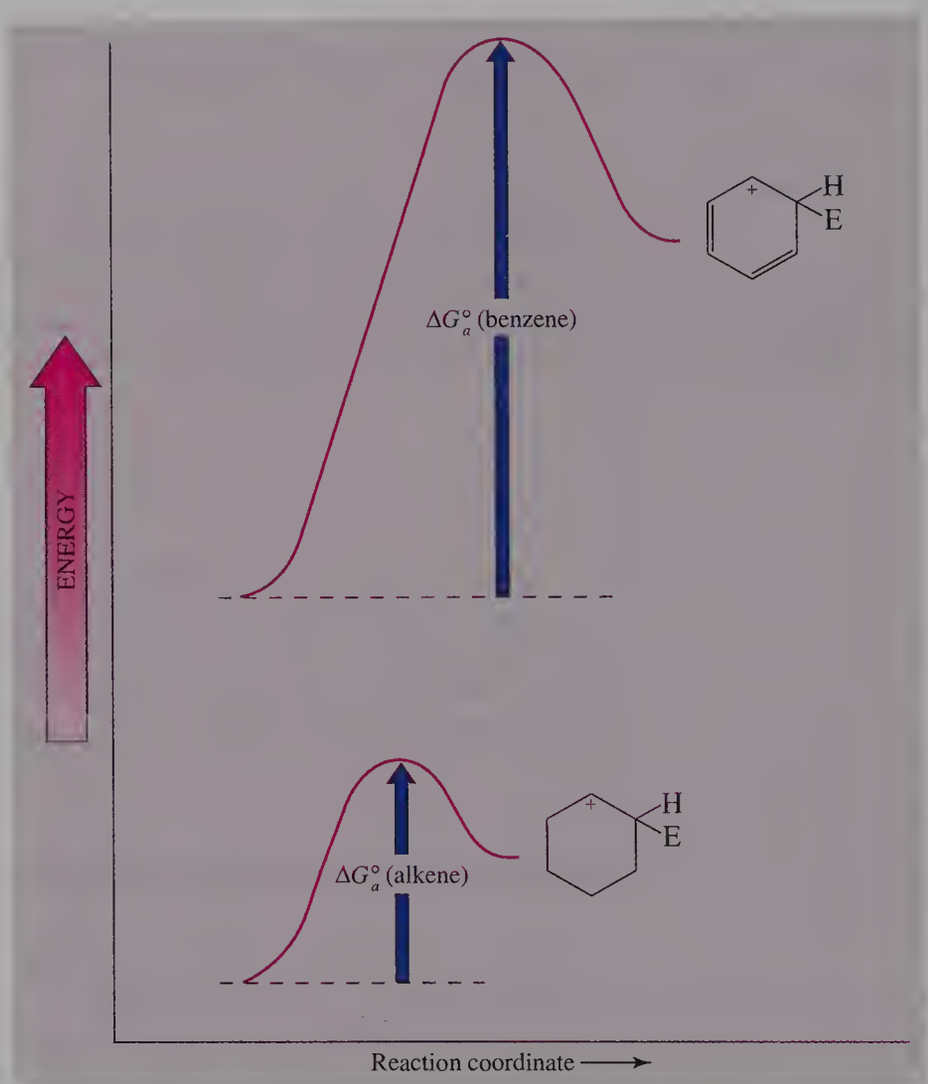
This carbocation is resonance stabilized, but is not aromatic because it has only four *p* electrons. It also has an sp^3-hybridized carbon atom, which prevents a closed π system. Therefore, it reacts much more easily than the original aromatic ring.



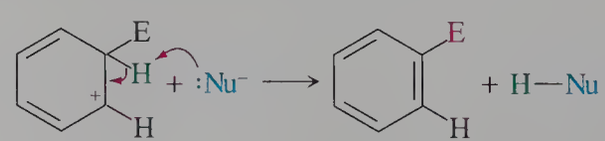
resonance forms of a cyclohexadienyl carbocation

As a consequence, attachment of the electrophile to a benzene ring has a larger activation barrier than electrophilic addition to an alkene (Figure 14.1). Therefore, the rates of electrophilic aromatic substitution reactions are slower than the rates of electrophilic addition reactions to alkenes for the same electrophile. For example, bromine reacts instantly with alkenes, but does not react at all with benzene except in the presence of a catalyst.

FIGURE 14.1
Electrophilic Addition to an Alkene vs. Benzene
The activation barrier for the electrophilic addition to benzene is larger than for the activation energy of electrophilic addition to an alkene because some of the resonance energy of benzene is lost in the transition state.

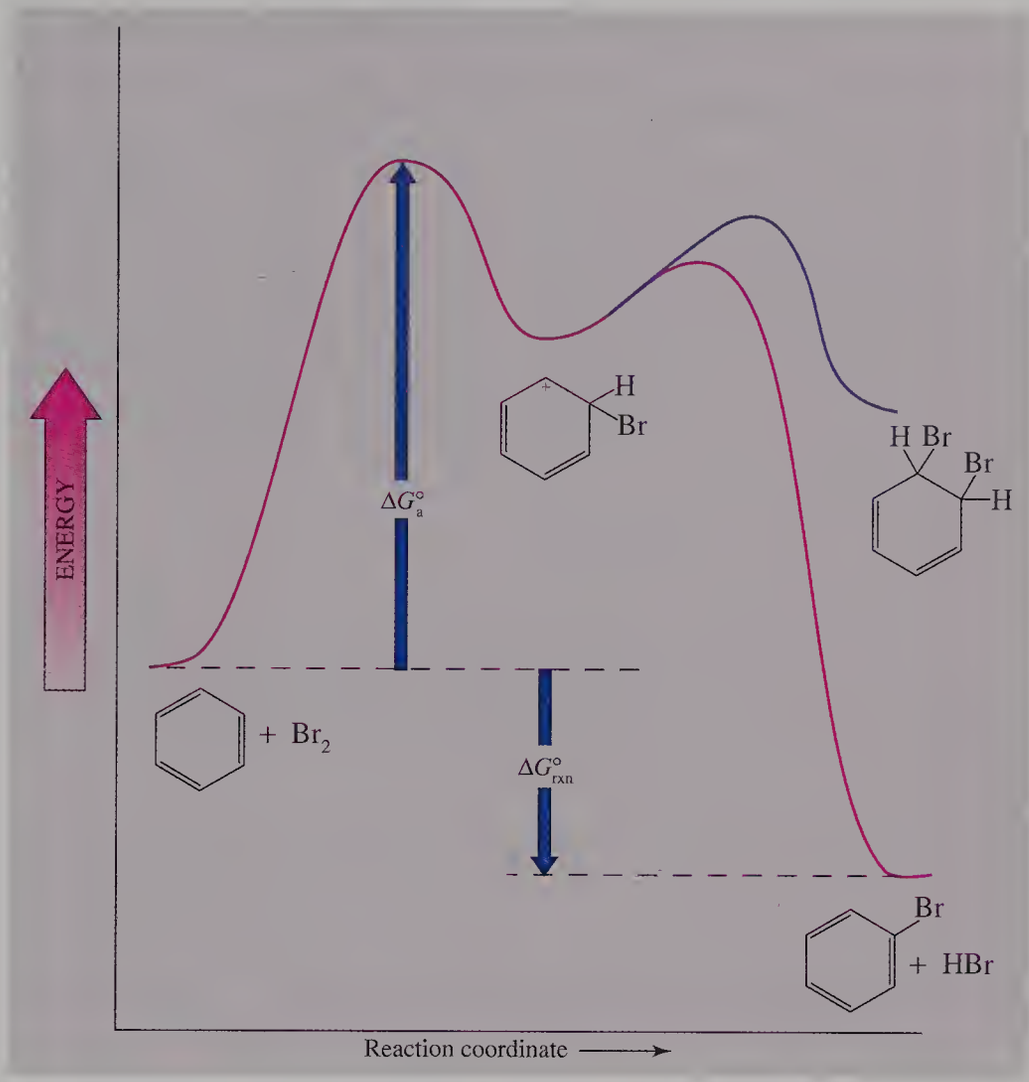


In the faster second step of the electrophilic substitution mechanism, the proton bound to the sp^3-hybridized ring carbon atom leaves, restoring the aromatic π system. A nucleophile acting as a base extracts the leaving proton.



The carbocation intermediate can potentially react with the nucleophile to give an addition product. However, the net addition reaction does not occur with benzene because the 150 kJ mole^{-1} (36 kcal mole^{-1}) of resonance energy for the benzene ring would be lost, making the overall reaction endothermic (Figure 14.2). In contrast, the stability of the aromatic ring remains in the substitution reaction.

FIGURE 14.2
Electrophilic Substitution vs. Addition for Benzene
The substitution product is more stable than the addition product because the resonance energy of benzene is preserved. The transition state energy of the second step of the substitution reaction is higher for addition because of the loss of resonance energy. In the second step of the substitution reaction some of the resonance energy is regained.



14.2 Typical Electrophilic Substitution Reactions

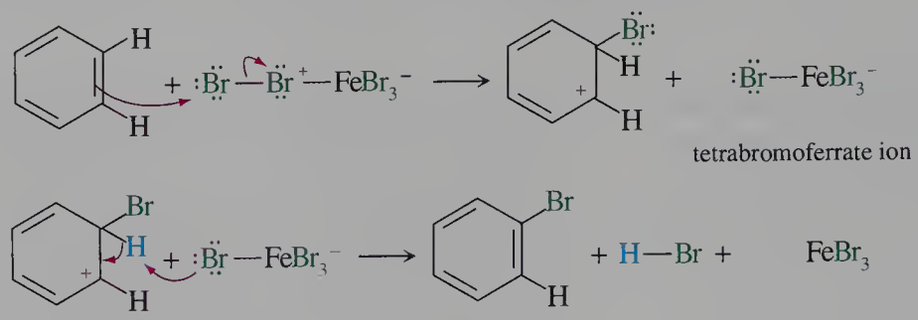
In the preceding discussion we used a generic electrophile, E^+. In this section we will consider some specific examples of electrophiles that react with aromatic rings.

Halogenation

Only the halogens bromine and chlorine are commonly used to halogenate aromatic rings. Bromination requires both Br_2 and a Lewis acid catalyst, $FeBr_3$. The catalyst generates a Lewis acid–Lewis base complex with a weakened Br—Br bond. The bromine atom bonded to iron carries a formal positive charge. As a consequence, the terminal bromine atom also carries a partial positive charge due to polarization of the bonded electron pair.

Lewis acid–Lewis base complex

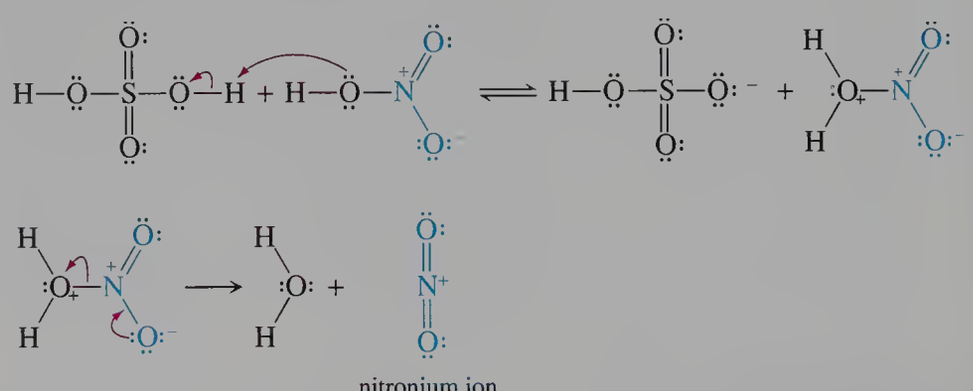
The more electrophilic bromine atom attacks the benzene ring to form a cyclohexadienyl ion. This step also forms a tetrabromoferrate ion, which removes a proton from the cyclohexadienyl ion in a subsequent step. This step also regenerates the iron(III) bromide, which continues to act as a catalyst in the reaction.



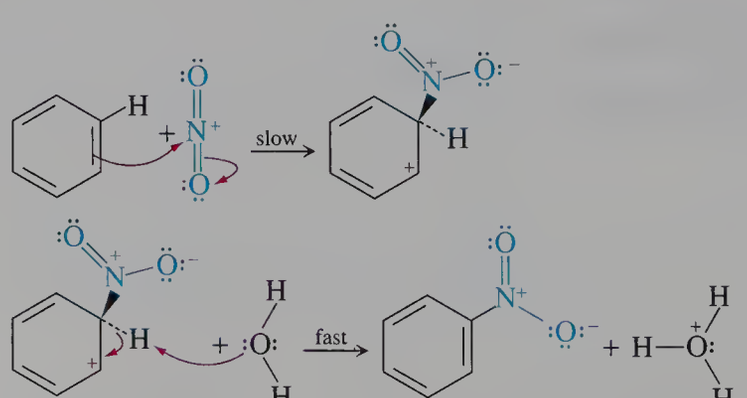
Chlorination, which proceeds in a similar manner, requires $FeCl_3$ as the Lewis acid catalyst. Fluorine reacts so strongly that multiple substitutions occur. Iodine, on the other hand, is unreactive, although iodobenzene compounds can be made using some special alternative reaction conditions.

Nitration

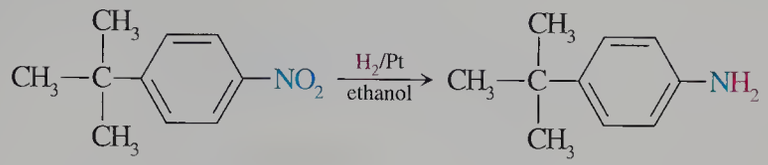
Nitration introduces a nitro group ($—NO_2$) onto an aromatic ring. Electrophilic aromatic substitution requires nitric acid (HNO_3), with sulfuric acid as a catalyst. The nitronium ion (NO_2^+) produced in two steps by the reaction of nitric acid with sulfuric acid, acts as the electrophile.



Nitration occurs by attack of the nitronium ion on the π system of the aromatic ring, followed by loss of a proton from the cyclohexadienyl carbocation to water.



Nitration of aromatic rings is an important reaction because the nitro group can readily be reduced to an amino group, a common functional group required in pharmaceutical compounds. Other substituents can subsequently replace the amino group (Section 14.8).

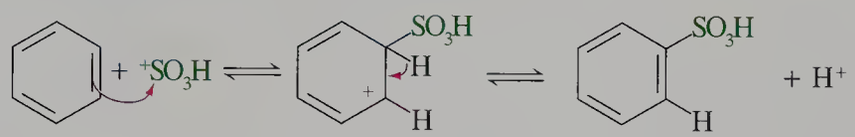


p-tert-butylnitrobenzene *p-tert*-butylaniline

Sulfonation

A sulfonic acid group (—SO_3H) can be substituted on an aromatic ring by an electrophilic aromatic substitution reaction called sulfonation. Although the reagent is SO_3, the reaction requires a mixture of SO_3 and sulfuric acid, called fuming sulfuric acid. The electrophile is $^+SO_3H$.

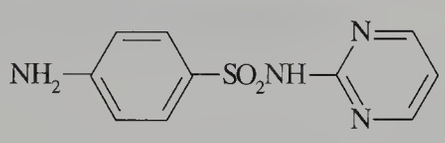
$$SO_3 + H_2SO_4 \longrightarrow {}^+SO_3H + HSO_4^-$$



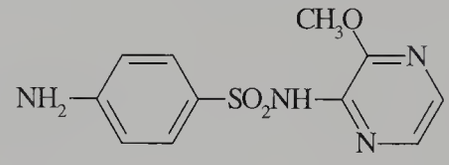
benzenesulfonic acid

The sulfonation reaction is less exothermic than halogenation or nitration. As a consequence, sulfonation or the reverse, desulfonation, occurs under the right reaction conditions. Sulfonation occurs in strong acid; desulfonation occurs in dilute aqueous acid. The reversibility of the sulfonation reaction forms the basis of the synthesis of some aromatic compounds because the sulfonic acid group may block a position on an aromatic ring, preventing substitution at that point. The sulfonic acid group is removed at the end of the synthesis.

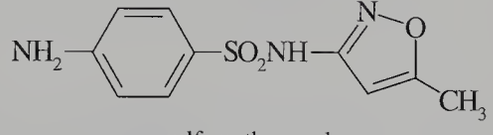
The sulfonic acid functional group, commonly found in azo dyes (Section 27.9), affects both the color of a compound and its solubility in water. A sulfonic acid group can be converted to the related sulfonamide group to form sulfa drugs.



sulfadiazine
(an antimalarial)



sulfalene
(an antilepral)

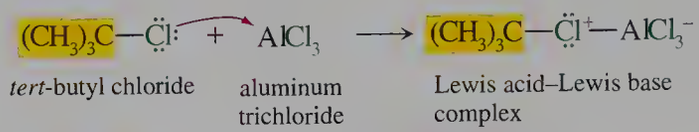


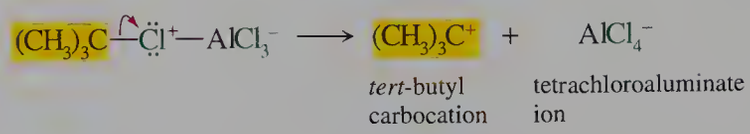
sulfamethoxazole
(an antibacterial)

Alkylation

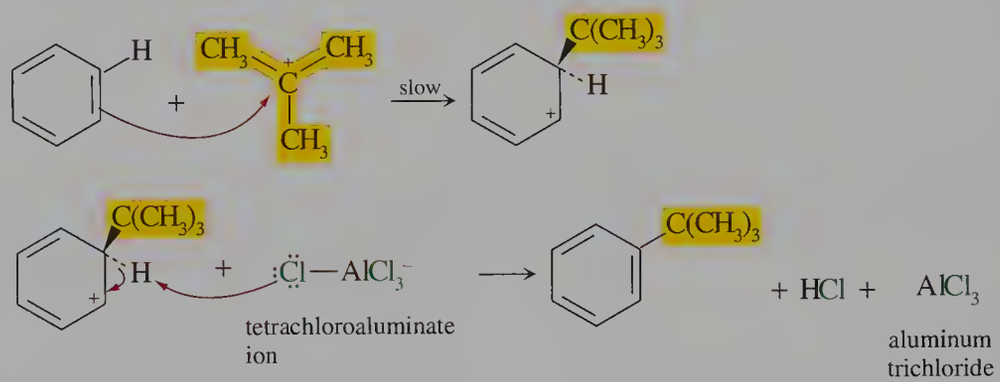
An alkyl group can substitute for a hydrogen atom of an aromatic ring in the **Friedel–Crafts alkylation** reaction. This reaction requires an alkyl halide, with an

aluminum trihalide as the catalyst. The catalyst produces an electrophilic species, which may be a carbocation or a carbocation complexed with a counter ion. For simplicity in writing equations, we will show only the free carbocation. The reaction is commonly carried out only with alkyl bromides or alkyl chlorides. Aryl halides and vinyl halides do not react because the carbocations derived from these compounds do not form under usual reaction conditions. Tertiary carbocations such as the *tert*-butyl carbocation readily form.





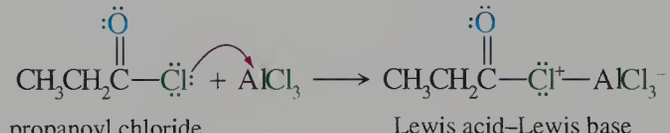
Alkylation of arenes by carbocations such as the *tert*-butyl carbocation occurs by a two-step process similar to those discussed for bromination and nitration.

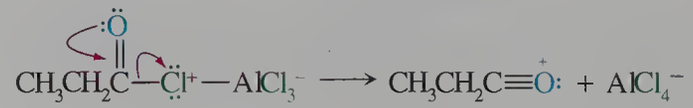


Secondary alkyl halides alkylate arenes by forming a secondary carbocation. However, primary alkyl halides do not form carbocations under Friedel–Crafts conditions. Instead, the alkyl group transfers directly to the aromatic ring from the Lewis acid–Lewis base complex, which has a highly polarized carbon halogen bond.

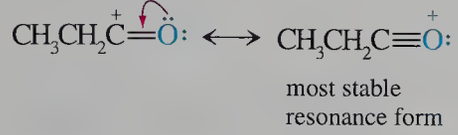
Acylation

An acyl group can replace hydrogen in an aromatic ring by a reaction called **Friedel–Crafts acylation**. The reaction requires an acyl halide and the corresponding aluminum trihalide. The reaction is commonly carried out only with acyl chlorides. The electrophile is shown as an acyl cation (acylium ion), formed from a Lewis acid–Lewis base complex of aluminum trichloride and the acyl chloride.

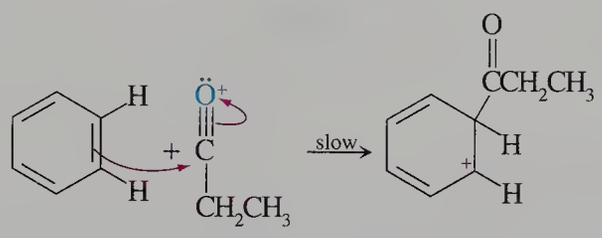


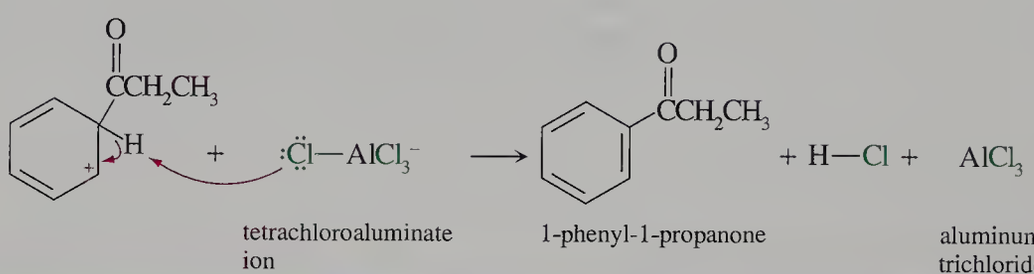


Acyl cations are resonance stabilized. The more stable form has an octet of electrons on both carbon and oxygen atoms, and a formal positive charge on the oxygen atom. However, to give a stable product, reaction of the acyl cation with an aromatic ring must occur at the acyl carbon atom.



Acylation of arenes by carbocations, such as the propanoyl cation, occurs by a two-step process similar to those discussed for bromination, nitration, and alkylation.



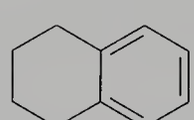


Problem 14.1

Draw the structures of all possible products formed by monosubstitution of *o*-dibromobenzene in a chlorination reaction. Do the same for *m*- and *p*-dibromobenzene.

Problem 14.2

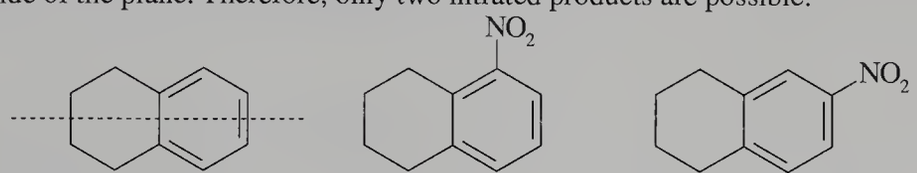
Draw the structures of all possible products formed by mononitration of tetralin.



tetralin

Sample Solution

The molecule has a plane of symmetry perpendicular to the plane of the page that bisects both the aromatic and saturated rings. There are two nonequivalent hydrogen atoms on either side of the plane. Therefore, only two nitrated products are possible.

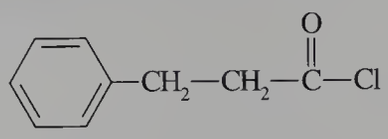


Problem 14.3

Write the structures of the two possible products formed by sulfonation of naphthalene. At 80 °C isomer I constitutes 96% of the reaction mixture. At 165 °C, isomer II is 85% of the reaction mixture. When isomer I is heated in sulfuric acid at 165 °C, it is converted into isomer II. Explain these observations. Based on steric considerations, which of the two isomers is likely to be more stable?

Problem 14.4

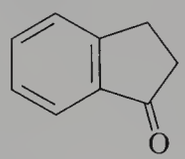
Reaction of 3-phenylpropanoyl chloride with $AlCl_3$ yields a compound with the molecular formula C_9H_8O. Write the structure of the compound and explain its origin.



3-phenylpropanoyl chloride

Sample Solution

The general Friedel–Crafts reaction discussed in this section is an intermolecular reaction between an aromatic compound and an acyl halide. However, if the acyl halide also contains an aromatic ring, an intramolecular reaction can easily occur. Such a unimolecular reaction is entropically favored over a bimolecular reaction when the ring formed contains either five or six atoms. Thus, the reaction that occurs is a Friedel–Crafts reaction in which the acyl chloride acylates the ortho position.



14.3 Limitations of Friedel–Crafts Reactions

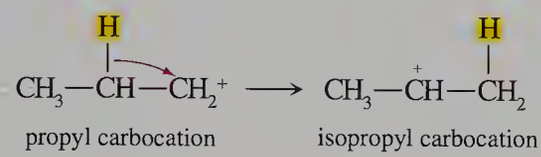
Neither Friedel-Crafts alkylation nor acylation occurs on aromatic rings that have one of the groups $-NO_2$, $-SO_3H$, $-C{\equiv}N$, or any carbonyl-containing group, bonded directly to the aromatic ring. The carbonyl-containing compounds include aldehydes, ketones, carboxylic acids, and esters. All of these substituents make the benzene ring less reactive (Section 14.4)

A second limitation of the Friedel–Crafts alkylation reaction is the difficulty of stopping the reaction after the introduction of a single alkyl group. Alkyl groups make the benzene ring more reactive, so the alkylated product reacts more readily in subsequent substitution reactions than the original reactant. In contrast, Friedel–Crafts acylation yields a less reactive product than the original reactant, and multiple acylations do not occur.

The third limitation of Friedel–Crafts alkylation reaction is the structural rearrangement of the alkyl carbocation generated from the alkyl halide. A rearrangement of the alkyl group produces a different product than the one desired. For example, the reaction with 1-chloropropane in the presence of $AlCl_3$ yields a small amount of propylbenzene, but a larger amount of the isomer, isopropylbenzene.

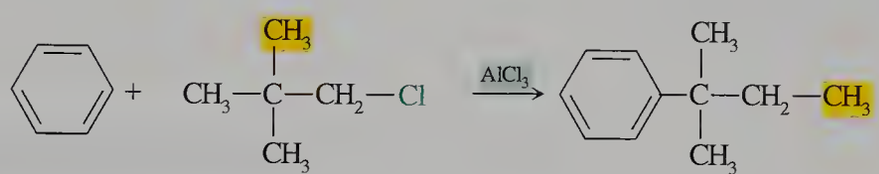
major product minor product

Isomerization of carbocations in the Friedel–Crafts reaction occurs by a **hydride** ($H:^-$) **shift**, which converts a less stable carbocation into a more stable one. In the Friedel–Crafts reaction using 1-chloropropane, the Lewis acid–Lewis base complex of 1-chloropropane and $AlCl_3$ rearranges. (We recall from Section 3.13 that the order of carbocation stability is tertiary > secondary > primary. This order of stability controls the rearrangement reactions, discussed in Sections 7.4 and 8.11, involving addition of hydrogen halide to alkenes and the substitution reactions of alkyl halides, respectively.) For simplicity, the equation shows rearrangement of the free primary carbocation to a secondary carbocation. A hydrogen atom and the bonding electron pair ($H:^-$) shift from the C-2 to the C-1 atom.



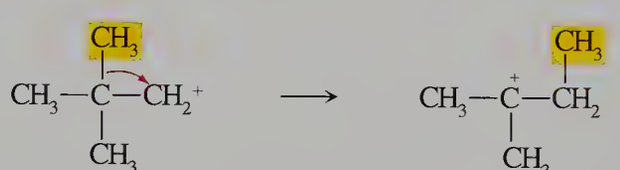
propyl carbocation — isopropyl carbocation

Isomerization of carbocations in the Friedel–Crafts reaction can also occur by an **alkyl group shift**. The alkylation of benzene with 1-chloro-2,2-dimethylpropane yields only (1,1-dimethylpropyl)benzene.



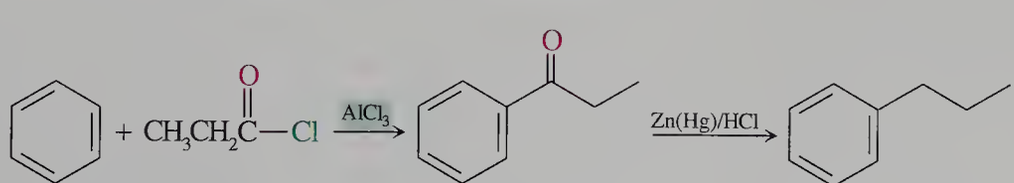
1-chloro-2,2-dimethylpropane — (1,1-dimethylpropyl)benzene

The reaction probably occurs by way of a Lewis acid–Lewis base complex. However, the product results from transfer of a methyl group and its electron pair (a methide ion) from the quaternary carbon atom to the primary carbon atom. Using free carbocations, this methide shift converts the primary carbocation to a more stable tertiary carbocation.



2,2-dimethylpropyl carbocation (1° carbocation) — 1,1-dimethylpropyl carbocation (3° carbocation)

Acylium ions produced in the Friedel–Crafts reaction do not rearrange. The acyl group in the product can be reduced using a zinc–mercury amalgam and HCl (this is called a Clemmensen reduction) to produce an alkylbenzene. This circumvents the rearrangement of primary alkyl groups that occurs in the Friedel–Crafts alkylation reaction. For example, acylation of benzene with propanoyl chloride followed by a Clemmensen reduction yields propylbenzene.



Problem 14.5

Predict the structure of the major product formed in the Friedel–Crafts alkylation of benzene with 1-chlorobutane.

Problem 14.6

Reaction of 2-methylpropene with benzene in the presence of H_3PO_4 yields *tert*-butylbenzene. Propose a mechanism for this reaction.

Problem 14.7

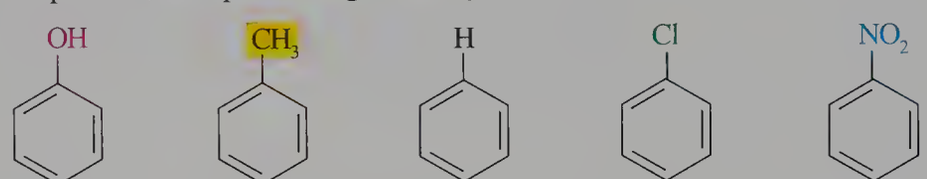
Outline a synthesis of 2-methyl-1-phenylpropane (isobutylbenzene) starting from benzene and using a Friedel–Crafts reaction.

14.4 Substituent Effects on Reactivity of Aromatic Rings

To this point, we have discussed only electrophilic substitution reactions of benzene itself. Now let's examine the effect that a substituent already bonded to the aromatic ring has on ring attack by an electrophile to attach a second substituent. For a substitution reaction on benzene, only one product results. But if a second substituent adds to a substituted benzene, any of three possible products—the ortho, meta, and para isomers—can result. We would like to know how the original substituent affects (1) the rate of formation of these products and (2) the distribution of the products.

Effects of Ring Substituents on Reaction Rate

To examine the effect of a substituent on the rate of electrophilic aromatic substitution, let us compare the rate of nitration of benzene to those of several substituted benzenes. The relative rate of reaction of phenol is 10^{10} as fast as that of nitrobenzene. (For comparison, the speed of light is only about 10^8 as fast as the speed of jogging.)



phenol	toluene	benzene	chlorobenzene	nitrobenzene
10^3	25	1	3×10^{-2}	1×10^{-7}

Phenol and toluene are nitrated faster than benzene, whose relative rate of reaction is set at 1. Both a hydroxyl group and a methyl group make the aromatic ring more reactive compared to benzene, and these groups are called **activating groups**. On the other hand, chlorobenzene and nitrobenzene react more slowly than benzene. The chloro and nitro groups are called **deactivating groups** because they make the aromatic ring less reactive. Table 14.1 lists some common substituents and divides them into activating and deactivating groups with regard to electrophilic aromatic substitution.

TABLE 14.1
Effect of Ring Substituents on Aromatic Substition

Strongly activating

$-NH_2$, $-NHR$, $-NR_2$
$-OH$, $-OCH_3$

Weakly activating

$-CH_3$, $-CH_2CH_3$, $-R$

Weakly deactivating

$-F$, $-Cl$, $-Br$

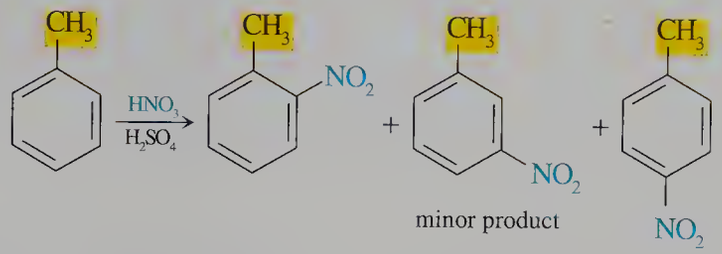
Strongly deactivating

$-\overset{\overset{O}{\|}}{C}-R$, $-\overset{\overset{O}{\|}}{C}-OH$
$-C\equiv N$
$-NO_2$, $-CF_3$, $-CCl_3$

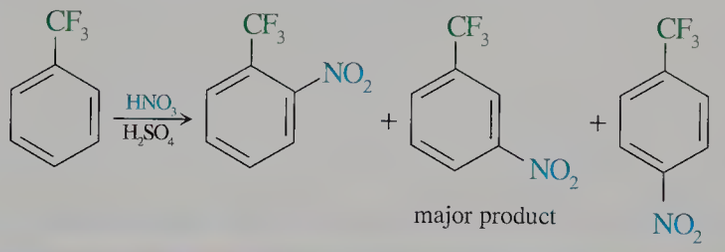
Orientation Effect of Substituents

Now let's consider the distribution of products formed in the nitration of toluene. The nitro group that attacks the ring can bond at three nonequivalent sites to give *o*-, *m*-, or *p*-nitrotoluene. When we examine the product distribution, we find that the ortho and para isomers predominate and that very little of the meta isomer forms. The methyl group directs or orients the incoming substituent into positions ortho and para to itself and is therefore called an **ortho,para director**. All groups

that activate the aromatic ring toward further substitution are ortho,para directors. The weakly deactivating halogens also act as ortho,para directors.

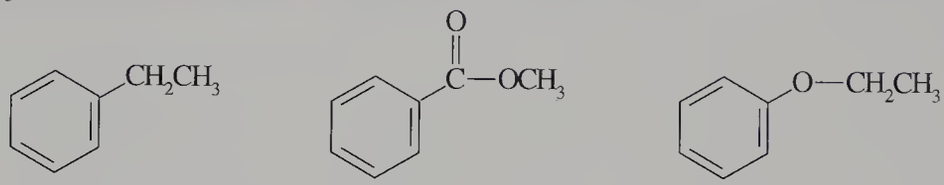


A second class of ring substituents, known as **meta directors**, directs incoming substituents into the meta position. These groups include nitro, trifluoromethyl, cyano, sulfonic acid, and any group with a carbonyl carbon atom bonded directly to the ring. For example, in a nitration reaction, the trifluoromethyl group orients the incoming nitro group to a position meta to itself. Very small amounts of the ortho and para isomers form. All deactivating groups (except halogens) are meta-directing groups.



Problem 14.8

Arrange the following compounds in order of increasing rate of reaction with bromine and $FeBr_3$.



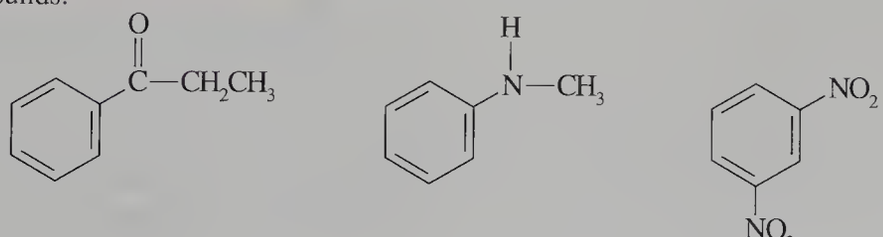
ethylbenzene | methyl benzoate | ethoxybenzene

Sample Solution

Ethylbenzene contains an alkyl substituent, and this compound is slightly more reactive than benzene. Methyl benzoate has a carbonyl carbon atom bonded to the aromatic ring. As a result, its rate of bromination will be significantly slower than that of benzene. Ethoxybenzene is an ether—it structurally resembles anisole, which is an ether derived from phenol. The oxygen atom attached directly to the ring causes a significant rate increase over that of benzene. Thus the order of reactivity in an electrophilic aromatic substitution reaction such as bromination is methyl benzoate < ethylbenzene < ethoxybenzene.

Problem 14.9

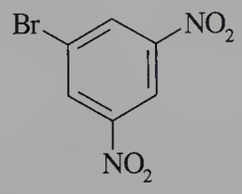
Predict the structure of the product(s) formed in the bromination of each of the following compounds.



propiophenone | *N*-methylaniline | *m*-dinitrobenzene

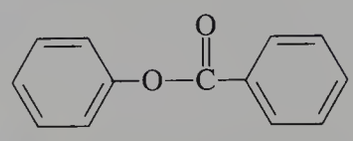
Sample Solution

Propiophenone has a carbonyl group bonded to the benzene ring that should direct the bromine to the meta position. *N*-Methylaniline resembles aniline, and the bromine should be directed to the ortho and para positions. Two isomeric compounds should result. The third compound has two nitro groups. Each one directs the electrophile onto the ring in positions meta to itself. Thus both groups direct the bromine into the same position. The product is 3,5-dinitrobromobenzene.



Problem 14.10

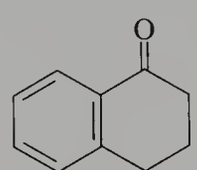
Which of the two aromatic rings of phenyl benzoate would be nitrated? Predict the structure of the product(s) formed.



phenyl benzoate

Problem 14.11

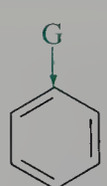
Which two of the four possible products should form in the nitration of tetralone?



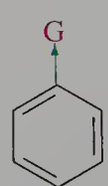
tetralone

14.5 Interpretation of Rate Effects

In the preceding section, we saw that a substituent influences both the rate and distribution of products in electrophilic aromatic substitution reactions. These two properties relate directly. A single model based on the ability of the substituents to either donate or withdraw electron density from the aromatic ring makes both properties clear. Let's consider the effect of a group, G, on the electron density of the benzene ring.



If G is an electron donor, the ring gains electron density.

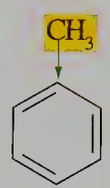


If G is an electron acceptor, the ring loses electron density.

Any substituent that donates electron density to the aromatic ring makes the ring more reactive toward attack by an electrophile. A substituent that withdraws electron density from the aromatic ring decreases the electron density in the ring and makes it less reactive toward an attacking electrophile. Therefore, all activating groups listed in Table 14.1 are electron-donating groups. The deactivating groups are electron-withdrawing groups. Substituents can donate or withdraw electron density by inductive or resonance effects.

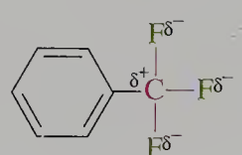
Inductive Effects of Substituents

In Chapter 6, we learned that alkyl groups stabilize double bonds and carbocations. Alkyl groups also transfer electron density to the benzene ring by an inductive effect.



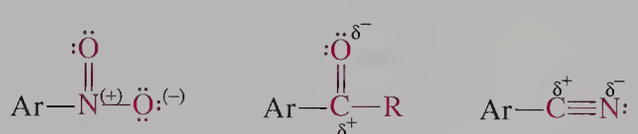
A methyl group is inductively electron donating.

The halogens are more electronegative than a benzene ring, so they withdraw electron density from a benzene ring. Any functional group with a partial positive charge on the atom bonded to the aromatic ring also withdraws electron density from the ring by an inductive effect. Examples include the trifluoromethyl group, whose fluorine atoms pull electrons away from the carbon atom to which they are bonded. To compensate, the carbon atom bearing the fluorine atoms withdraws electron density from the benzene ring.



The trifluoromethyl group is inductively electron withdrawing.

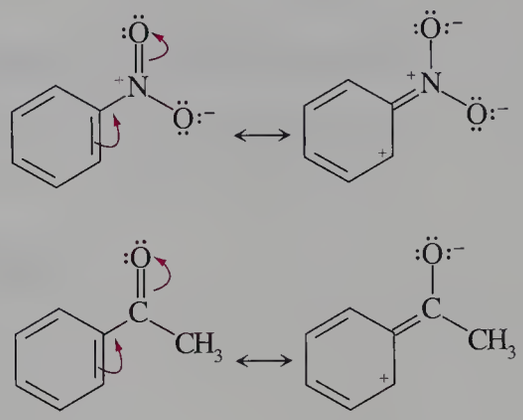
Other common electron-withdrawing substituents are nitro and cyano groups and any group with a carbonyl carbon atom bonded directly to the aromatic ring. The nitrogen atom of the nitro group has a formal positive charge. The carbon atom of a carbonyl or a cyano group has a partial positive charge.



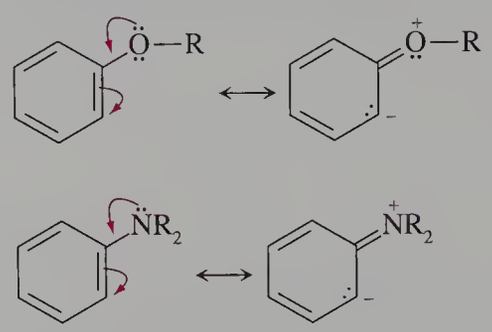
Resonance Effects of Substituents

Next, let's consider how resonance effects shift electron density into or out of a benzene ring. Resonance effects are depicted by moving electrons and drawing alternate resonance forms. Nitro, cyano, and carbonyl-containing groups have *sp*- or sp^2-hybridized atoms bonded directly to the benzene ring. These atoms have π

orbitals conjugated with the ring. First, consider the resonance effects of the nitro group. Because oxygen is more electronegative than nitrogen, the electron pair in a nitrogen–oxygen double bond can "shift" onto the oxygen atom. An electron pair can simultaneously "shift" out of the ring to make a carbon–nitrogen double bond, leaving a positive charge on the aromatic ring. Because a positive charge develops in the ring, it is less reactive toward electrophiles. A similar effect for the acyl group also makes the ring less reactive toward electrophiles.



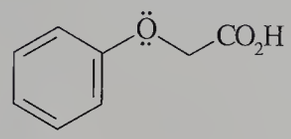
Some substituents have atoms with lone pair electrons that can shift to the ring by resonance. As a consequence, the ring develops a partial negative charge and becomes more reactive toward electrophiles. Groups with an unshared electron pair on the atom attached to the ring include hydroxyl (—OH), alkoxy groups such as methoxy (CH_3O—), and amino (—NH_2) or any substituted amino groups (—NHR, —NR_2). These groups all donate electrons to the aromatic ring by resonance.



Groups that can donate electrons by resonance are also electronegative. Therefore they can also withdraw electron density from the ring by an inductive effect. These substituents take electron density from the ring by an inductive effect and give it back by resonance. A group containing a second period element bonded directly to the aromatic ring donates electrons by resonance. Examples include amino and hydroxyl groups. The 2*p* orbital of these second period atoms effectively overlaps with the 2*p* orbital of a ring carbon atom. As a result, donation of electrons by resonance is more important than inductive electron withdrawal. This situation, however, does not hold true for chlorine or bromine. These electronegative atoms also pull electrons out of the aromatic ring by an inductive effect. However, the 3*p* orbital of chlorine and the 4*p* orbital of bromine overlap poorly with the 2*p* orbital of carbon, so electron donation by resonance is less effective than the electron-withdrawing inductive effect.

Problem 14.12

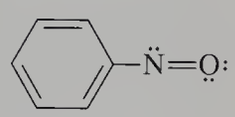
A selective herbicide used to kill broadleaf weeds is made by chlorinating phenoxyacetic acid. Is the substituent an activating or deactivating group?



phenoxyacetic acid

Problem 14.13

Is the nitroso group an activating or deactivating group? Consider both inductive and resonance contributions.



nitrosobenzene

Sample Solution

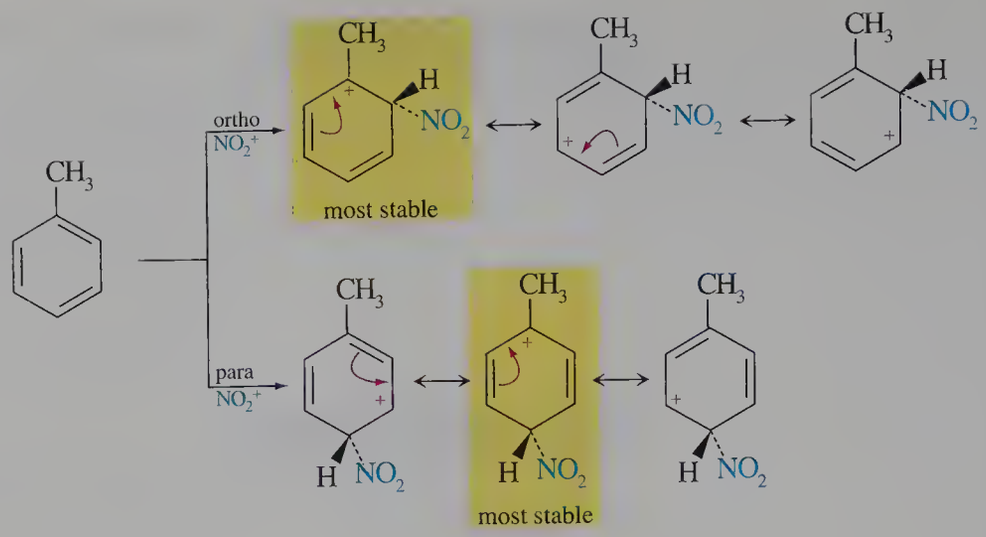
At first glance one might expect the nitroso group to behave like a nitro group. Both have a nitrogen atom directly bonded to the benzene ring and both have the electronegative oxygen atom bonded to it. However, there is no formal charge on the nitrogen atom of the nitroso group as there is in the nitro group. Thus, the nitroso group does not withdraw electrons as strongly as does the nitro group. Based only on inductive effects the nitroso group should be less deactivating than the nitro group.

The nitroso group has a lone pair of electrons on the nitrogen atom that can be donated to the benzene ring in alternate resonance forms. (The nitro group cannot donate electrons by resonance.) Therefore the nitroso group is expected to have a resonance contribution in donating electrons that is opposed by its electron-withdrawing inductive effect. The properties of the nitroso group thus resemble those of the halogens. In fact, because nitrogen is a second period element, it should effectively donate electrons by resonance.

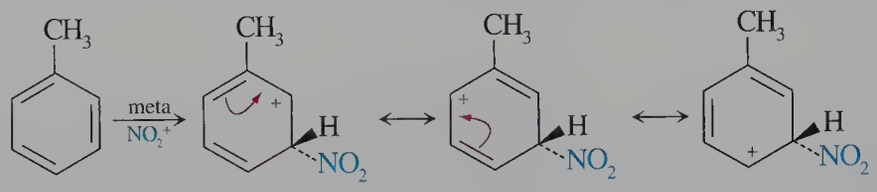
14.6 Interpretation of Directing Effects

We noted earlier that—with the exception of the halogens—ortho, para directors activate the ring toward electrophilic substitution by supplying electron density to the ring. But why are the ortho and para positions especially susceptible to attack? To answer this question, consider the stability of the cyclohexadienyl carbocation formed in the first step of the electrophilic aromatic substitution mechanism. The regioselectivity of the reaction is controlled by the stability of the carbocation. To determine the stability of a cyclohexadienyl carbocation we must compare all the possible resonance forms. Thus we compare the stability of the intermediate carbocations resulting from attack at the ortho and para positions with those resulting when an electrophile attacks at the meta position.

First, we will consider the nitration of toluene at the ortho and para positions. Attack at either the ortho or the para position results in one resonance structure with a positive charge on the ring carbon atom bonded to the methyl group. This tertiary carbocation makes a major contribution to the stability of the resonance hybrid.



Now consider nitration at the meta position. The resonance structures show that positive charge cannot reside on the carbon atom attached to the methyl group. Only secondary carbocations are possible, and they are less stable than tertiary carbocations.



Cyclohexadienyl carbocations resulting from ortho or para substitution are more stable and form faster than the cyclohexadienyl carbocation resulting from meta attack. The reaction coordinate diagrams for the formation of all three cyclohexadienyl carbocations are shown in Figure 14.3. The methyl group donates electrons to the ring, making the intermediates more stable than the cyclohexadienyl carbocation derived from benzene. The formation of the ortho- and para-substituted products results from greater stabilization of the related intermediates compared to the intermediate leading to the meta-substituted product.

Next, let's consider the ortho,para-directing effect of a hydroxyl group or any other group that can donate an unshared pair of electrons by resonance. An attack either ortho or para to the hydroxyl group leads to an intermediate that is resonance

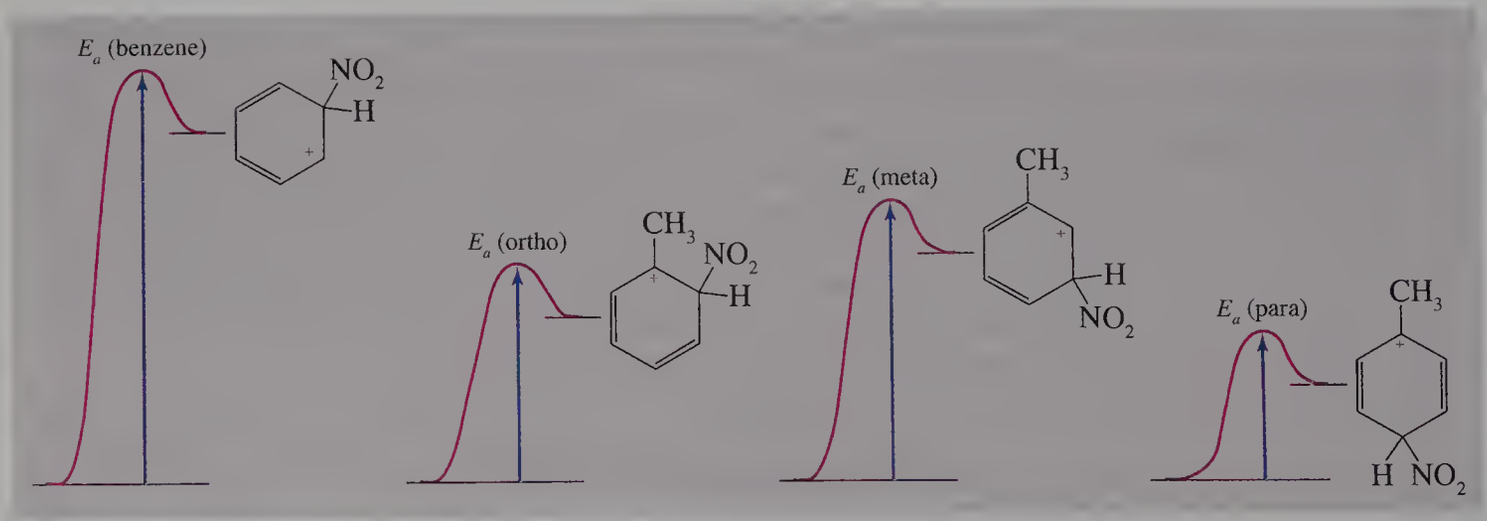
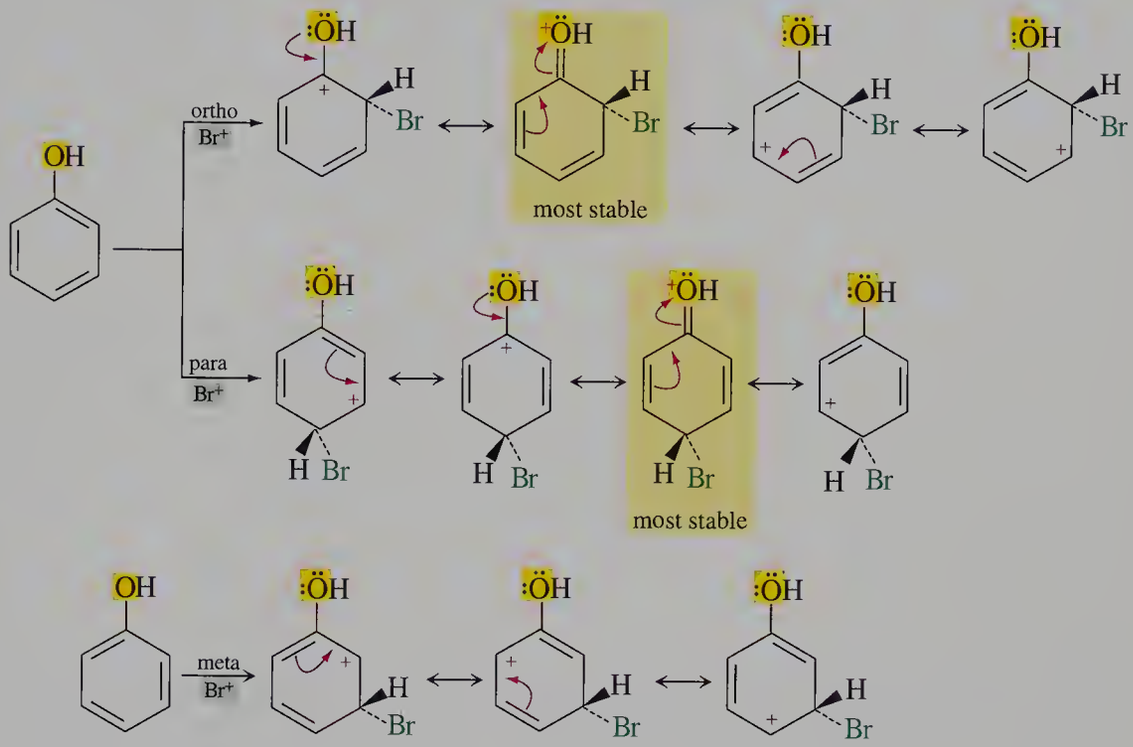
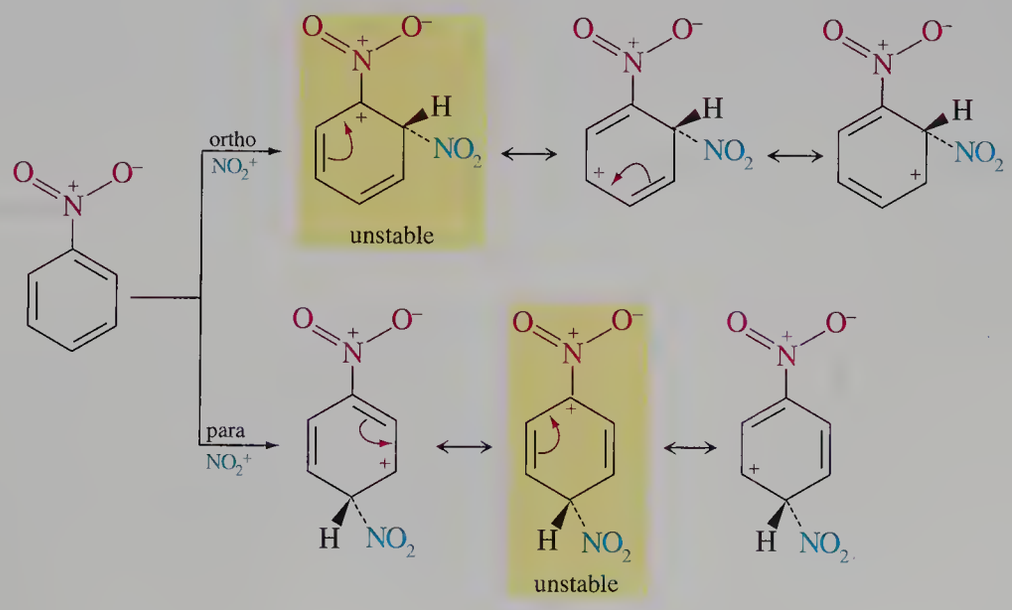


FIGURE 14.3 Transition State Energies for Substitution of Toluene
Substitution at any position of toluene occurs at a faster rate than substitution of benzene. However, substitution occurs faster at the ortho and para positions than at the meta position.

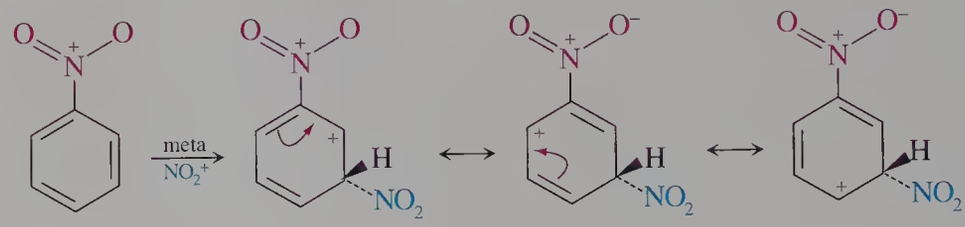
stabilized by the oxygen atom of the hydroxyl group. As in the case of the methyl group, a contributing structure exists in which the positive charge resides on the carbon atom bonded to the substituent. An electron pair provided by oxygen stabilizes this positive charge. No such stabilization is possible for a group that attacks meta to the hydroxyl or amino substituent. Hence, ortho or para substitution occurs instead of meta.



We saw in Table 14.1 that some substituents strongly deactivate the ring with respect to electrophilic aromatic substitution. All the strong deactivating groups withdraw electron density from the ring and are meta directors. Where does the preference for attack at the meta position come from in this case? First, let's consider the possible nitration of nitrobenzene at the ortho and para positions. In one of the resonance forms for the cyclohexadienyl carbocation resulting from ortho or para substitution, a positive charge resides on a carbon atom bonded to the original nitro group. The nitrogen atom of the nitro group has a formal positive charge, and its proximity to the carbon atom bearing a positive charge makes these resonance forms unstable.



Next, consider an attack at the meta position. None of the resonance forms of the intermediate has a positive charge on the carbon atom bonded to the nitro group—whose nitrogen atom, we noted above, has the formal charge of +1. The resonance forms of the intermediates resulting from meta attack are therefore more stable overall than the resonance forms of the intermediates formed from ortho and para substitutions. Hence, meta substitution is favored.



Reaction coordinate diagrams for the substitution of nitrobenzene at the ortho, meta, and para positions are shown in Figure 14.4. The nitro group originally bonded to the aromatic ring makes the ring less reactive than benzene. As a result, the activation barrier for the formation of the intermediate leading to all three cyclohexadienyl carbocations is higher than for formation of the intermediate from benzene. However, the increase in the activation barrier is smaller for formation of the meta intermediate than for the other two intermediates. So the meta position is less deactivated than the ortho and para positions.

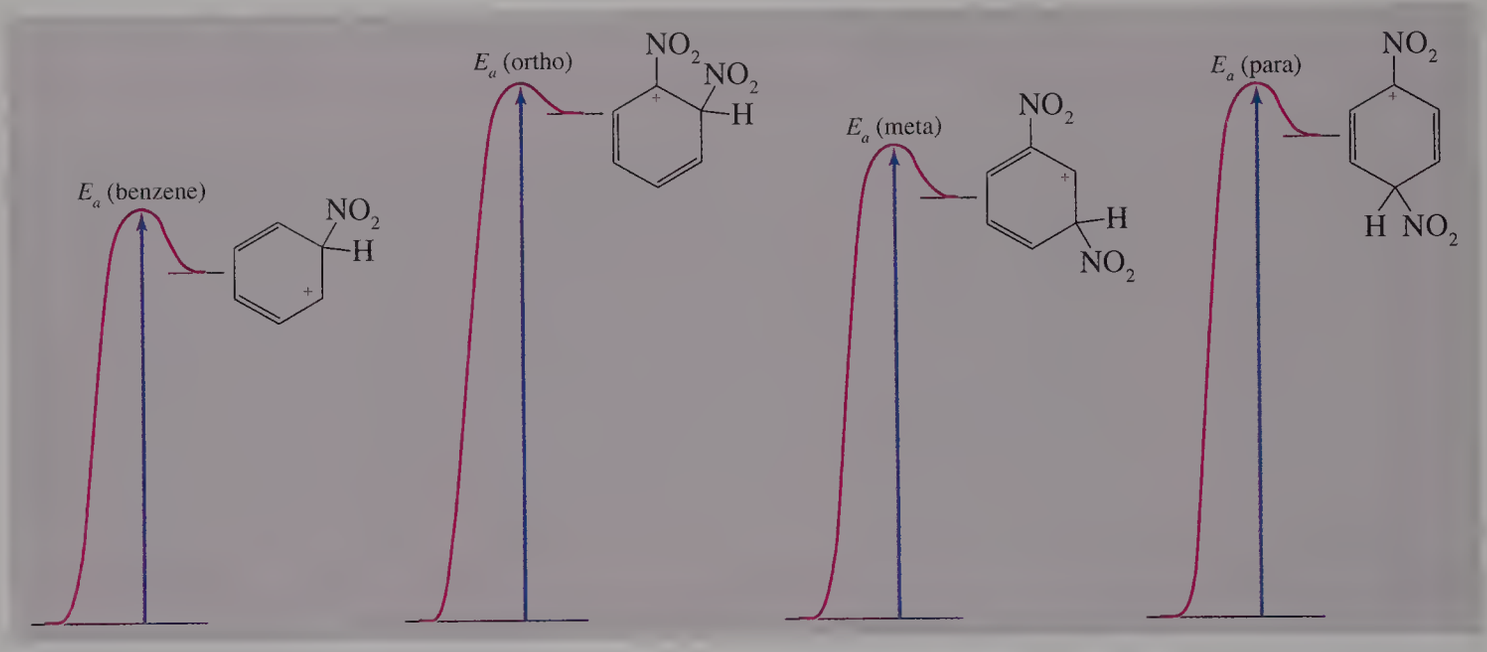
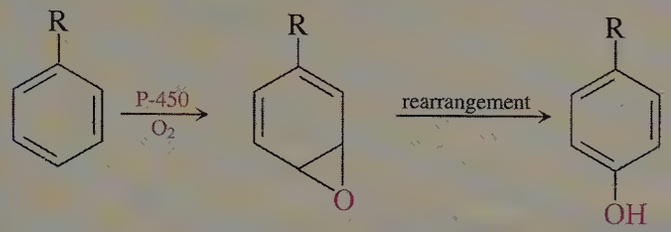


FIGURE 14.4 Transition State Energies for Substitution of Nitrobenzene
Substitution occurs at a slower rate at any of the positions of nitrobenzene than for substitution on benzene. Of the three possible reactions, substitution occurs faster at the meta position than at either the ortho or para position.

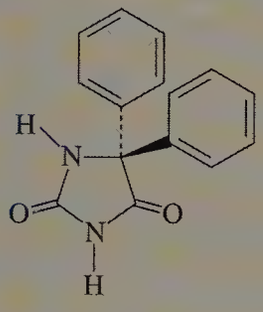
Table 14.1 shows that halogens are weakly deactivating. Yet these deactivating groups are ortho,para directors. Why? The answer lies in their electronegativity. Because the halogens are more electronegative than a benzene ring, they withdraw electron density from the ring by an inductive effect. But halogens have lone pair electrons that can be donated by resonance to the carbocation intermediate. This resonance effect only comes into play if the entering electrophile attacks ortho or para

Oxidation of aromatic compounds by cytochrome P-450 often yields phenols. Although the process shown below appears to be aromatic hydroxylation, the reaction occurs by way of a three-membered arene oxide, which rearranges to a phenol when the substituent is an electron-releasing group.

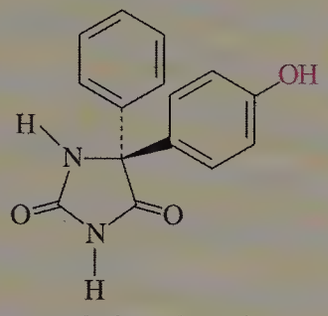


(an arene) (an arene oxide) (a phenol)

Some drugs contain aromatic rings that are hydroxylated when metabolized. Hydroxylation most commonly occurs at the para position. Phenytoin, an anticonvulsant, is an example. The phenolic compounds react further to form water-soluble derivatives.

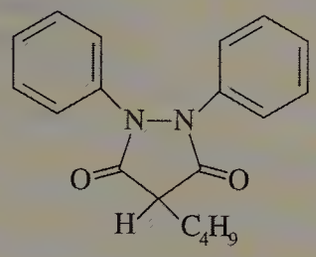


phenytoin



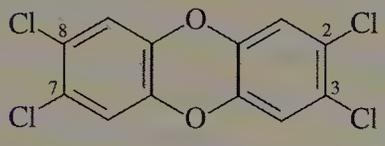
p-hydroxyphenytoin

When drugs are hydroxylated in the liver, some products are also pharmacologically active. The site of hydroxylation of phenylbutazone, an anti-inflammatory agent, is at the para position. This hydroxylated product has been produced in the laboratory and is marketed under the trade names Tandearil and Oxalid.



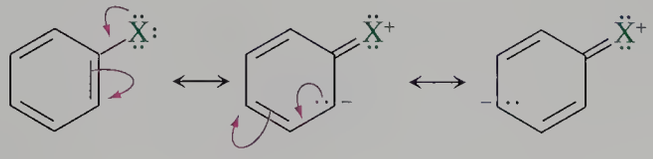
phenylbutazone

We described the deactivating effect of halogens on the reactivity of aromatic rings. The environmental pollutants dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) and PCBs (polychlorinated biphenyls) have many deactivating groups. This effect has grave environmental and biological consequences. The substituents on the aromatic ring affect the ease of hydroxylation; electron-withdrawing groups deactivate the ring toward the initial epoxidation. Because the aromatic ring loses electrons in the oxidation process, the electron-withdrawing groups slow the rate of biological oxidation and phenols, which the body can excrete, are not formed. As a result, aromatic compounds tend to persist in the bodies of organisms that inadvertently ingest them. Since these halogenated compounds are nonpolar, they are soluble in fatty tissue, or "lipophilic".



2,3,7,8-tetrachlorobenzo-*p*-dioxin

to the halogen atom. Consequently, the halogens are ortho,para directors, even though they are weakly deactivating,



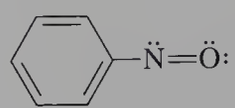
We noted earlier that neither the 3*p* orbital of chlorine nor the 4*p* orbital of bromine cannot overlap effectively with the 2*p* orbital of carbon, so these atoms do not donate electrons effectively to the ring.

Problem 14.14

The major product of the nitration of phenylboronic acid is the meta isomer. Consider the electronic structure of boron and account for the meta-directing effect of the $-B(OH)_2$ group.

Problem 14.15

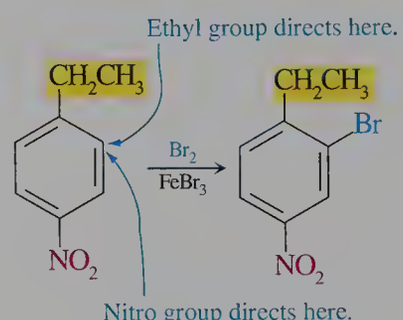
Electrophilic aromatic substitution of nitrosobenzene yields a mixture of ortho and para products, but reaction of nitrobenzene yields the meta product. Account for this difference.



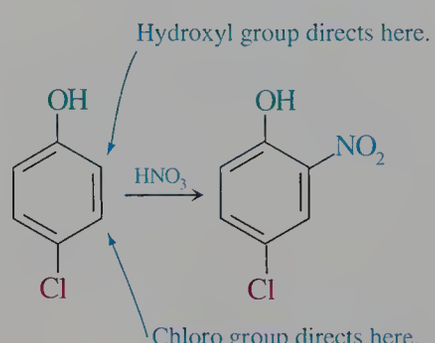
nitrosobenzene

14.7 Multiple Substituent Effects

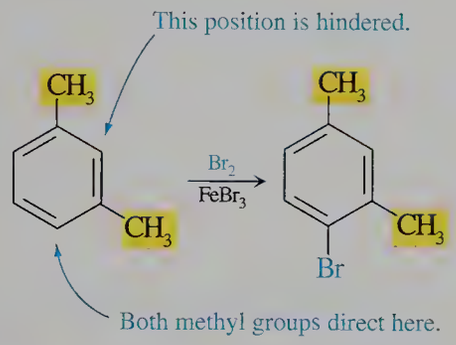
When a benzene ring has two or more substituents, they both affect the site of attack by the electrophile and the reactivity of the ring. When each of the two groups directs the electrophile to the same position, the groups "reinforce" each other, and only one product results. For example, consider the bromination of *p*-ethylnitrobenzene. Bromination takes place at the position ortho to the ortho,para-directing ethyl group and meta to the meta-directing nitro group.



The more activating substituent has the dominant influence if the directing effects of two individual substituents oppose each other, although a mixture of products commonly results. For example, nitration of *p*-chlorophenol yields 4-chloro-2-nitrophenol because the hydroxyl group is a strongly activating group, whereas the chloro group is weakly deactivating.



When two positions are similarly activated, substitution occurs at the least hindered site. Substitution, therefore, seldom occurs at positions located between two substituents. For example, bromination of *m*-xylene occurs at the C-4 position ortho to one methyl group and para to the other. This position is less hindered than the C-2 position, ortho to both methyl groups.



Problem 14.16

Nitration of *o*-chlorotoluene yields a mixture of four chloronitrotoluene isomers. Considering the directing influences of the chlorine atom and methyl group, and their respective effects on reactivity, explain why a mixture results.

Problem 14.17

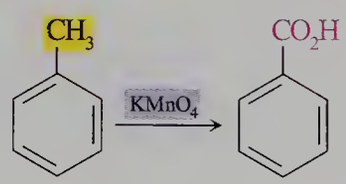
Nitration of isopropylbenzene gives a mixture containing 30% and 63% of the ortho and para isomers, respectively. Nitration of *tert*-butylbenzene gives a mixture containing 16% and 73% of the ortho and para isomers, respectively. Why does the ratio of the amounts of the ortho and para isomers differ for these two alkylbenzenes?

14.8 Functional Group Modification

Functional group modifications are important because electrophilic aromatic substitution can place only a few functional groups directly on an aromatic ring. Modifying a group already bonded to the aromatic ring can produce other groups. When a functional group changes, ortho,para- or meta-directing properties can also change.

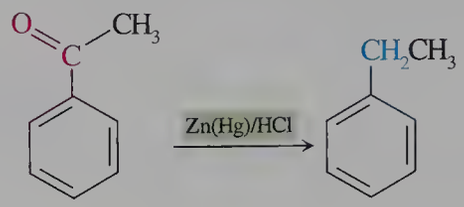
Conversion of an Alkyl Group to a Carboxyl Group

We recall that the oxidation of alkyl side chains is one reaction that modifies a substituent bonded to an aromatic ring. For example, a methyl group introduced by a Friedel–Crafts alkylation can be changed to a carboxylic acid group. This reaction converts an ortho,para-directing methyl group into a meta-directing carboxylic acid group ($-CO_2H$).



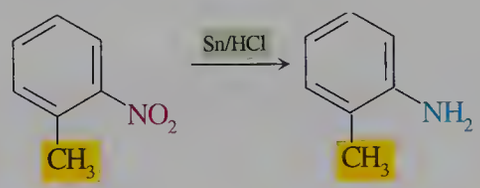
Conversion of an Acyl Group to an Alkyl Group

An acyl group bonded to a benzene ring can be converted into an alkyl group by reduction with a zinc–mercury amalgam in HCl (Section 14.3). Since an acyl group has a carbonyl carbon atom directly attached to the ring, it is a deactivating, meta-directing substituent. However, an alkyl group is an activating, ortho,para-directing group.



Conversion of a Nitro Group to an Amino Group

Electrophilic aromatic substitution can attach a nitro group directly to a benzene ring, but cannot attach an amino group in one step. However, after a nitro group is introduced, it can easily be reduced to an amino group, producing an aniline. This reaction transforms a strongly deactivating meta-directing nitro group into a strongly activating ortho,para-directing amino group.



Conversions of Amino Groups

If an aromatic ring has an amino group, the possibilities for further functional group modifications vastly increase. The amino groups of anilines can be converted into many other groups. The door to other functional groups is opened by converting the amino group into an aryl diazonium ion, $Ar—N_2^+$. A diazonium ion results from reaction of an aniline with nitrous acid (HNO_2, prepared by reaction of sodium nitrite with sulfuric acid). This step, which produces a diazonium ion, is called **diazotization**.

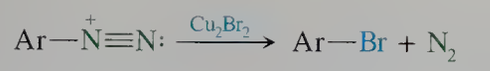
$$Ar—NH_2 \xrightarrow{HNO_2} Ar—\overset{+}{N}\equiv N:$$

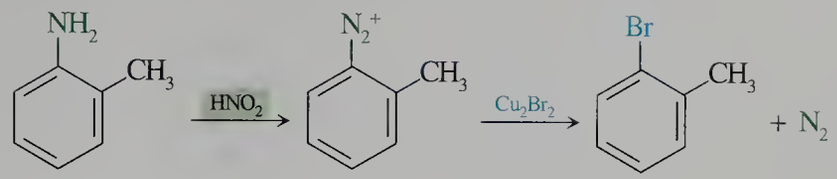
(a diazonium ion)

In 1884, the German chemist Traugott Sandmeyer found that diazonium ions react with nucleophiles supplied in the form of a Cu(I) salt. These nucleophiles replace the diazonium group and release nitrogen gas.

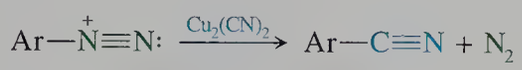
$$Ar—\overset{+}{N}\equiv N: + :Nu^- \longrightarrow Ar—Nu + N_2$$

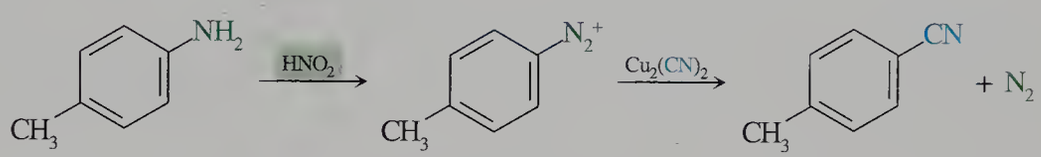
For example, a solution of an aromatic diazonium ion can be treated with Cu_2Cl_2 or Cu_2Br_2 to yield chlorobenzene or bromobenzene, respectively. These reactions are known collectively as the **Sandmeyer reaction**.



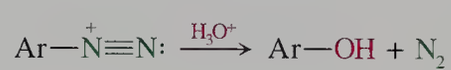


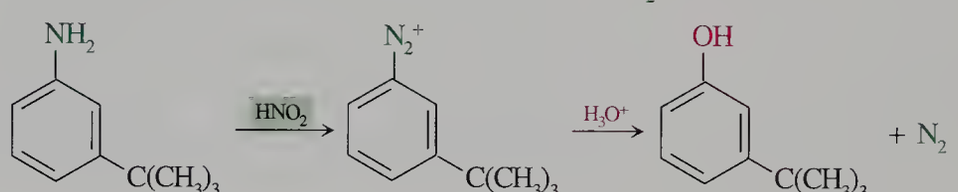
Cuprous salts of the cyanide ion result in the formation of aryl nitriles.



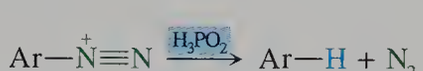


Phenols can be synthesized by reaction of the aryldiazonium compound with hot aqueous acid. This reaction is the best way to attach an —OH group to an aromatic ring.



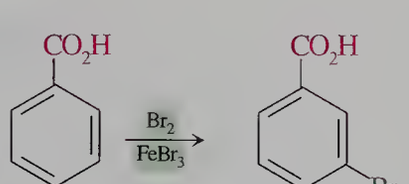


Hypophosphorous acid (H_3PO_2) is used to replace the diazonium group by a proton. This process can be used to remove the amino substituent from the aromatic ring after its role as a directing group in a synthesis concludes.



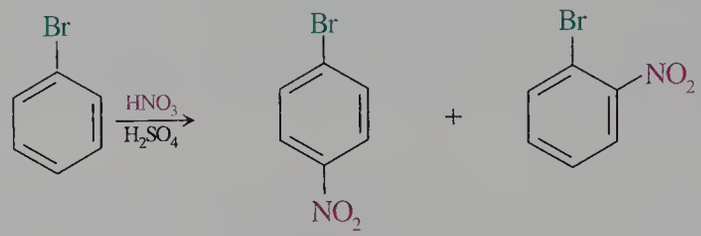
14.9 Synthesis of Substituted Aromatic Compounds

The goal of chemical synthesis is preparation of a desired compound in high yield, and the by-products should be easy to separate from the major product. The synthesis of aromatic compounds using starting materials with a meta-directing group meets these criteria. For example, let's consider the synthesis of *m*-bromobenzoic acid from benzoic acid. We can carry out this conversion in one step by treating benzoic acid with bromine and iron(III) bromide. The product is a solid (mp 155 °C), which we can separate from the small amounts of ortho- and para-substituted isomers by recrystallization.



m-bromobenzoic acid

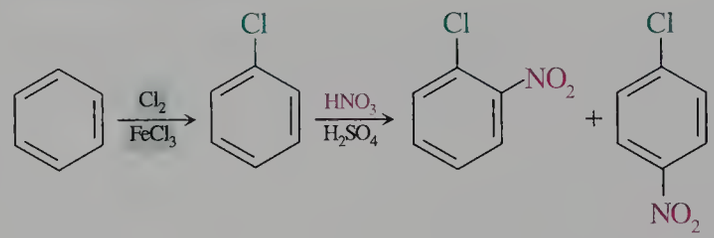
Substitution reactions of compounds with ortho,para-directing groups already on the ring invariably give mixtures with substantial amounts of the two isomeric products. We recall that the para isomer is more symmetrical and usually has a higher melting point than the ortho isomer (Section 13.8). Para isomers also have lower solubility, and may be crystallized from a mixture of ortho and para isomers (Section 13.8). For example, *p*-bromonitrobenzene (mp 127 °C) obtained by nitration of bromobenzene can be crystallized and separated from *o*-bromonitrobenzene (mp 43 °C).



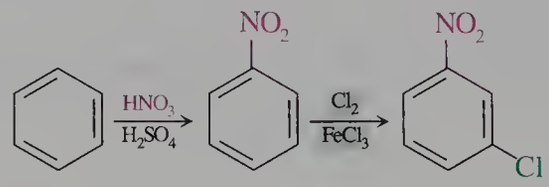
p-bromonitrobenzene *o*-bromonitrobenzene

Order of Substitution of Groups

Chemists often want to design benzene derivatives with two or more substituents strategically placed around the ring. A project of this type begins with an analysis of the ortho,para- or meta-directing characteristics of the substituents. For example, consider the problem of synthesizing *m*-chloronitrobenzene. A nitro group is meta directing, a chloro group ortho,para directing. The order in which we add these groups is clearly important. If chlorination precedes nitration, the entering nitro group will be directed to form mostly *o*-chloronitrobenzene and *p*-chloronitrobenzene. Very little of the desired meta isomer will form.

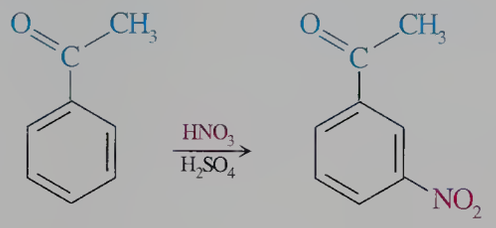


We can obtain the desired compound by introducing the nitro group first and the chlorine group second. Because the nitro group is a meta director, the entering chlorine atom is directed to the desired meta position.



Other factors to consider in designing a synthetic method include limitations of each type of substitution process and the possible reaction of the second reactant with the substituent already on the ring. We recall that Friedel–Crafts acylation does not occur when the ring contains a meta-directing group. For example, *m*-nitroace-

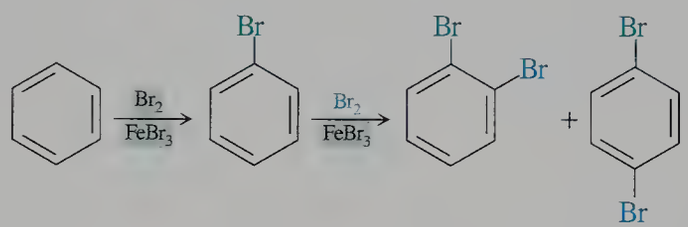
tophenone does not result from acetylating nitrobenzene, but it is formed from nitration of acetophenone.



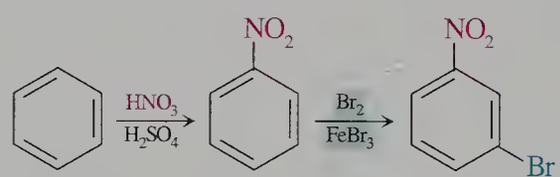
m-nitroacetophenone

Modification of Ring Substituents

Now we consider a task that appears at first glance to be impossible, the synthesis of *m*-dibromobenzene. Why impossible? Because the bromo groups are meta to each other, but bromine is an ortho,para director! Direct bromination of benzene would place the first bromine atom on the ring. That bromine atom would then direct the second bromine atom into the ortho or para position.



However, we know that a nitro group is a meta director. So, we first make nitrobenzene, then brominate it to obtain *m*-bromonitrobenzene.



We recall that a nitro group can be converted to a bromo group by (1) reducing the nitro group to an amino group, (2) converting the amino group to a diazonium group, and (3) treating the diazonium compound with copper(I) bromide. The procedure requires several steps, but it accomplishes the apparently impossible task of preparing *m*-dibromobenzene.

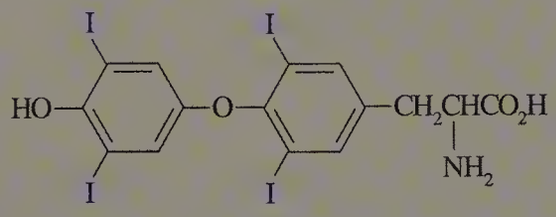
Problem 14.18

Which of the following procedures will yield 4-chloro-2-ethylnitrobenzene?

(a) chlorination of *o*-ethylnitrobenzene
(b) nitration of *m*-chloroethylbenzene
(c) Friedel–Crafts alkylation of *p*-chloronitrobenzene

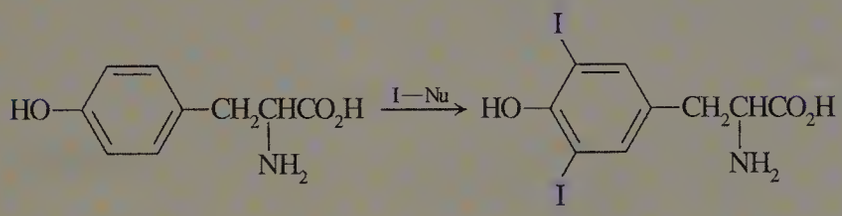
Biosynthesis of Thyroxine

Thyroxine, a hormone responsible for control of metabolism and growth, is synthesized in the thyroid gland and released into the bloodstream.



thyroxine

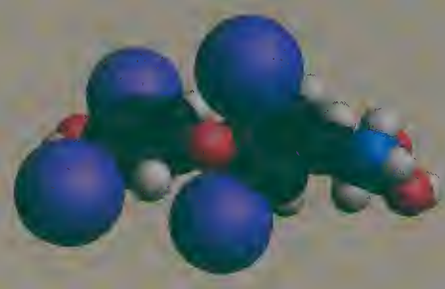
One of the steps in the production of thyroxine is the iodination of the amino acid tyrosine. Although most iodine compounds are not strong electrophiles, the source of iodine is represented in the equation with a bond to the standard symbol for a nucleophile.



tyrosine 3,5-diiodotyrosine

We note that the aromatic ring of tyrosine has a hydroxyl group and a methylene group, both of which activate the ring. The reaction requires these groups because iodine is a poor electrophile. The iodine adds ortho to the hydroxyl group because the hydroxyl group donates electrons more effectively than a methyl group. The double iodination gives 3,5-diiodotyrosine. These reactions occur at lower temperatures and under milder conditions than those in the laboratory because they are enzyme catalyzed.

The iodination of tyrosine occurs in the thyroid gland by an electrophilic substitution mechanism. Subsequent coupling of two equivalents of 3,5-diiodotyrosine to give thyroxine also occurs in the thyroid gland by a mechanism that is beyond the scope of this text.



thyroxine

Problem 14.19

Devise a synthesis of *m*-bromoaniline starting from benzene.

Sample Solution

Bromine, which is an ortho,para director, can be introduced directly onto the benzene ring by reaction with bromine and $FeBr_3$. The amino group of aniline is also an ortho,para director but it can only be introduced by first nitrating benzene and then reducing the nitro compound. Recall that the nitro group is a meta director.

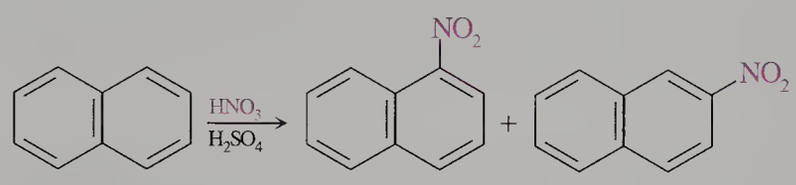
Bromination of benzene followed by nitration gives a mixture of *o*- and *p*-bromonitrobenzene. The desired meta isomer is not formed. Nitration of benzene gives nitrobenzene—a compound that directs subsequent electrophiles to the meta position. Thus, bromination of nitrobenzene followed by reduction of the product gives the desired *m*-bromoaniline.

Problem 14.20

Devise a synthesis of each of the following compounds from benzene.
(a) *p*-nitrobenzoic acid (b) *m*-bromophenol (c) *m*-bromochlorobenzene

14.10 Polycyclic and Heterocyclic Aromatic Compounds

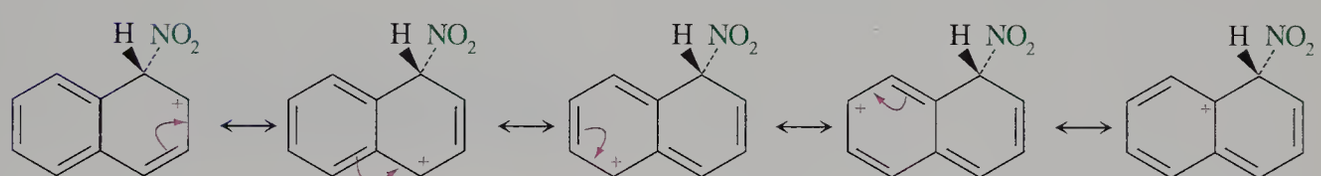
Polycyclic aromatic hydrocarbons also undergo electrophilic substitution reactions, and they are generally more reactive than benzene. For example, the nitration of naphthalene requires only the nitronium ion formed in nitric acid, whereas the nitration of benzene requires a sulfuric acid catalyst. Because most polycyclic aromatic hydrocarbons are not as symmetrical as benzene, mixtures of isomers may form even when the first substituent attacks the ring. For example, substitution in naphthalene can occur at two nonequivalent sites. Nitration gives two isomers in a 10:1 ratio with 1-nitronaphthalene as the major isomer.



1-nitronaphthalene
major isomer

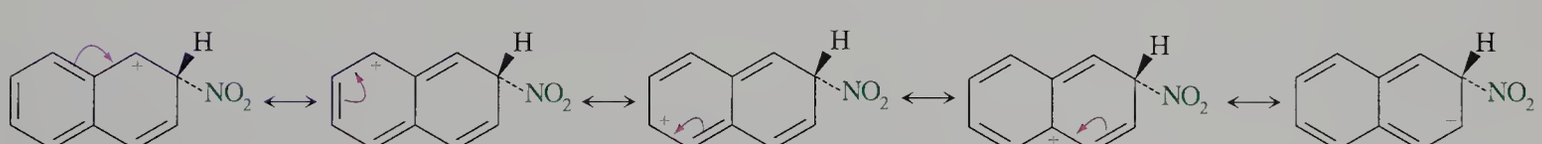
2-nitronaphthalene
minor isomer

As in the case of electrophilic substitution of benzene, the stability of the carbocation intermediates formed from naphthalene determines the product distribution. Depicting the carbocation formed by attack at the C-1 position requires five resonance forms, none equivalent in energy. The two resonance forms with Kekulé benzene rings are more stable than the other three resonance contributors.



more stable more stable

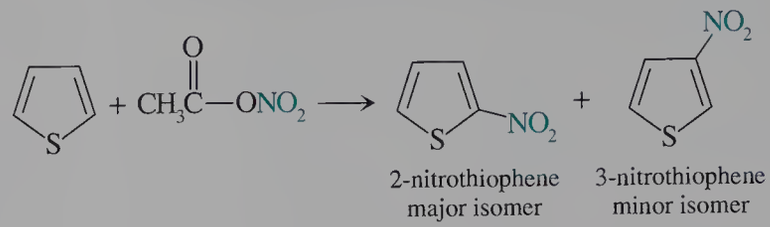
Depicting the carbocation formed by attack at the C-2 position also requires five nonequivalent resonance forms, but only one resonance structure has a Kekulé benzene ring. The carbocation intermediate formed from attack at the C-2 position is therefore less stable than the intermediate formed from attack at the C-1 position.



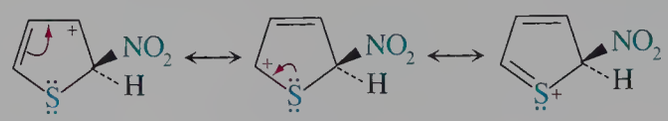
more stable

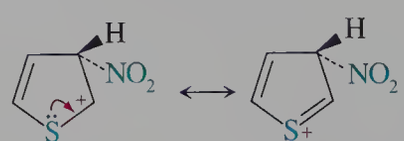
Furan, pyrrole, and thiophene are all more reactive than benzene in electrophilic aromatic substitution reactions. The order of reactivity is pyrrole > furan > thiophene > benzene. These compounds react under milder conditions than benzene and require less electrophilic reagents. For example, thiophene is nitrated using acetyl nitrate without any strong acid catalyst. The major substitution

product results from attacking the carbon atom at the 2-position. (The sulfur ring atom is assigned the number 1.)



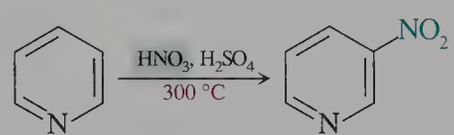
As in the case of benzene derivatives, the amounts of the two isomeric substituted thiophenes formed are related to the energies of the intermediate carbocations. The intermediate carbocation derived from substitution at C-2 has three resonance forms, but the cation intermediate that results from substitution at C-3 has only two resonance forms.



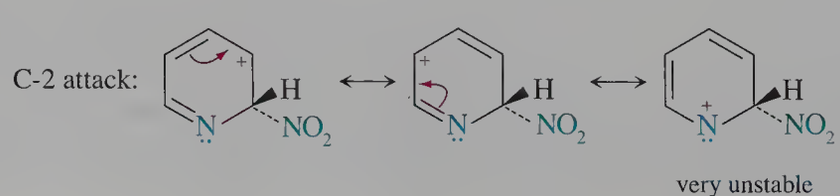


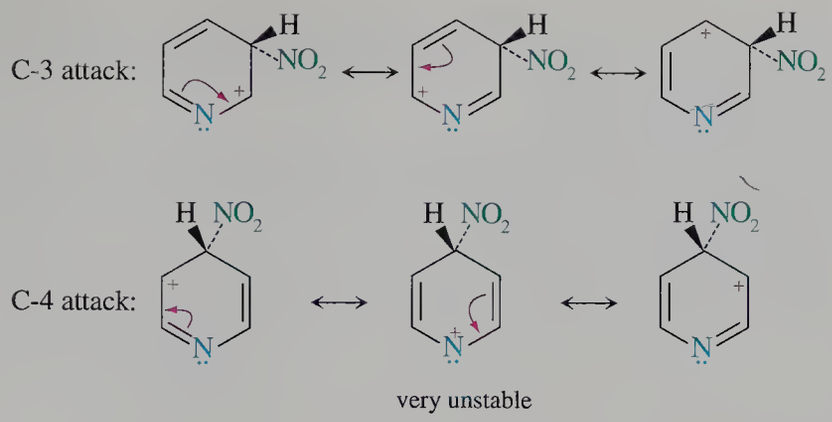
Both sets of resonance contributors have one form with a positive charge on sulfur—a sulfonium cation. The sulfur atom has a lone pair of electrons and an octet of electrons. The resonance structures containing this electronic arrangement are more stable than those with charged carbon atoms that do not have an octet of electrons. Because both sets of resonance contributors have stabilized forms, the difference in energy of the two carbocation intermediates depends on the number of other resonance forms. There are more resonance contributors for substitution at the C-2 position, and the electrons in this carbocation are more delocalized, resulting in a more stable structure.

Pyridine strongly resists electrophilic aromatic substitution. Pyridine substitution reactions require higher temperatures than benzene substitution reactions. For example, nitration of pyridine occurs at 300 °C, whereas nitration of benzene occurs at 50 °C. The reaction yields 3-nitropyridine. (The ring nitrogen atom is assigned the number 1.)



The resistance to electrophilic aromatic substitution and the predominant 3-substitution of pyridine can be explained by examining the resonance structures for the intermediate carbocations.

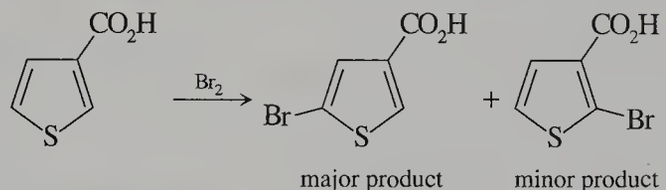




All three carbocations are destabilized by the inductive effect of the nitrogen atom, so electrophilic attack is not favored in any of the cases. One of the resonance forms representing the carbocation intermediate in the C-2 and C-4 cases has a positive charge on a nitrogen atom, which is electron deficient. This nitrogen atom has only six electrons in its valence shell. Substitution at C-2 and C-4 produces unstable resonance forms relative to the carbocation derived from C-3 substitution.

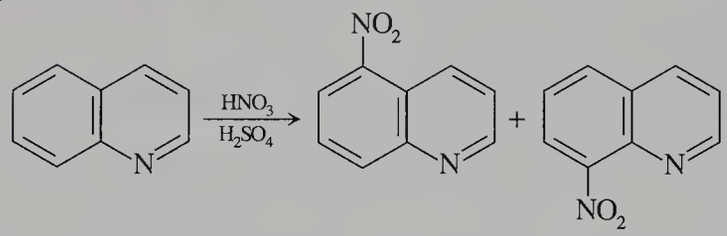
Problem 14.21

Explain why the relative amounts of the indicated products are formed. Why doesn't a third isomeric compound form?



Problem 14.22

Explain why the two indicated products form and why substitution occurs in only one of the two rings.



EXERCISES

Electrophiles

14.1 Some activated rings may be hydroxylated by reacting hydrogen peroxide (H_2O_2) with acid. What is the formula of the electrophile? How does it form?

14.2 Reactive aromatic rings can be iodinated using iodine monochloride (ICl). What is the electrophile?

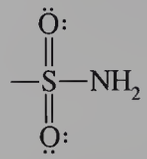
14.3 Benzene can be mercurated with mercuric acetate to give phenylmercuric acetate using perchloric acid ($HClO_4$) as a catalyst. What is the electrophile? How does it form?

14.4 An aromatic ring can be alkylated with a tertiary butyl group by treating *tert*-butyl alcohol, $(CH_3)_3COH$, with acid. What is the formula of the electrophile? How does it form?

Properties of Ring Substituents

14.5 Consider the thiomethyl group, $—S—CH_3$. Predict whether it is an activating or deactivating group. Will it be ortho,para directing or meta directing?

14.6 The sulfonamide group is found in sulfa drugs. Consider its structure and determine if it is an activating or deactivating group. Will it be ortho,para directing or meta directing?



14.7 Nitration of *N*,*N*-dimethylaniline, $C_6H_5N(CH_3)_2$, in 85% sulfuric acid gives a meta nitro compound as the major product. What is the structure of the ring substituent responsible for the orientation of the nitro product?

14.8 The percentages of meta nitro product formed in the nitration of benzene compounds containing the $CH_3—$, $ClCH_2—$, $Cl_2CH—$, and $Cl_3C—$ groups are 5%, 16%, 34%, and 64%, respectively. Explain this trend in the data.

Reagents for Substitution

14.9 What reagent is required for each of the following reactions? Write the structure of the principal product(s) expected from the reaction.

(**a**) bromination of anisole (**b**) sulfonation of toluene
(**c**) nitration of benzoic acid (**d**) acetylation of bromobenzene

14.10 What reagent is required for each of the following reactions? Write the structure of the principal product(s) expected from the reaction.

(**a**) chlorination of bromobenzene (**b**) Friedel–Crafts methylation of anisole
(**c**) Friedel–Crafts acetylation of toluene (**d**) nitration of trifluoromethylbenzene

Friedel–Crafts Alkylation and Acylation

14.11 Write the structure of the product resulting from the Friedel–Crafts alkylation of benzene using chlorocyclohexane and aluminum trichloride.

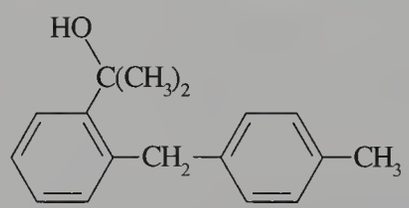
14.12 What product results from the Friedel–Crafts alkylation of benzene using 1-chloro-2-methylpropane and aluminum trichloride?

14.13 Alkylation of benzene can be accomplished using an alkene such as propene and an acid catalyst. Identify the electrophile and the product.

14.14 Write the structure of the product formed by alkylation of *p*-methylanisole using 2-methyl-1-propene and sulfuric acid.

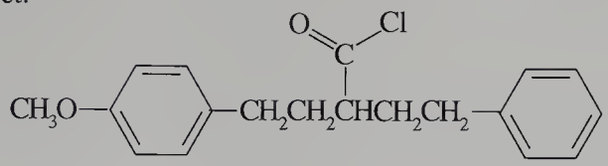
14.15 Reaction of toluene with isopropyl alcohol, $(CH_3)_2CHOH$, using sulfuric acid gives a mixture of largely two isomers with molecular formula $C_{10}H_{14}$. Write the structures of these compounds. How does the electrophile form?

14.16 The following compound reacts with sulfuric acid to give a tricyclic hydrocarbon with molecular formula $C_{17}H_{18}$. Write its structure.



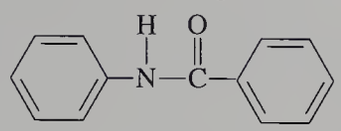
14.17 4-Phenylbutanoyl chloride reacts in carbon disulfide with aluminum trichloride to give a ketone with molecular formula $C_{10}H_{10}O$. Write the structure of the product.

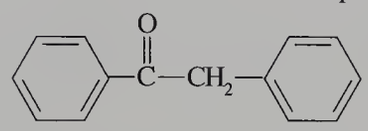
14.18 The following compound undergoes an intramolecular Friedel–Crafts acylation to give a cyclic ketone. Write the structure of the expected product.



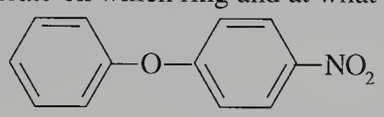
Aromatic Substitution Reactions

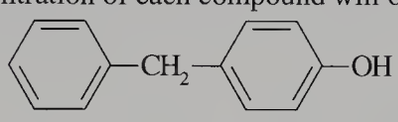
14.19 Indicate on which ring and at what position bromination of each compound will occur.

(a) 

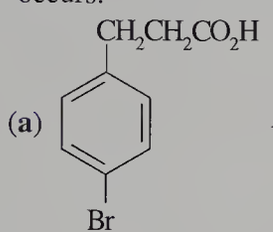
(b) 

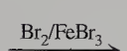
14.20 Indicate on which ring and at what position nitration of each compound will occur.

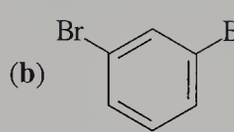
(a) 

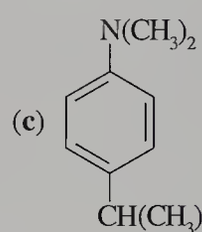
(b) 

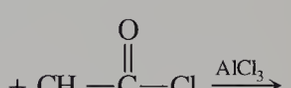
14.21 Write the structure of the major product of each of the following reactions, assuming that only monosubstitution occurs.

(a) 

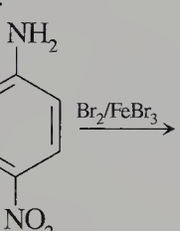


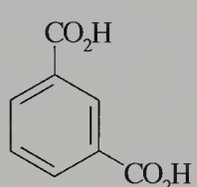
(b) 

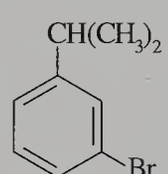
(c) 

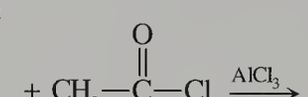


14.22 Write the structure of the major product of each of the following reactions, assuming that only monosubstitution occurs.

(a) 

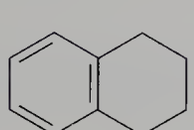
(b) 

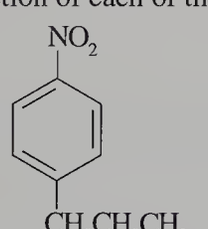
(c) 

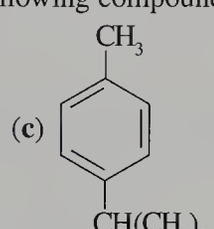


Functional Group Transformations

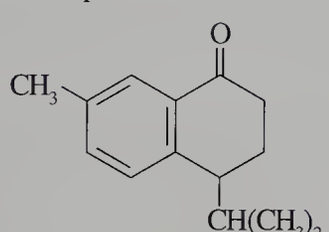
14.23 Write the product of the reaction of each of the following compounds with potassium permanganate.

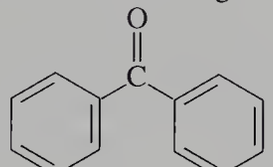
(a) 

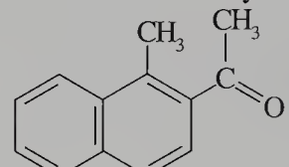
(b) 

(c) 

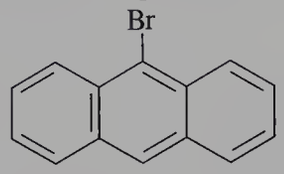
14.24 Write the product of the reaction of each of the following compounds with a zinc–mercury amalgam and HCl.

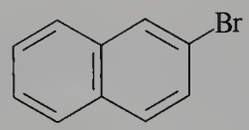
(a) 

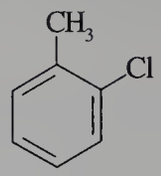
(b) 

(c) 

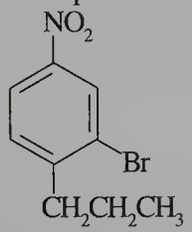
14.25 Write the product of the reaction of each of the following compounds in THF with magnesium followed by reaction with D_2O.

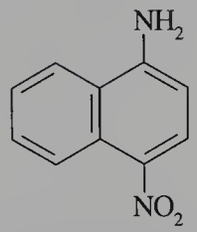
(a) 

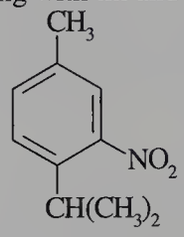
(b) 

(c) 

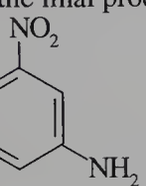
14.26 Write the product of the reaction of each of the following with tin and HCl.

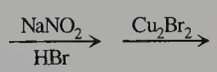
(a) 

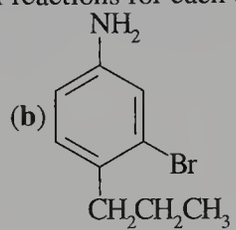
(b) 

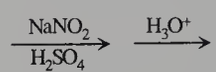
(c) 

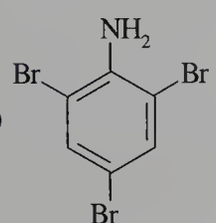
14.27 Write the final product of the sequence of reactions for each of the following compounds.

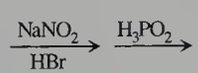
(a) 



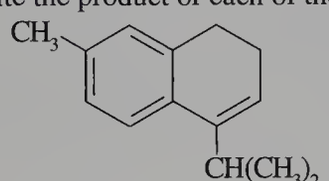
(b) 

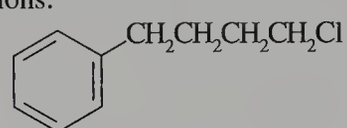


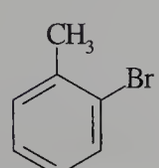
(c) 



14.28 Write the product of each of the following reactions.

(a) 

(b) 

(c) 

Synthesis of Aromatic Compounds

14.29 What reagent is required for each of the following reactions? Will an ortho and para mixture of products or the meta isomer predominate?

(**a**) nitration of bromobenzene (**b**) sulfonation of nitrobenzene
(**c**) bromination of ethylbenzene (**d**) methylation of anisole

14.30 What reagent is required for each of the following reactions? Will an ortho and para mixture of products or the meta isomer predominate?

(**a**) bromination of benzoic acid (**b**) acetylation of isopropylbenzene
(**c**) nitration of acetophenone (**d**) nitration of phenol

14.31 Starting with benzene, describe the series of reagents and reactions required to produce each of the following compounds.

(**a**) *p*-bromonitrobenzene (**b**) *m*-bromonitrobenzene
(**c**) *p*-bromoethylbenzene (**d**) *m*-bromoethylbenzene

14.32 Starting with benzene, describe the series of reagents and reactions required to produce each of the following compounds.
(**a**) *m*-bromobenzenesulfonic acid (**b**) *p*-bromobenzenesulfonic acid
(**c**) *p*-nitrotoluene (**d**) *p*-nitrobenzoic acid

14.33 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(**a**) 3,5-dinitrochlorobenzene (**b**) 2,4,6-trinitrotoluene (**c**) 2,6-dibromo-4-nitrotoluene

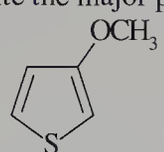
14.34 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(**a**) 2,4,6-tribromobenzoic acid (**b**) 2-bromo-4-nitrotoluene (**c**) 1-bromo-3,5-dinitrobenzene

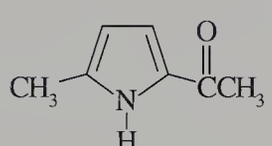
14.35 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(**a**) *m*-bromophenol (**b**) *m*-bromoaniline (**c**) *p*-methylphenol

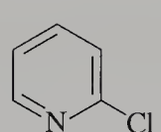
14.36 Starting with either benzene or toluene, describe the series of reagents and reactions required to produce each of the following compounds.
(**a**) *m*-bromochlorobenzene (**b**) *p*-methylbenzonitrile (**c**) 3,5-dibromotoluene

Heterocyclic and Polycyclic Aromatic Compounds

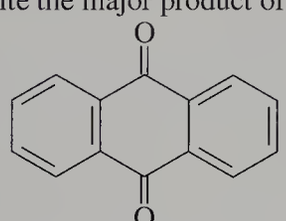
14.37 Write the major product of the reaction of each of the following compounds with a nitrating agent.

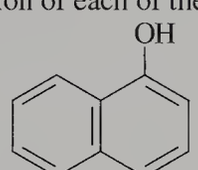
(**a**) 

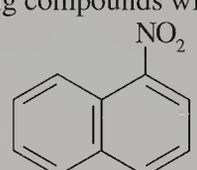
(**b**) 

(**c**) 

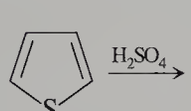
14.38 Write the major product of the reaction of each of the following compounds with a brominating agent.

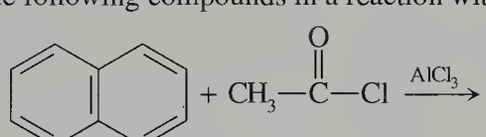
(**a**) 

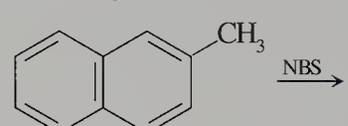
(**b**) 

(**c**) 

14.39 Write the product of each of the following compounds in a reaction with the indicated reagent.

(**a**) 

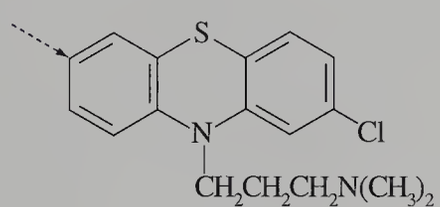
(**b**) 

(**c**) 

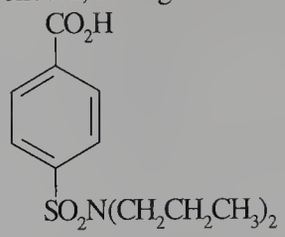
14.40 The relative amounts of the ortho-, meta-, and para-sulfonated products of toluene at 0 °C are 43%, 4%, and 53%, respectively. The relative amounts of the ortho-, meta-, and para-sulfonated products of toluene at 100 °C are 13%, 8%, and 79%, respectively. Explain why the para/ortho ratio is larger at the higher temperature.

Metabolic Oxidation of Aromatic Compounds

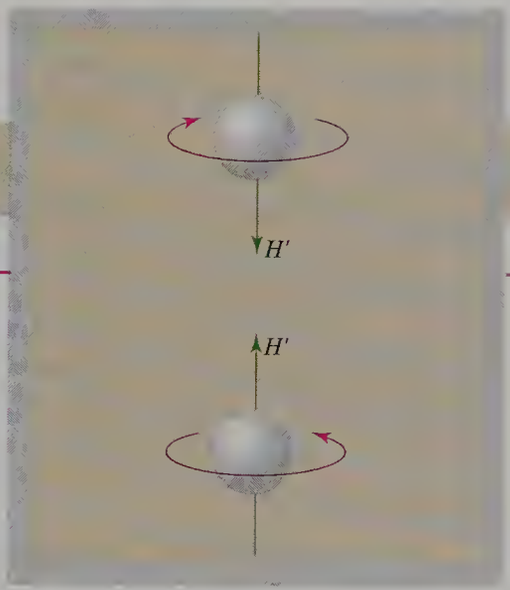
14.41 Explain why aromatic hydroxylation of chlorpromazine, an antipsychotic drug, occurs at the indicated position and in that ring.



14.42 Why doesn't aromatic hydroxylation of probenecid, a drug used to treat chronic gout, occur?



15



Spectroscopy and Structure Determination

15.1 Structure Determination

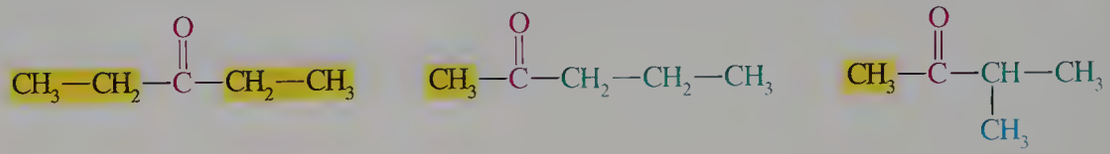
To understand the details of the biological function of a compound or to design a synthesis of a naturally occurring compound, we first must know its structure. The structure of a natural product is often very complex, and the compound may be available initially in only small quantities. How does a chemist learn the molecular structure of a compound obtained from a natural source or even from a chemical reaction of a known compound? To determine the structure of a naturally occurring compound from "scratch" is a difficult challenge. The determination of the structure of a compound synthesized in the laboratory from known reactants is a somewhat less demanding, but still complex, process.

At one time, organic chemists determined the structure of organic compounds by chemical reactions that related an unknown compound to other known compounds. The reactions used were oxidation, reduction, addition, substitution, or elimination reactions. To determine the structures of complex molecules, it was often necessary to use reactions that systematically degraded the large molecule into smaller molecules. Then the chemist could reason backwards to postulate what the structure of the original compound must have been to yield the observed products. Structure determination by chemical reactions is a time-consuming process that requires experimental skills and deductive reasoning. For example, consider the problem of determining the structure of a relatively simple compound with molecular formula $C_5H_{10}O$. Eighty-eight isomers are possible, including ethers, alcohols, aldehydes, and ketones. Many chemical reactions would be required to identify the functional group as well as the hydrocarbon skeleton. Structure determination by chemical reactions also has one severe limitation: Each reaction destroys part of the sample of the unknown compound.

Chemists now can determine structure by nondestructive spectroscopic techniques and recover the sample unchanged after they determine its spectrum. Spectroscopic determination requires only minuscule amounts of a compound, and the experimental methods require very little time. Spectroscopic methods provide information about the kinds of atoms present in the compound and how they are connected. In this chapter we first examine ultraviolet and infrared spectroscopy. These

two spectroscopic methods have been used in organic chemistry for more than 50 years. Then we will consider in detail nuclear magnetic resonance spectroscopy, a method that has been used for about 30 years. Each type of spectroscopy provides a different kind of information.

Ultraviolet spectroscopy provides information about the π system in a compound, so this method allows us to distinguish between conjugated and nonconjugated compounds. Infrared spectroscopy reveals the functional groups in a compound. For example, consider again the determination of the structure of a compound with molecular formula $C_5H_{10}O$. Although eighty-eight isomers are possible, infrared spectroscopy can limit the number of possible structures by identifying the functional group containing the oxygen atom. If infrared spectroscopy reveals that the compound is a ketone, the number of possible isomers drops to a more manageable three compounds.



Nuclear magnetic resonance provides information about the carbon–carbon framework of a compound. To further characterize the $C_5H_{10}O$ compound known to be a ketone by infrared spectroscopy, we must determine how the carbon atoms are distributed on either side of the carbonyl carbon atom. To determine the structure of the ketone we need to "see" either the structurally nonequivalent carbon nuclei or the nuclei of hydrogen atoms bonded to them. Nuclear magnetic resonance spectroscopy (NMR) provides this information. In this chapter we will first consider how to determine the molecular structure using information about structurally different hydrogen nuclei. With information about the hydrogen atoms, we can deduce how the carbon atoms are arranged in the structure. Then we will see how NMR spectroscopy can detect structural differences among the carbon atoms themselves.

15.2 Spectroscopy

Spectroscopy is a study of the interaction of electromagnetic radiation with molecules. Electromagnetic radiation encompasses X-rays; ultraviolet, visible, and infrared radiations; microwaves, and radio waves. Electromagnetic radiation can be described as a wave that travels at the speed of light (3×10^8 m/sec). Waves are characterized by a wavelength (λ, Greek lambda) and a frequency (ν, Greek nu). The wavelength is the length of one wave cycle, from crest to crest or trough to trough (Figure 15.1). The wavelength is expressed in the metric unit convenient for each type of electromagnetic radiation. The frequency is the number of waves that move past a given point in a unit of time. Frequency is usually expressed in hertz (Hz). Wavelength and frequency are inversely proportional and are related by $\lambda = c/\nu$, where c is the speed of light. As the wavelength of the electromagnetic radiation increases, the corresponding frequency decreases.

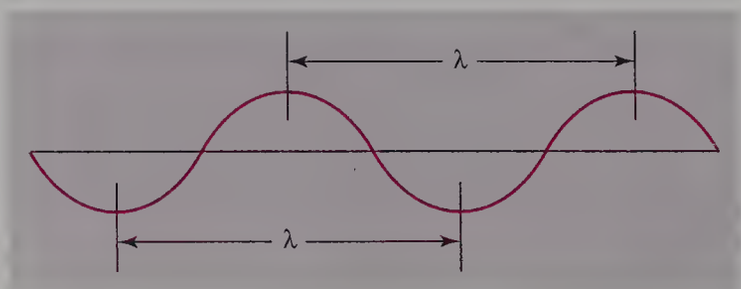


FIGURE 15.1 Electromagnetic Radiation
The wavelength of electromagnetic radiation is the distance between any two peaks or troughs of the wave.

The energy, E associated with electromagnetic radiation is quantized. The relationship is given by

$$E = h\nu = \frac{hc}{\lambda} = hc \times \frac{1}{\lambda}$$

where h is the proportionality constant known as Planck's constant. The energy of electromagnetic radiation is therefore directly proportional to its frequency, but inversely proportional to its wavelength. The energy of electromagnetic radiation is also directly proportional to the quantity $1/\lambda$, known as the **wavenumber.**

The frequency of ultraviolet radiation is higher than that of infrared radiation. Alternatively expressed, the wavelength of ultraviolet radiation is shorter than the wavelength of infrared radiation. Because ultraviolet radiation has a higher frequency, it has higher energy than infrared radiation (Figure 15.2).

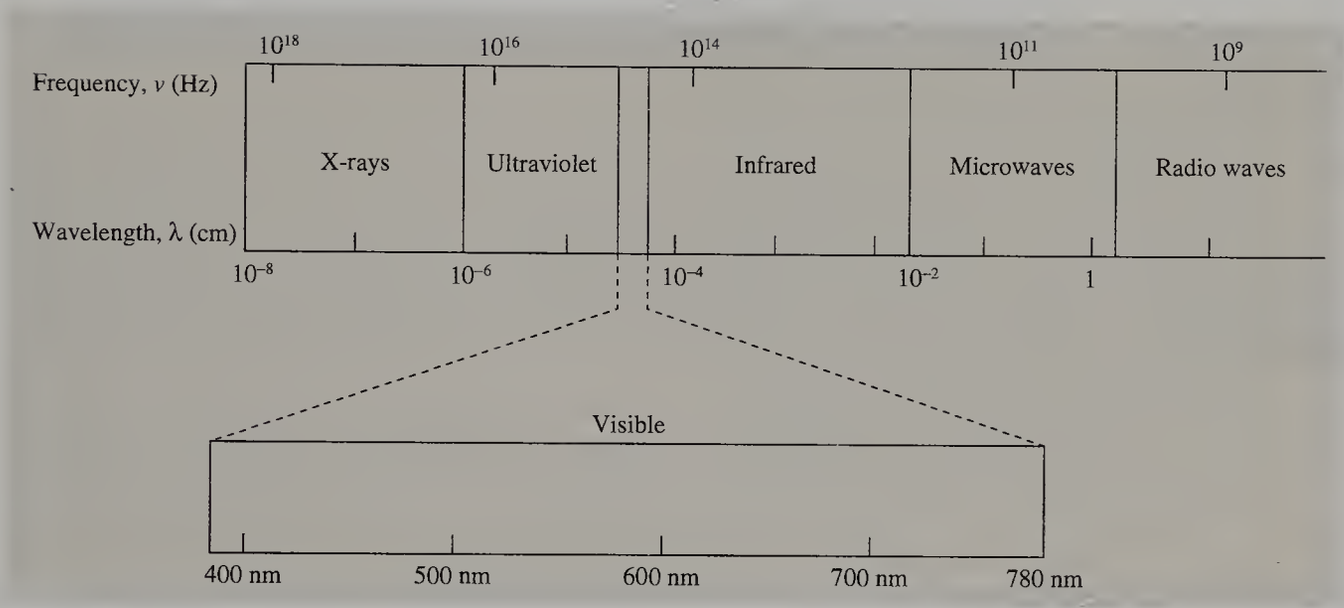


FIGURE 15.2 The Electromagnetic Spectrum
The regions of the spectrum used in organic chemistry are characterized by a frequency and a wavelength. Usually the wavelength or the reciprocal of the wavelength, the wavenumber, is used to identify absorptions of organic molecules. The relationship of the visible spectrum to other spectral regions is shown with the expansion of that region.

Molecules can absorb only certain discrete amounts of energy. To change the energy content of a molecule from E_1 to E_2, the energy difference $E_2 - E_1$ comes from characteristic electromagnetic radiation with a specific frequency (and wavelength). The energy absorbed by the molecule can change its electronic or vibrational energy. For example, ultraviolet radiation causes changes in the electron distribution in π orbitals; infrared radiation causes bonds to stretch and bond angles to bend.

In the various types of spectroscopy, radiation passes from a source through a sample that may or may not absorb certain wavelengths of the radiation. As the wavelength is systematically changed, a detector determines which wavelengths of light the sample absorbs. At a wavelength corresponding to the energy $E_2 - E_1$ necessary for a molecular change, the molecule absorbs the radiation emitted by the source. The amount of light absorbed by the molecule (absorbance) is plotted as a function of wavelength. At most wavelengths, the amount of radiation detected by the detector equals that emitted by the source because the molecule does not absorb radiation. At such wavelengths, a plot of absorbance on the vertical axis versus wavelength yields a horizontal line (Figure 15.3). When the molecule absorbs radiation of a spe-

cific wavelength, the amount of radiation arriving at the detector is less than that emitted by the source. This difference is recorded as an absorbance.

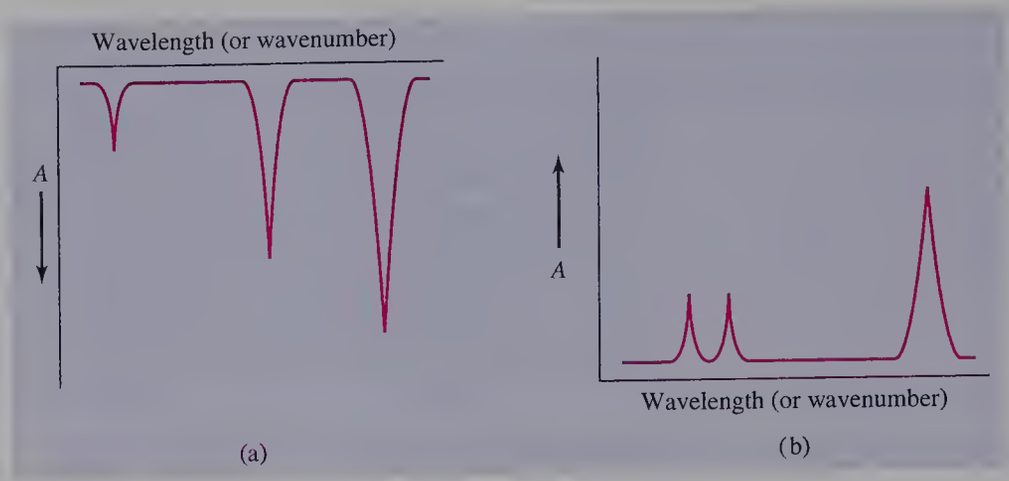


FIGURE 15.3 Features of a Spectrum
The portion of the spectrum where no absorption occurs is the base line. This horizontal line may be located at the top or bottom of a graph. Absorption then is recorded as a peak or "dip" from the base line. In an infrared spectrum (a) the base line is at top of the spectrum. In an ultraviolet spectrum (b) or an NMR spectrum, the base line is at the bottom of the spectrum.

15.3 Ultraviolet Spectroscopy

The ultraviolet region of the electromagnetic spectrum spans wavelengths from 200 to 400 nm (1 nm = 10^{-9} m). In the ultraviolet region of the electromagnetic spectrum, a molecule with conjugated double bonds absorbs energy. Sigma bonds and isolated carbon–carbon double bonds require electromagnetic radiation of higher frequency to absorb energy.

Ultraviolet (UV) spectra are simple in appearance. A UV spectrum is a plot of the absorbance of light on the vertical axis versus the wavelength of light (in nanometers, nm) on the horizontal axis (Figure 15.4). The wavelength corresponding to the top of the UV "peak" is called the λ_{max}. The absorbance depends on the structure of the compound and the concentration of the sample in the solution. Concentrations in the 10^{-3} to 10^{-5} M range are typically used to obtain a spectrum.

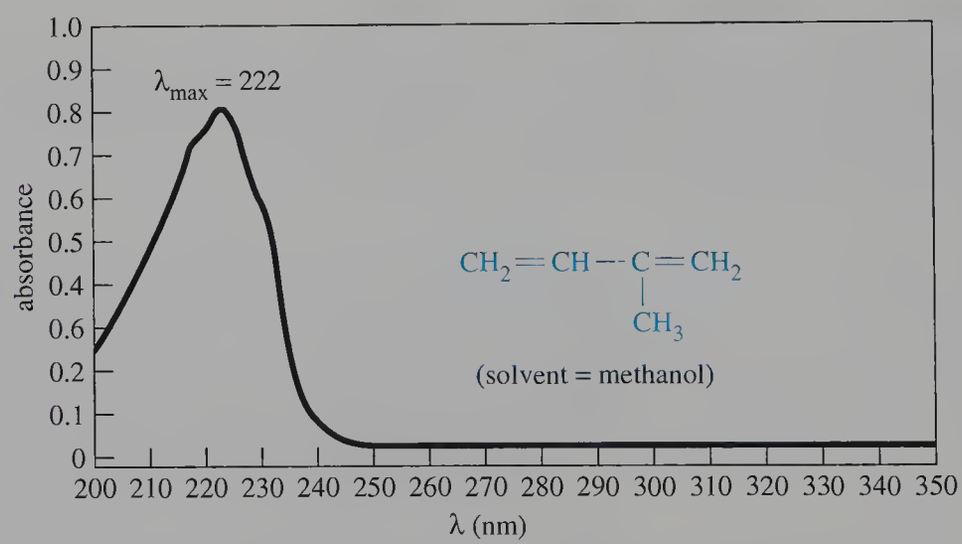
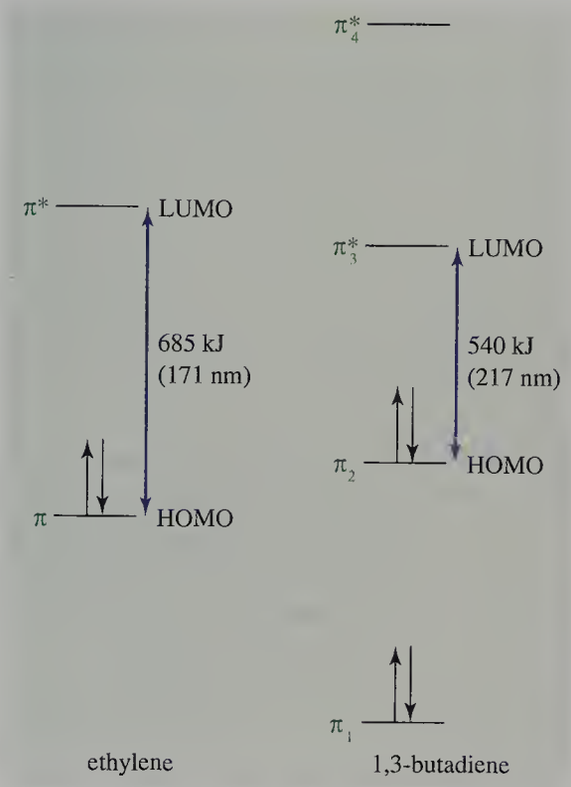


FIGURE 15.4 Ultraviolet Spectrum of Isoprene
The ultraviolet spectrum of isoprene dissolved in methanol is representative of the spectra of conjugated dienes. The position of maximum absorption occurs at 222 nm.

The energy absorbed by an unsaturated compound moves π electrons in bonding molecular orbitals of the ground state configuration into higher energy, antibonding molecular orbitals of an excited state. The specific wavelength of ultraviolet light required to "excite" the π electrons of an unsaturated compound depends on the difference in energy between the **highest occupied molecular orbital (HOMO)** and the **lowest unoccupied molecular orbital (LUMO)**.

There are only two π molecular orbitals in ethylene. In the ground state, the bonding electrons are in π_1, the HOMO. An electron is promoted to π_2, the LUMO, when a photon of light is absorbed whose energy is equal to the difference in energy between these two molecular orbitals. The process is called a $\pi \longrightarrow \pi^*$ transition (Figure 15.5).

FIGURE 15.5 Molecular Orbitals and Electronic Transitions



Let's consider the effect of conjugation on the energy required for a $\pi \longrightarrow \pi^*$ transition. The simplest conjugated diene is 1,3-butadiene. The energies of the four molecular orbitals of butadiene are compared in Figure 15.5 with the molecular orbitals of ethylene. As a result of conjugation, the total energy of the two bonding molecular orbitals of 1,3-butadiene (π_1 and π_2) are lower than two isolated bonding molecular orbitals of ethylene. However, note that the HOMO of butadiene (π_2) is higher in energy than the HOMO of ethylene. The LUMO (π_3) of butadiene is also lower in energy than the LUMO of ethylene. As a result, the $\pi \longrightarrow \pi^*$ transition of butadiene requires less energy than the $\pi \longrightarrow \pi^*$ transition for ethylene. The $\pi \longrightarrow \pi^*$ transition of ethylene is beyond the range of conventional ultraviolet spectrometers. The $\pi \longrightarrow \pi^*$ transition for butadiene occurs at 217 nm.

Although the explanation is beyond the scope of this text, it is a general feature of extensively conjugated systems that the energy difference between the HOMO and LUMO decreases as the extent of the conjugation increases. Certain substituents bonded to π systems alter the HOMO and LUMO in ways that can be understood using molecular orbital theory. The value of λ_{max} depends on both the type of conjugated system and its substituents.

15.4 Woodward–Fieser Rules

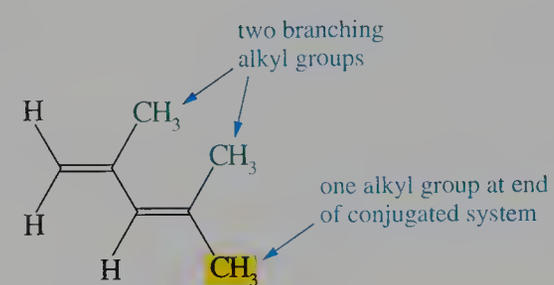
R. B. Woodward and L. F. Fieser of Harvard University developed a set of empirical rules that account for the λ_{max} of polyenes (Table 15.1). These rules consist of group contributions that are added to give a predicted λ_{max} that is usually within 1–2 nm of the experimental value. The base value for polyenes is 217 nm for butadiene, a compound that exists in an s-trans conformation and has no attached substituents. Ex-

tended conjugation markedly changes the λ_{max}. For each additional double bond in conjugation, 30 nm is added to the base value.

Table 15.1
Woodward–Fieser Rules

1. The base value of the $\pi \longrightarrow \pi^*$ transition for a trans conjugated diene is 217 nm.
2. Add 5 nm to the base value for any alkyl group attached to the carbon atoms of the conjugated systems.
3. Add 5 nm for any π bond that is exocyclic to a ring.
4. Add 39 nm for a cis arrangement of double bonds.
5. Add 30 nm for any additional double bonds that are in conjugation with the base system.

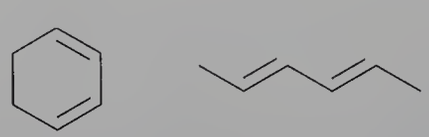
Although the extent of the conjugation is the primary feature affecting λ_{max}, the degree of substitution causes changes that are useful in structure determination. For example, the presence of an alkyl group such as methyl appended to one of the carbon atoms of the conjugated system causes approximately a 5-nm shift to longer wavelengths. Let's apply this alkyl group contribution to calculate the λ_{max} of 2,4-dimethyl-1,3-pentadiene.



2,4-dimethyl-1,3-pentadiene

The compound contains two conjugated double bonds. It should therefore absorb light near 217 nm, as butadiene does. However, two branching methyl groups and one methyl group (the C-5 atom) are bonded to the unsaturated carbon atoms of the butadiene-type system. When we add their contributions, we predict that the compound should absorb ultraviolet light at 217 + 3(5) = 232 nm.

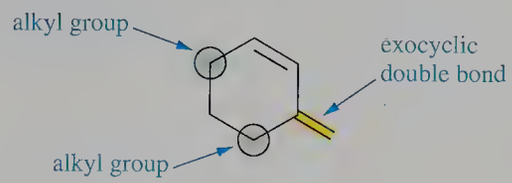
Although acyclic dienes usually exist in an s-trans conformation, cyclic dienes most often are in an s-cis conformation. These compounds absorb light at higher wavelength compared to similarly substituted s-trans compounds. Both 1,3-cyclohexadiene and 2,4-hexadiene have two alkyl groups bonded to a diene system. 2,4-Hexadiene absorbs at 227 nm, a value predicted by adding 2(5 nm) to the 217-nm base value. However, 1,3-cyclohexadiene absorbs at 256 nm, a difference of 39 nm from the predicted value.



1, 3-cyclohexadiene 2, 4-hexadiene

Consequently, for compounds in which two of the double bonds of a polyene are constrained in a cis relationship, the structural increment is 39 nm. Because the two double bonds are in a common ring, this structural arrangement is called **homoannular**.

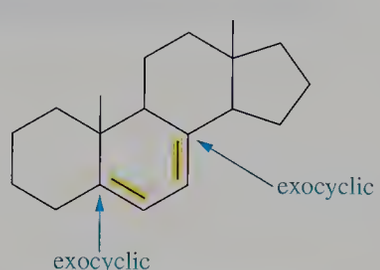
A double bond is **exocyclic** if it is outside a ring but shares one carbon atom with the ring. This structural arrangement increases the λ_{max} by 5 nm. For example, 3-methylenecyclohexene absorbs at 232 nm.



3-methylenecyclohexene

We "predict" this value by using 217 nm as the base for an s-trans diene. Then we add 2(5 nm) for two alkyl groups, the ring C-4 and C-6 atoms attached to the butadiene unit. Finally, we add 5 nm for the exocyclic double bond.

One or more double bonds can occupy one ring and also be exocyclic to a second ring. For example, the two double bonds contained within the middle ring of the following compound are both exocyclic, but each to a different ring.



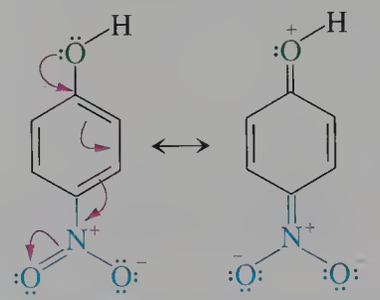
Color and Structure

Compounds that absorb only in the ultraviolet region appear colorless because they absorb no "visible" light. A compound appears colored only if absorption occurs in some portion of the visible spectrum. Some naturally occurring compounds with extensively conjugated double bonds absorb at such long wavelengths that the λ_{max} occurs in the visible region (400 to 800 nm) of the spectrum. (The Woodward–Fieser rules cannot be applied to these compounds.) β-Carotene, which is present in carrots, absorbs light in the blue-green region of the spectrum at 455 nm. Because it absorbs blue-green light, the light that reaches our eyes is yellow-orange. We see the complement of the absorbed light. The color of a compound therefore provides qualitative information about its λ_{max} (Table 15.2).

Table 15.2
Absorbed Light and Reflected Color

Absorbed wavelength (nm)	*Reflected color*
400 (violet)	yellow-green
450 (blue)	orange
510 (green)	purple
590 (orange)	blue
640 (red)	blue-green
730 (purple)	green

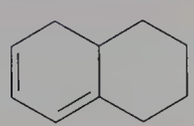
Some kinds of conjugated molecules, such as aromatic compounds, have only ultraviolet absorptions and are colorless. Aromatic compounds may be colored if they have substituents to extend the conjugation. For example, benzene absorbs at 254 nm and is therefore colorless. Phenol and nitrobenzene are also colorless. However, *p*-nitrophenol has a faint yellow color because the two substituents—one electron donating and the other electron withdrawing—interact to extend the conjugation. By studying the effect of substituents on aromatic rings and other classes of conjugated compounds, chemists have compiled information relating structural effects on ultraviolet spectra that make it possible to establish the structures of "unknown" compounds.



resonance contributors of *p*-nitrophenol

Problem 15.1

Predict the λ_{max} for each of the following compounds.



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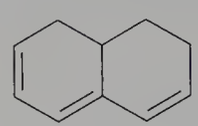
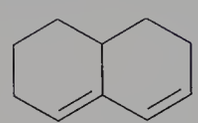


II



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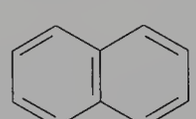
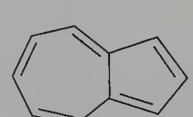
Problem 15.2

Naphthalene and azulene are isomers that have extensively conjugated π systems. Naphthalene is a colorless compound, but azulene is blue. Deduce information about the absorption of electromagnetic radiation by these two compounds.



naphthalene



azulene

15.5 Infrared Spectroscopy

Atoms in a molecule do not remain at fixed positions with respect to each other. Molecules vibrate at various frequencies that depend on molecular structure, their bonds stretching and contracting slightly. Similarly, the angle between two atoms bonded to a common central atom regularly expands and contracts by a small amount at a frequency that also depends on molecular structure. These vibrational and bending frequencies correspond to the frequency of light in the infrared region of the electromagnetic spectrum.

Different bonds or bond angles in a molecule absorb light of individually characteristic energy. The number of different absorptions is therefore large for even the simplest of organic molecules. The infrared spectrum of 1-methylcyclopentene is shown in Figure 15.6. The wavenumber ($1/\lambda$) given on the bottom of the graph, is

plotted against absorbance of light by the sample. An absorption corresponds to a "peak" pointed toward the bottom of the graph. Because the wavenumber of absorbed light is directly proportional to its energy, absorptions at high wavenumber (toward the left of the graph) represent molecular vibrations that require high energy. The plot also gives the corresponding value of the wavelength for the absorption. The energy of absorbed light is inversely proportional to the wavelength. Absorptions that occur at higher wavelength (toward the right of the graph) thus represent molecular vibrations that require low energy.

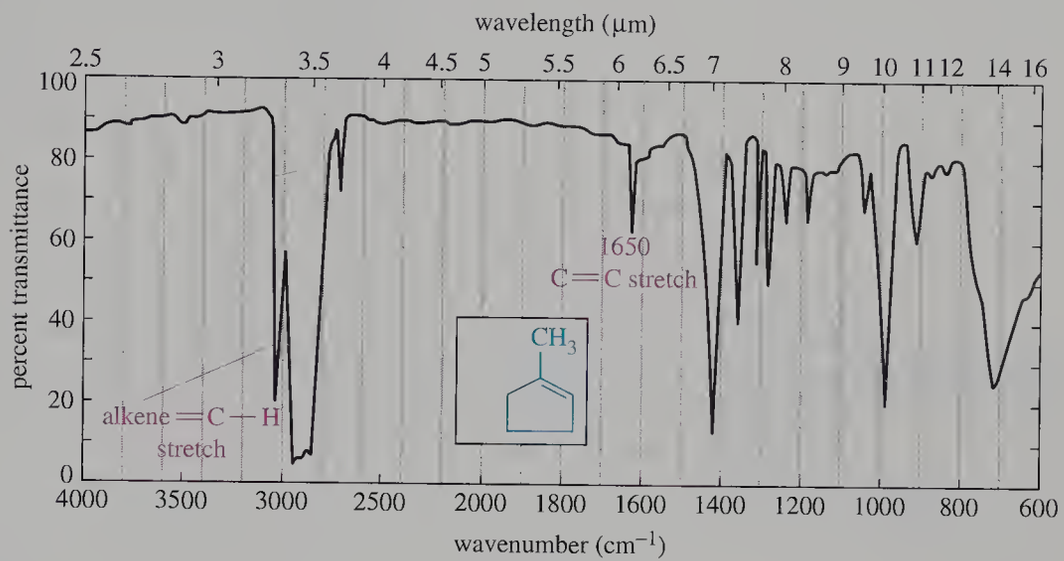


FIGURE 15.6 Infrared Spectrum of 1-Methylcyclopentene

Although the total of all molecular vibrations results in a complex infrared spectrum, some simple methods allow us to interpret and compare absorptions. As a first approximation, the motion of two bonded atoms relative to each other can be considered independently of the rest of the molecule. The vibrational frequency of the individual bond relates to the force constant (f) of the bond and the masses of the two atoms (m_1 and m_2) by the following equation.

$$\bar{\nu} = \frac{1}{2\pi c}\sqrt{\frac{f(m_1 + m_2)}{m_1 m_2}}$$

The force constants are roughly proportional to the bond dissociation energies. Hence, the force constants increase in the order single bond < double bond < triple bond. Furthermore, because polar bonds, such as the carbonyl group, have higher bond dissociation energies than carbon–carbon double bonds, the force constant for a C=O group is larger than for a C=C group.

The effect of atomic mass is relatively small, except for bonds to hydrogen. Although absolute masses must be used in the above expression, we can determine the contribution of mass by substituting the atomic weights in the $(m_1 + m_2)/m_1 m_2$ part of the expression.

$$\text{For C—C:}\quad \frac{12.0 + 12.0}{12.0 \times 12.0} = 0.17 \qquad \text{For C—O:}\quad \frac{12.0 + 16.0}{12.0 \times 16.0} = 0.15$$

$$\text{For C—H:}\quad \frac{12.0 + 1.0}{12.0 \times 1.0} = 1.08$$

As a consequence, the mass contribution sets bonds to hydrogen such as C—H, N—H, and O—H apart from bonds that do not contain hydrogen atoms.

The regions of the infrared spectrum in which common bond types absorb are listed in Table 15.3. These values illustrate the effect of both force constants of multiple bonds and the mass effect of the hydrogen atom.

Table 15.3
Approximate Values of Infrared Absorptions

Bond	*Absorption Region (cm^{-1})*
C—C, C—N, C—O	800–1300
C=C, C=N, C=O	1500–1900
C≡C, C≡N	2000–2300
C—H, N—H, O—H	2850–3650

15.6 Structure Identification Using Infrared Spectroscopy

The infrared spectrum of an organic molecule is complex, and a peak-by-peak analysis is very difficult. However, the total spectrum is characteristic of the compound and can be used to establish the identity of an "unknown" compound. If the spectrum of the "unknown" has all of the same absorption peaks— including both wavelength and intensity—as a compound of known structure, then the two samples are identical. If the "unknown" has one or more peaks that differ from the spectrum of a known, then the two compounds are not identical, or there may be an impurity in the "unknown" sample that causes the extra absorption. On the other hand, if the "unknown" lacks even one absorption peak that is present in the known structure, the unknown has a different structure from that of the known. For example, if the infrared spectrum of a compound of molecular formula C_6H_{10} lacks an absorption at 1650 cm^{-1}, the compound is not 1-methylcyclopentene (Figure 15.6).

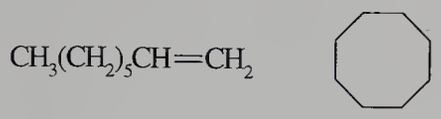
Characteristic Group Vibrations

Although the infrared spectrum of an organic compound is complex, distinctive bands appear in spectra of compounds with common functional groups. Distinctive absorptions corresponding to the vibration of specific bonds or functional groups are called **group vibrations**. We can therefore use the presence or absence of these absorptions to characterize a compound. For example, the absorption at 1650 cm^{-1} in 1-methylcyclopentene is due to the stretching of a carbon–carbon double bond (Figure 15.6). Although the exact position of a carbon–carbon double bond absorption varies slightly for various alkenes, all carbon–carbon double bonds absorb energy in the 1630–1670 cm^{-1} region. Isomers such as cyclohexene, methylenecyclopentane, or 3-methylcyclopentene will have an absorption in the 1630–1670-cm^{-1} region. However, the spectra will differ in some other areas, telling us that the compounds are not identical to the known 1-methylcyclopentene.

15.7 Identifying Hydrocarbons

When we first started to study organic chemistry, we learned that hydrocarbons are classified as saturated or unsaturated depending on the presence of multiple bonds (Section 4.1). Multiple bonds decrease the number of hydrogen atoms in a molecular formula below the number given in C_nH_{2n+2}, the molecular formula for a saturated acyclic hydrocarbon. However, the molecular formulas of hydrocarbons do not

unambiguously indicate the presence or absence of a multiple bond. Both 1-octene and cyclooctane have the same molecular formula, C_8H_{16}.



1-octene cycloctane

The structural features present in 1-octene and absent in cyclooctane are a carbon–carbon double bond and sp^2-hybridized C—H bonds. If these features give rise to characteristic group absorptions, then 1-octene will have them and cyclooctane will not.

Now, also consider the difference between 1-octyne and an isomeric bicyclic hydrocarbon.

1-octyne (a bicyclic hydrocarbon)

The structural features present in 1-octyne and absent in the bicyclic hydrocarbon are a carbon–carbon triple bond and *sp*-hybridized C—H bond. If these features give rise to characteristic group absorptions, then 1-octyne will have them and an isomeric bicyclic hydrocarbon will not.

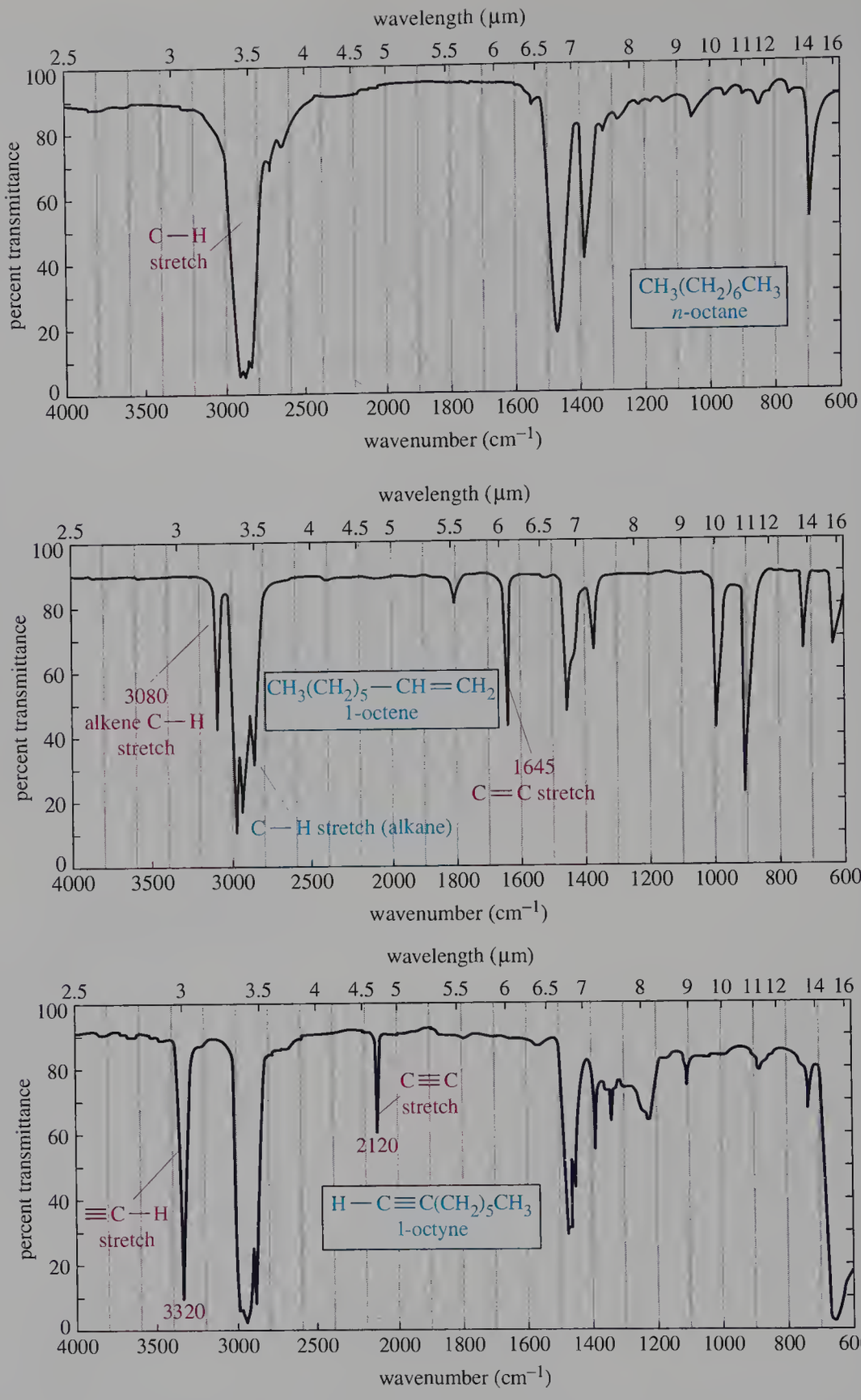
The infrared energy absorbed by a C—H bond depends on the hybridization of the carbon atom (Table 15.4). Carbon–hydrogen bonds become stronger in the order $sp^3 < sp^2 < sp$ because the increased *s* character of the carbon atom keeps the bonding electrons closer to the carbon atom. The energy required to stretch the bond therefore increases in the same order.

Table 15.4
Characteristic Infrared Group Frequencies

Class	*Group*	*Wavenumber (cm^{-1})*
alkane	C—H	2850–3000
alkene	C—H	3080–3140
	C=C	1630–1670
alkyne	C—H	3300–3320
	C≡C	2100–2140
alcohol	O—H	3400–3600
	C—O	1050–1200
ether	C—O	1070–1150
aldehyde	C=O	1725
ketone	C=O	1700–1780

The sp^3-hybridized C—H bonds in saturated hydrocarbons such as octane (Figure 15.7) absorb infrared radiation in the 2850–3000 cm^{-1} region. The sp^2-hybridized C—H bonds in alkenes such as 1-octene absorb energy at 3080 cm^{-1}. This peak appears separately from the absorptions associated with the sp^3-hybridized C—H bonds in this molecule (Figure 15.7). The isomeric cyclooctane would not have the 3080-cm^{-1} absorption. An *sp*-hybridized C—H bond in a molecule such as 1-octyne (Figure 15.7) absorbs infrared radiation at 3320 cm^{-1}. An isomeric bicyclic hydrocarbon with no multiple carbon–carbon bonds, and hence no sp^2- or *sp*-hybridized carbon atoms, would have absorptions only in the 2850–3000 cm^{-1} region.

FIGURE 15.7 Infrared Spectra of Hydrocarbons



Hydrocarbons can also be classified by absorptions of the carbon–carbon bonds. Carbon–carbon bond strength increases in the order single < double < triple. Thus, the wavenumber position (cm^{-1}) of the absorption corresponding to stretching these bonds increases in the same order. Saturated hydrocarbons, both alkanes and cycloalkanes, contain many carbon–carbon single bonds that absorb in the 800–

1000 cm^{-1} region, but the intensity is very low. Carbon–carbon single bonds present in unsaturated compounds also absorb in the same region. Many other molecular bond stretching vibrations and bond angle bending modes occur in the same region and are much more intense. Therefore this region hence has limited diagnostic value. Moreover, we already know that most organic compounds have carbon–carbon single bonds.

Unsaturated hydrocarbons are identified by the absorption for the carbon–carbon double bond, which occurs in the 1630–1670 cm^{-1} region. The intensity of the absorption decreases with increased substitution. Terminal alkenes have the most intense absorptions. The double bond in 1-octene absorbs at 1640 cm^{-1} (Figure 15.7).

The absorption for carbon–carbon triple bonds occurs in the 2100–2140 cm^{-1} region. Terminal alkynes have the most intense absorption; internal (disubstituted) alkynes have lower intensity absorptions. The triple bond in 1-octyne absorbs at 2120 cm^{-1} (Figure 15.7).

Problem 15.3

Explain how you could distinguish between the following two compounds by infrared spectroscopy.

Sample Solution

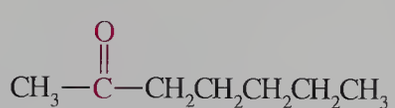
Each compound has structural features that are not present in the isomer. For example, the alkyne has a carbon–carbon triple bond as well as an *sp*-hybridized C—H bond. This compound should have absorptions in the 2100–2140 cm^{-1} and the 3300–3320 cm^{-1} region, and the diene should not have absorptions in either region.

15.8 Identifying Oxygen-Containing Compounds

Many functional groups contain oxygen with characteristic infrared absorptions (Table 15.4). The characteristic group frequencies of aldehydes and ketones range from 1700 to 1780 cm^{-1}. The carbon–oxygen double bond of carbonyl compounds requires more energy to stretch than does the carbon–oxygen single bond of ethers and alcohols. Consequently, aldehydes and ketones absorb infrared radiation at higher wavenumber positions than alcohols and ethers (1050–1200 cm^{-1}).

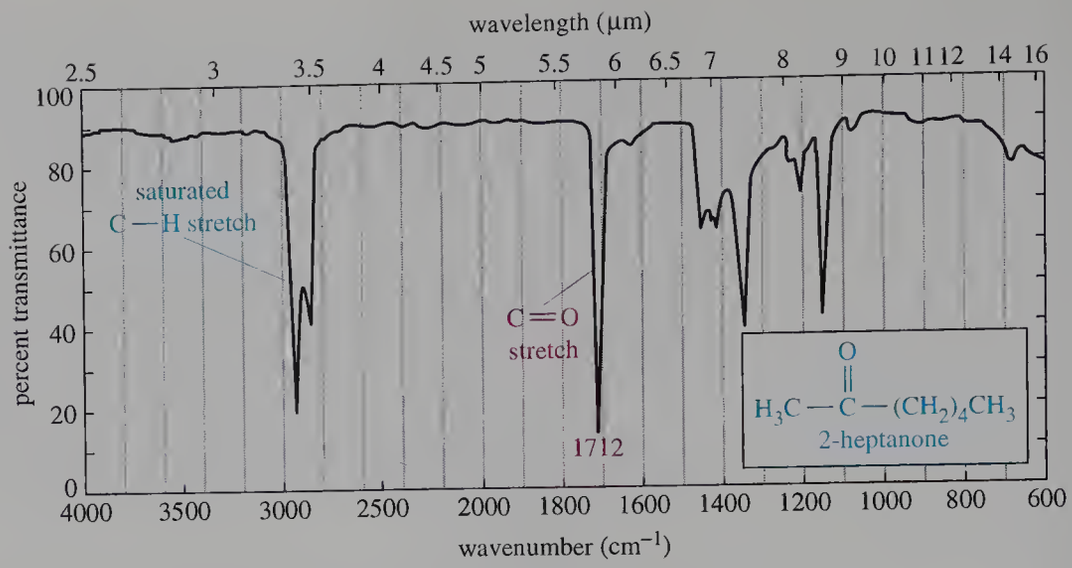
The Carbonyl Group

The absorption for a carbonyl group is extremely intense and easily detected because it lies in a region of the infrared spectrum that has no conflicting absorptions. Note that carbon–carbon double bond stretching vibrations are at a slightly lower wavenumber position than those of carbonyl compounds. Figure 15.8 shows a typical spectrum of a ketone for 2-heptanone. The carbonyl stretching vibration occurs at 1712 cm^{-1}.



2-heptanone

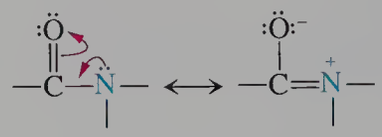
FIGURE 15.8 Infrared Spectrum of 2-Heptanone



The position of the carbonyl group absorption depends on the inductive and resonance effects of atoms bonded to the carbonyl carbon atom. A carbonyl group is represented by two contributing resonance forms.

contributing resonance forms of a carbonyl group

Because less energy is required to stretch a single bond than a double bond, any structural feature that stabilizes the contributing polar resonance form with a carbon–oxygen single bond will cause the infrared absorption to occur at a lower wavenumber position. As a result, any group that donates electrons to the carbonyl carbon atom by resonance causes a shift in the absorption to lower wavenumbers. We recall that the nitrogen atom is very effective in donating electrons to aromatic rings by resonance (Section 14.5). A similar effect is found in amides, where nitrogen donates electrons to the carbonyl group. Such substituents decrease the double bond character of the carbonyl group. As a result, an amide carbonyl group absorbs in the 1650–1690 cm^{-1} region, that is, at a lower wavenumber than for ketones.



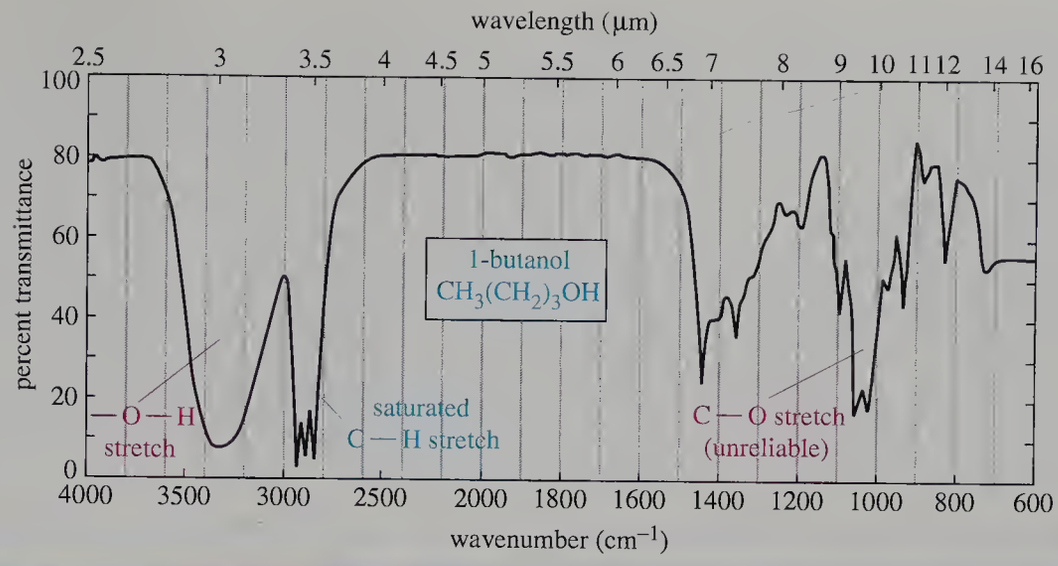
resonance forms of an amide

Alcohols and Ethers

The carbon–oxygen single bond stretching vibration of alcohols and ethers appears in a region complicated by many other absorptions. However, the absorption of a carbon–oxygen single bond is more intense than the absorption of carbon–carbon single bonds. The presence of a hydroxyl group is better established by the oxygen–hydrogen stretching vibration that occurs as an intense broad peak in the 3360-cm^{-1} region. The spectrum of 1-butanol illustrates this absorption (Figure 15.9).

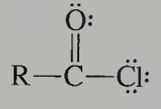
Ethers can be identified by a process of elimination. If a compound contains an oxygen atom and the infrared spectrum lacks absorptions characteristic of a carbonyl group or a hydroxyl group, we can conclude that the compound is an ether.

FIGURE 15.9 Infrared Spectrum of 1-Butanol



Problem 15.4

The carbonyl group of an acid chloride absorbs at 1800 cm^{-1}. Explain why this value is at a higher wavenumber than for an aldehyde or ketone.



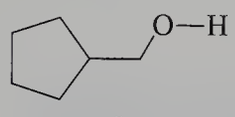
an acid chloride

Sample Solution

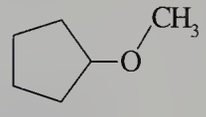
Chlorine does not effectively donate electrons by resonance via its 3*p* orbitals. Thus, the dipolar resonance form of a carbonyl group is less important, and the carbonyl group has more double bond character than an aldehyde or ketone. The chlorine atom also inductively withdraws electrons, destabilizing the dipolar resonance form. As a result the carbonyl infrared absorption should require more energy than for a ketone and will occur at a higher wavenumber position.

Problem 15.5

Explain how you could distinguish between the following two compounds by infrared spectroscopy.



I



II

15.9 Bending Deformations

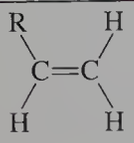
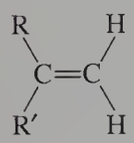
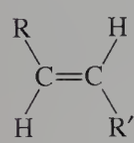
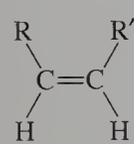
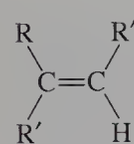
All of the infrared absorptions presented to this point are stretching vibrations that result from atomic motions along the axis of the bond. However, a second vibration can occur in a direction perpendicular to the bond. Such motion, called bending, is common for C—H bonds. Bending motions occur in directions defined with respect to a selected plane. In the case of alkenes and aromatic compounds, bending motions for several C—H bonds often occur in concert with each other, and they provide important information about isomeric structures.

Alkenes

Alkenes have out-of-plane bending modes in the 1000–800 cm^{-1} region. The absorptions are sufficiently intense to be useful in assigning structures (Table 15.5). Terminal alkenes produce the two most reliable absorption patterns. The two C—H bonds of compounds of the type $R_2C{=}CH_2$ bend in concert with each other, and the absorption occurs in the 895–885 cm^{-1} region. For compounds of the type $RCH{=}CH_2$, the two methylene C—H bonds absorb in the 910–905 cm^{-1} region, and the other C—H bond absorbs in the 995–985 cm^{-1} region. These two types of terminal alkenes can therefore be distinguished.

Both trans- and cis-substituted alkenes as well as trisubstituted alkenes each have one C—H out-of-plane bending mode. However, the absorption for the cis isomer is often ambiguous.

Table 15.5
Out-of-Plane C—H Bending of Alkenes

Compound	*Absorption*
	995–985 cm^{-1} 910–905 cm^{-1}
	895–885 cm^{-1}
	980–965 cm^{-1}
	690 (?) cm^{-1}
	840–790 cm^{-1}

Aromatic Compounds

The absorptions due to the out-of-plane bending of aromatic compounds depend on the substitution pattern. The C—H bonds on adjacent carbon atoms bend out of the plane of the aromatic ring in unison. Table 15.6 lists absorptions as a function of the number of adjacent hydrogen atoms.

Table 15.6
Out-of-Plane Bending of Aromatic Ring Hydrogen Atoms

Number of adjacent hydrogen atoms	*Wavenumber (cm^{-1})*
5	770–730
4	770–735
3	810–750
2	860–800
1	900–860

In addition to the absorptions that depend on the number of adjacent hydrogen atoms, another absorption occurs in the 745–690 cm^{-1} region for monosubstituted, 1,3-disubstituted, and 1,2,3-trisubstituted compounds. For *m*-xylene, this absorption occurs at 690 cm^{-1}. Absorptions also occur at 770 cm^{-1} and 880 cm^{-1} for the three adjacent hydrogen atoms at the C-4, C-5, and C-6 atoms and for the single C—H bond at the C-2 atom, respectively.

Problem 15.6

Draw the structures of the two dehydration products of 1-methylcyclohexanol and describe how infrared spectroscopy can be used to establish their structures.

Problem 15.7

Describe how 3-methylpyridine and 4-methylpyridine can be distinguished by infrared spectroscopy.

Sample Solution

3-Methylpyridine has one hydrogen atom at the C-2 position that has no adjacent C—H bonds. It also has three adjacent hydrogen atoms at the C-4, C-5, and C-6 positions. Thus this compound should have two out-of-plane bending absorptions similar to that of a meta-

disubstituted benzene compound. 4-Methylpyridine has two adjacent hydrogen atoms at the C-2 and C-3 positions and an equivalent set at the C-5 and C-6 positions. Only one out-of-plane absorption similar to that of a para-disubstituted benzene compound should be seen.

15.10 Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance spectroscopy provides the most information about the structure of a compound because it directly probes the nuclei of the entire carbon framework or the nuclei of the bonded hydrogen atoms. The method depends on a property called nuclear spin. Nuclear spin varies from element to element and among isotopes of an element. Those nuclei with no nuclear spin, such as ^{12}C and ^{16}O, are NMR inactive, as are all nuclei with both an even number of protons and an even number of neutrons. A nucleus with a spin is characterized by a spin quantum number that may either be a half-integer or an integer. Hydrogen has a spin number of $\frac{1}{2}$. Like the electron, the hydrogen atom can be detected with two different spin orientations in a magnetic field. The isotope deuterium, with a spin number of 1, can be detected with three different spin orientations. In this chapter we will only consider the ^{1}H isotope.

Different spin numbers also occur with carbon isotopes. Most carbon atoms in organic molecules are ^{12}C and cannot be detected by NMR spectroscopy. Their locations in a structure must therefore be inferred from the NMR of the hydrogen atoms bonded to them. However, about 1% of carbon atoms are ^{13}C, detectable by NMR. Although ^{13}C is somewhat more difficult to detect experimentally, NMR studies of this isotope in organic compounds provide confirmatory support for a structure proposed using NMR of hydrogen atoms. Because some carbon atoms are not directly bonded to hydrogen atoms, the direct detection of carbon using ^{13}C NMR spectroscopy is important. For example, the presence of a carbonyl group may be inferred from the behavior of a hydrogen atom bonded to an adjacent carbon atom. However, ^{13}C NMR spectroscopy "sees" the carbonyl carbon atom itself.

Detection of Nuclear Spin

The ^{1}H nucleus spins around its axis in either of two directions described as clockwise and counterclockwise. Because the nucleus carries a charge, a magnetic moment results from the spinning nucleus. Consequently, hydrogen nuclei are tiny magnets with two possible orientations in the presence of an external magnetic field. They may be aligned with the external magnetic field—the lower energy state—or against it. If a spinning hydrogen nucleus with its magnetic moment aligned with the external field is irradiated with electromagnetic radiation in the radio-frequency range, it absorbs energy and "flips" to spin in the opposite direction (Figure 15.10). Hence, absorption of energy results in a higher energy state for the hydrogen nucleus.

The energy associated with electromagnetic radiation in the radio-frequency range is very small. For example, 60 MHz corresponds to approximately 0.0238 J $mole^{-1}$. The radio frequency required to change the spin of a nucleus such as hydrogen depends on the strength of the external magnetic field. A field strength of approximately 14,000 gauss increases the energy difference between the two spin states by 0.0238 J $mole^{-1}$. The radio frequency required to change spin states is therefore 60 MHz. Increasing the strength of the external magnetic field increases the energy difference between the two spin states. An NMR spectrometer with an 84,000-gauss field requires a radio frequency of 360 MHz to change the spin state of hydrogen atoms.

An NMR experiment can be done by selecting a magnetic field strength and

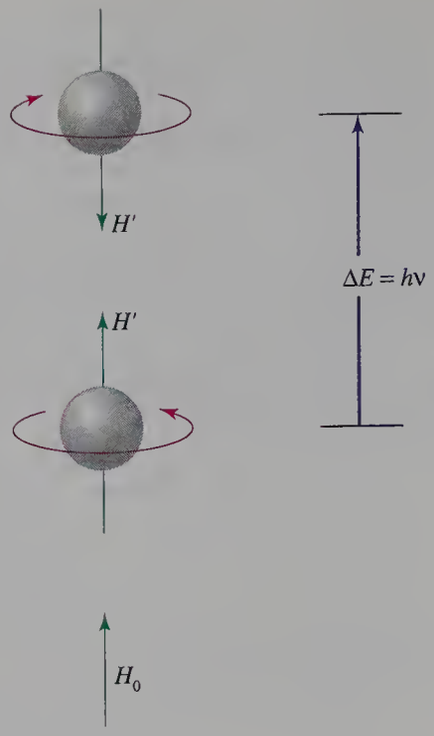


FIGURE 15.10
Absorption of Electromagnetic Radiation by a Nucleus
When the magnetic moment of a spinning nucleus (H') is aligned with the magnetic field of an NMR spectrometer, (H_0) low energy results. Absorption of specific frequency causes a change in the spin of the nucleus and results in a magnetic moment opposed to the magnetic field of the instrument.

then varying the radio-frequency radiation to find the proper frequency to make the hydrogen atom "flip." Alternatively, a constant radio frequency may be used while the magnetic field strength is varied to cause a difference in the energy of the nuclei corresponding to the energy of the electromagnetic radiation. In practice, this latter technique is the easier to use.

15.11 Chemical Shift

Using a constant radio frequency, the magnetic field strength required to "flip" the spin of various hydrogen atoms within a molecule depends upon the environment of the hydrogen atom. If all hydrogen atoms absorbed the same electromagnetic radiation in an NMR experiment at the same magnetic field strength, then only a single absorption would be observed. As a consequence, we would only know that the molecule contained hydrogen atoms.

The hydrogen nuclei in organic molecules are surrounded by electrons. The circulation of electrons around a nucleus sets up a small, induced, local magnetic field opposite to the applied external magnetic field (Figure 15.11). The local field affects the magnetic environment of the hydrogen nuclei. When a local field opposes the external magnetic field, we say that the nucleus is **shielded**. The effective field "felt" by the nucleus is the applied magnetic field minus the local magnetic field generated by the electrons.

$$H_{\text{effective}} = H_{\text{applied}} - H_{\text{local}}$$

The Delta Scale

Local magnetic fields result from the movement of electrons. They differ throughout the molecule because the number and types of bonds differ. As a result, the degree of shielding of each hydrogen nucleus is unique, and distinct resonances called **chemi-**

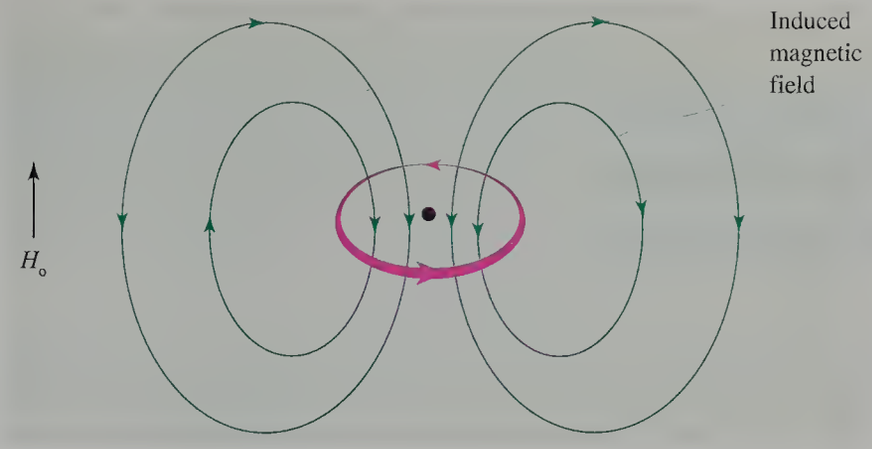


FIGURE 15.11 Shielding of a Nucleus by Electrons
The magnetic field induces electron circulation about the nucleus of the hydrogen atom. The magnetic field induced by the electron is opposed to the magnetic field of the instrument.

cal shifts occur for each structurally nonequivalent hydrogen atom in a molecule. Chemical shifts are measured relative to a reference compound—usually tetramethylsilane in the case of hydrogen atoms. At a constant radio frequency, the external magnetic field required to "flip" the spin of a hydrogen atom is larger for the more shielded nucleus. The hydrogen atoms of tetramethylsilane are more shielded than hydrogen atoms bonded to carbon atoms bearing electronegative atoms.

The strengths of the local magnetic fields for various hydrogen atoms are about 10^{-6} times that of the applied magnetic field. Thus, the magnetic fields required to flip various structurally different hydrogen nuclei in a molecule differ by parts per million (ppm). Rather than using absolute values of the field strength, chemists use a relative scale termed the **delta scale**. An NMR chart is labeled on the horizontal axis with the delta scale in which one delta unit (δ) is 1 ppm of the magnetic field used. The mathematical basis for the delta scale is

$$\delta = \frac{\text{chemical shift (Hz)}}{\text{frequency of NMR in Hz}} = \frac{V_{\text{sample}} - V_{\text{TMS}}}{V_0} \times 10^6$$

The equation is usually written using hertz, a unit of frequency, rather than gauss, a magnetic field unit. The numerator gives the differences between the resonance position of hydrogen atoms in the sample and those in tetramethylsilane (TMS). This value is about 10^{-6} that of the frequency of the NMR spectrometer. Hence, the quotient is multiplied by 10^6 to obtain delta units.

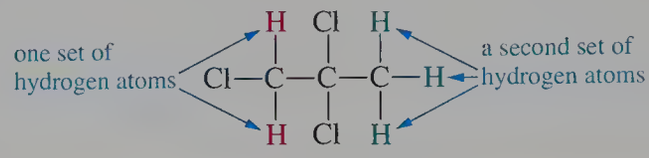
Effect of Operating Radio Frequency

The difference between the resonances of a sample and a reference varies directly with the operating frequency of the NMR spectrometer. For example, if the resonance of a nucleus in a sample differs from the resonance of the reference nucleus by 120 Hz for an NMR spectrometer operating at 60 MHz, the delta value is 2. If the operating frequency of another NMR spectrometer is 360 MHz, we find that the difference between the resonances of the sample and the reference is 720 Hz. The delta value is still 2. The delta scale is therefore a chemical shift scale that is independent of the operating frequency (and field) of the instrument.

The chemical shift of the methyl hydrogen atoms of tetramethylsilane, $(CH_3)_4Si$, which is used as a reference, is defined as 0 δ. By convention, an absorption that occurs at lower field than tetramethylsilane (TMS) appears to the left of the TMS absorption and is assigned a positive δ value. The scale is labeled with δ units or ppm increasing from right to left with 0 δ for TMS on the right.

15.12 Detecting Sets of Nonequivalent Hydrogen Atoms

When we examine the NMR spectrum, we can tell how many sets of structurally equivalent hydrogen atoms are contained in a molecule. Consider the NMR spectrum of 1,2,2-trichloropropane shown in Figure 15.12. The spectrum consists of peaks at 2.2 and 4.0 δ. There are two different sets of hydrogen atoms in 1,2,2-trichloropropane. Each set of hydrogen atoms gives rise to one peak. The reasons for the specific assignment of the individual resonances to each type of hydrogen are outlined in Section 15.13.



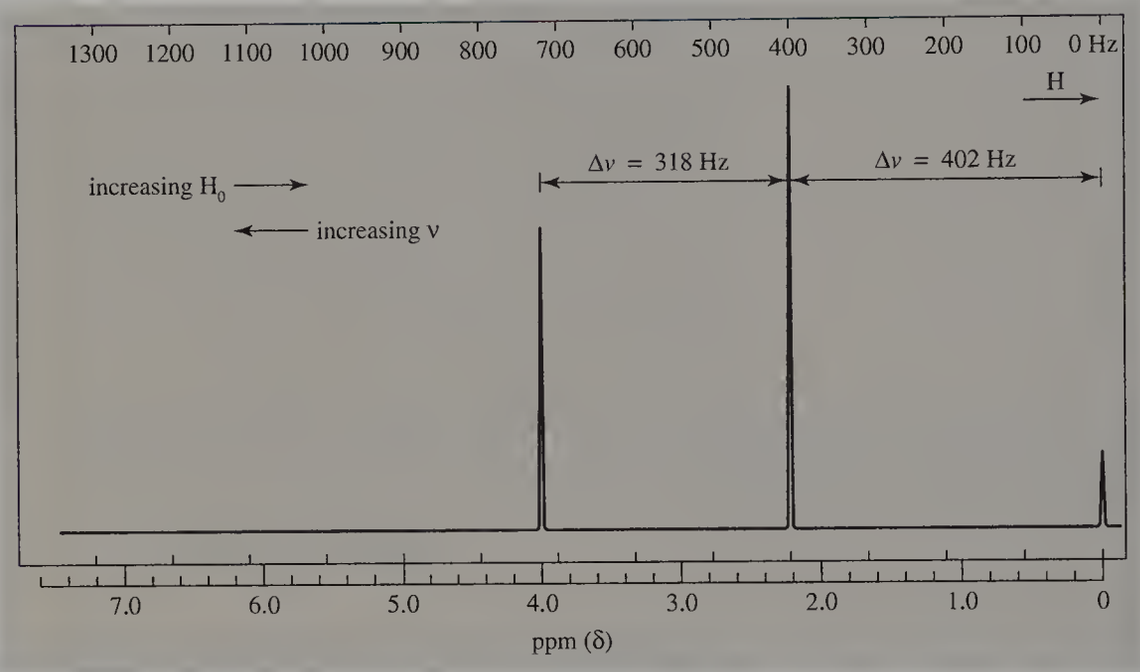
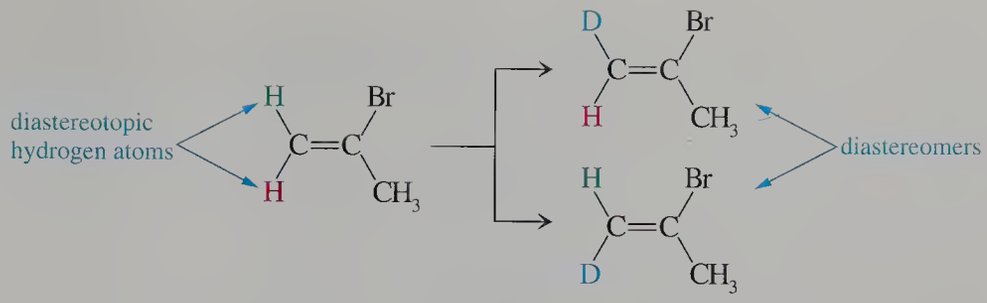


FIGURE 15.12 NMR Spectrum of 1,2,2-Trichloropropane
The three equivalent hydrogen atoms bonded to the C-3 atom absorb about 2.2 δ. The two equivalent hydrogen atoms bonded to the C-1 atom absorb at 4.0 δ.

We can deduce the structure of the compound from its NMR spectrum because the number of sets of equivalent hydrogen atoms in a molecule and the number of resonances in its spectrum are related. To correctly assign a structure based on a spectrum, we must understand the concept of equivalence. We are reasonably adept at determining equivalence or nonequivalence of hydrogen atoms from our experience of looking at structural formulas. The two hydrogen atoms bonded in a methylene unit of 1,2,2-trichloropropane are equivalent, as are the three hydrogen atoms of the methyl group of the same compound.

Diastereotopic and Enantiotopic Hydrogen Atoms

Some hydrogen atoms may appear to be equivalent because they are bonded to the same carbon atom, yet they are not equivalent. Such hydrogen atoms are usually diastereotopic (Section 9.12) and have different chemical shifts. We can determine if two hydrogen atoms are diastereotopic by replacing either of the atoms by a deuterium atom. We recall that this test was applied in Section 9.12. Consider, for example, the two diastereotopic geminal hydrogen atoms of 2-bromopropene.



Replacing the hydrogen atom cis to the bromine atom gives a different diastereomer from replacing the hydrogen atom cis to the methyl group. The hydrogen atoms are diastereotopic because their environments differ. As a result, their chemical shifts differ. The hydrogen atom cis to the bromine atom appears at 5.3 δ. The other hydrogen atom bonded to the same carbon atom has 5.5 δ. The difference in chemical shift is small. Some diastereotopic hydrogen atoms "accidentally" have the same chemical shift or differ too little to detect experimentally. Nevertheless, the hydrogen atoms are still diastereotopic. We must recognize diastereotopic hydrogen atoms to properly interpret an NMR spectrum.

We recall that some protons are enantiotopic (Section 9.12). The methylene protons of 1,2,2-trichloropropane are enantiotopic. Replacing one hydrogen atom with deuterium gives a chiral compound, the enantiomer of the compound formed by replacing the other hydrogen atom with deuterium. As seen in Figure 15.12, enantiotopic hydrogen atoms have the same chemical shift.

Problem 15.8

The chemical shift of methylene chloride as measured with a 60-MHz instrument is 5.30 δ. What is the separation in Hz from TMS? What is the δ value as measured with a 200-MHz instrument?

Problem 15.9

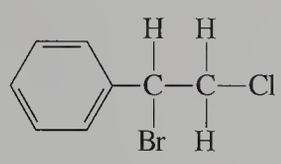
How many sets of nonequivalent hydrogen atoms are contained in each of the following ketones?

(a) $CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_2-CH_3$ (b) $CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_3$

(c) $CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{CH}-CH_3$

Problem 15.10

Classify the two hydrogen atoms bonded to the chlorine-bonded carbon atom of the following compound.



Sample Solution

The benzylic carbon atom is a chiral center. Thus, the two hydrogen atoms bonded to the adjacent carbon atom are diastereotopic. These hydrogen atoms should not have the same chemical shift.

15.13 Structural Effects on Chemical Shift

The various hydrogen resonances appear between 0 and 10 δ for most organic molecules. This range is conveniently divided into regions that reflect certain structural characteristics. The electronegativity of atoms directly bonded to the carbon bearing the hydrogen atom and a "special" magnetic field generated by π systems both affect chemical shifts.

Electronegativity Effects

As noted above, electronegative atoms, such as chlorine, deshield the hydrogen atom of a Cl—C—H unit. The degree of deshielding, as measured by a shift to lower field (larger δ value), increases with the electronegativity of the atom. The trend within the group of halogens is shown below.

	CH_3I	CH_3Br	CH_3Cl	CH_3F
chemical shift δ:	2.1	2.7	3.1	4.3

A similar effect of the electronegativity of the atom on the chemical shift occurs within a row of the periodic table.

	CH_3CH_3	$(CH_3)_3N$	$(CH_3)_2O$	CH_3F
chemical shift δ:	0.9	2.2	3.1	4.3

The effects of several groups bonded to a common atom are cumulative, and often additive. For example, the chlorinated methanes show a nearly linear shift to lower field with increased numbers of chlorine atoms.

	CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$
chemical shift δ:	0.9	3.1	5.3	7.3

Effect of π Electrons

Hydrogen atoms bonded to sp^2-hybridized carbon atoms absorb energy at lower fields than hydrogen atoms bonded to saturated sp^3-hybridized carbon atoms. For example, hydrogen atoms in alkenes absorb energy in the 5–6 δ region. The hydrogen atoms bonded to an aromatic ring absorb energy in the 7–8 δ region. The reason for these substantial shifts to low field is related to the magnetic fields associated with the motion of electrons in the molecular orbitals of these compounds. Figure 15.13 shows the magnetic field generated by circulating π electrons in benzene. A deshielding effect is "felt" by any hydrogen atoms located in the same plane as the benzene ring. A related phenomenon also affects the hydrogen atoms bonded to the sp^2-hybridized carbon atoms of alkenes.

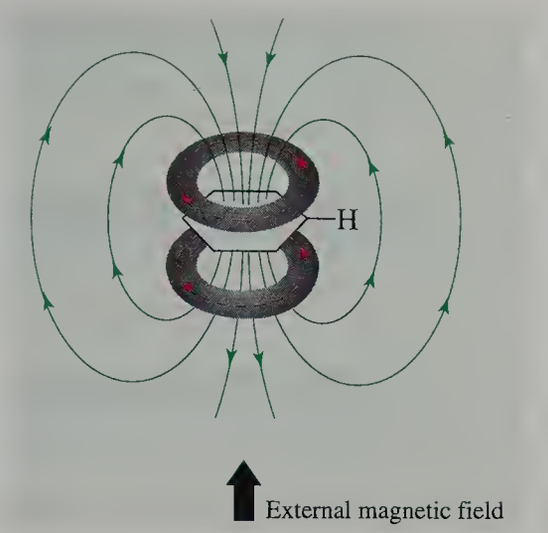


FIGURE 15.13 Effect of π Electrons on Chemical Shift of Benzene
The circulation of the π electrons of benzene results in a substantial current which induces a local magnetic field. The induced magnetic field reinforces the external magnetic field. Thus, a lower magnetic field is required to change the spin orientation of the hydrogen atoms that are coplanar with the aromatic ring.

The deshielding effect of the π systems on nearby hydrogen atoms falls off with distance. For example, benzylic and allylic hydrogen atoms are deshielded, but less so than hydrogen atoms bonded directly to the sp^2-hybridized atom. The resonances of the allylic and benzylic methyl groups occur at approximately 2.0 δ and 2.5 δ, respectively.

Use of Empirical Correlations

The position of absorption for hydrogen atoms bonded to a variety of functional groups such as carbonyl groups can be explained. However, such theoretical treatments are not required to use NMR data to determine structure. It is only necessary to accumulate data from a few model compounds to identify group structural contributions to the chemical shift. Groups such as halogen atoms, carbonyl carbon atoms, and aromatic rings affect chemical shifts, and several features can simultaneously influence the chemical shift. The effects are cumulative, but not necessarily additive. Table 15.7 lists examples of group contributions to chemical shifts.

Table 15.7
Chemical Shifts of Hydrogen Atoms

Partial structural formula	*Chemical shift (ppm)*	*Partial structural formula*	*Chemical shift (ppm)*
$-CH_3$	0.7–1.3	$Br-\underset{}{\overset{}{C}}-H$	2.5–4.0
$-CH_2-$	1.2–1.4		
$-\underset{}{\overset{}{C}}-H$	1.4–1.7	$I-\underset{}{\overset{}{C}}-H$	2.0–4.0
$C=C-CH_3$	1.6–1.9	$-O-\underset{}{\overset{}{C}}-H$	3.3–4.0
$-\overset{O}{\overset{\|\|}{C}}-CH_3$	2.1–2.4	$C=C-H$	5.0–6.5
$-C\equiv C-H$	2.5–2.7	$Ar-H$	6.5–8.0
$Cl-\underset{}{\overset{}{C}}-H$	3.0–4.0	$-\overset{O}{\overset{\|\|}{C}}-H$	9.7–10.0

Problem 15.11

Explain why the chemical shift of the hydrogen atoms of $(CH_3)_4Sn$ appears at higher field than TMS.

Problem 15.12

1,3-Dichlorobutane has resonances 1.60, 2.15, 3.72, and 4.27 ppm below TMS. Assign each resonance to the individual hydrogen atoms.

Problem 15.13

Estimate the δ values of 3,5-dibromopyridine.

15.14 Relative Peak Areas and Proton Counting

The set of hydrogen atoms bonded to the C-1 atom of 1,2,2-trichloropropane has an absorption at 4.0 δ, and the set of hydrogen atoms bonded to the C-3 atom has its absorption at 2.2 δ. This assignment can be made because hydrogen atoms bonded to a carbon atom that is also bonded to an electronegative atom absorb energy at a lower field. However, "proton counting" is another method to confirm this assignment. The area of each resonance is proportional to the relative numbers of hydrogen atoms of each kind.

The relative area of a resonance is obtained from an electronic integrator used after the spectrum has been recorded. The integrated area is equal to the vertical displacement of a "stair step" superimposed on the resonance peak. These vertical distances have ratios equal to the ratios of the number of hydrogen atoms. For example, the ratio of the integrated intensities of the two resonances of 1,2,2-trichloropropane is 3:2 (Figure 15.14).

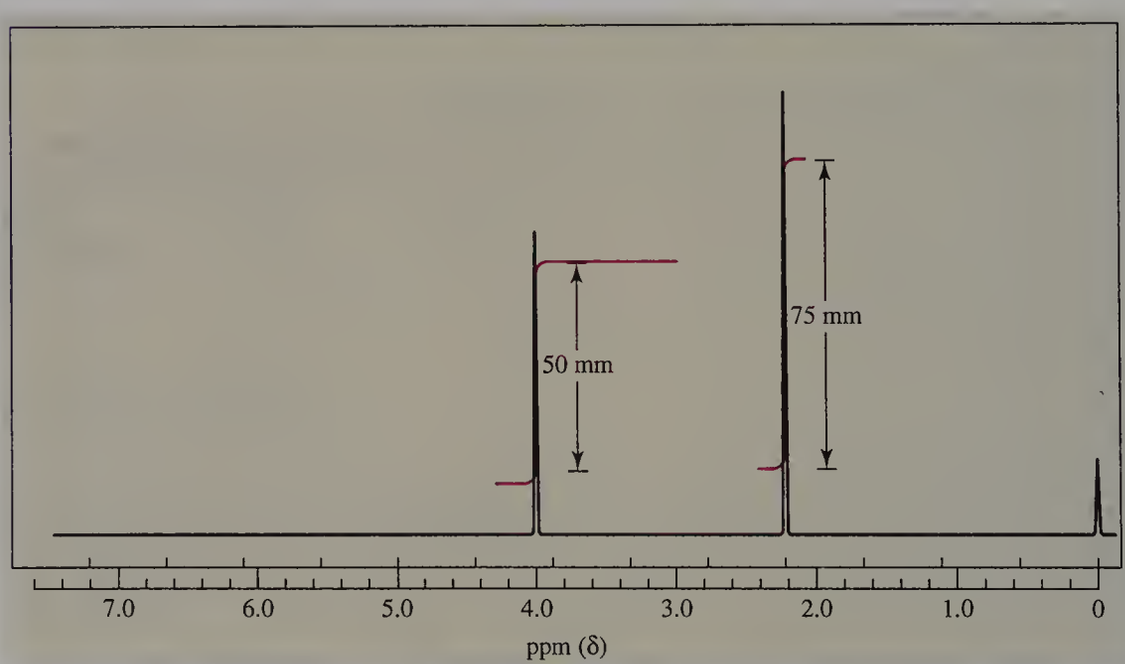


FIGURE 15.14
Integrated Intensities of an NMR Spectrum
The area of each resonance is proportional to the number of hydrogen atoms. The vertical distances of the "stair steps" shown measure those areas. The ratio of 75 to 50 mm is 3:2, which corresponds to the numbers of hydrogen atoms bonded to the C-3 and C-1 atoms, respectively, in 1,2,2-trichloropropane.

Problem 15.14

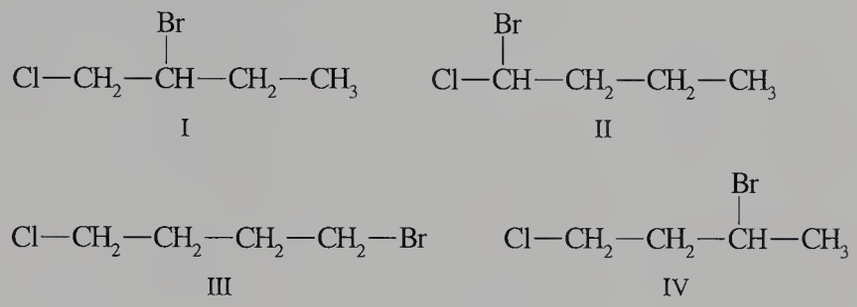
What are the relative intensities of the absorptions of each of the following compounds?

(a) 1,2-dichloro-2-methylpropane (b) 1-bromo-2,2-dimethylpropane

(c) 1,4-cyclohexadiene

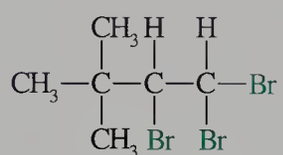
Problem 15.15

Which of the following isomers can be distinguished from the others solely on the basis of the number of NMR absorptions and their intensities?



15.15 Spin–Spin Splitting

In 1,2,2-trichloropropane, each of the two sets of hydrogen atoms produces a single peak. Now consider the spectrum of 1,1,2-tribromo-3,3-dimethylbutane (Figure 15.15).



1,1,2-tribromo-3,3-dimethylbutane

The nine equivalent hydrogen atoms of the three equivalent methyl groups give rise to the intense peak at 1.2 δ. The hydrogen atoms bonded to the C-1 and C-2 atoms are nonequivalent. The resonance of the hydrogen atom at the C-1 atom is located at 6.4 δ because two electronegative bromine atoms are bonded to that carbon atom. The resonance of the hydrogen atom at the C-2 atom is located at 4.4 δ because only one bromine atom is bonded to the carbon atom. The intensities of the absorptions and the chemical shifts of the hydrogen atoms appear as predicted from molecular structure.

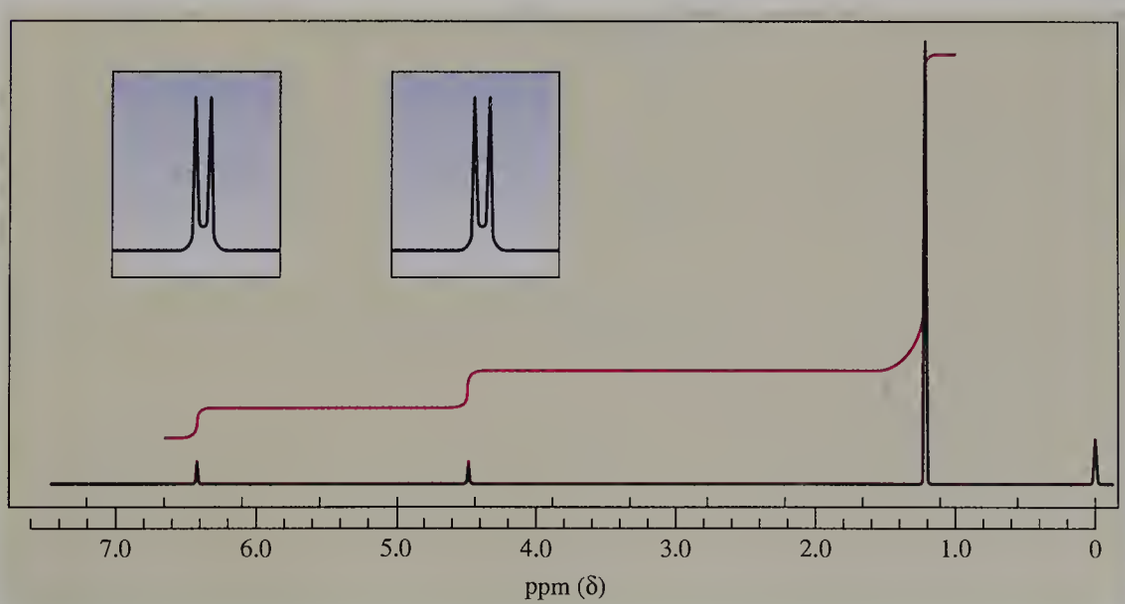


FIGURE 15.15
NMR Spectrum of 1,1,2-Tribromo-3,3-dimethylbutane
The inserts show the doublets for the resonances at 4.4 and 6.4 δ. The total integrated area of each doublet is proportional to one hydrogen atom.

Both the 4.4 δ and 6.4 δ absorptions of 1,1,2-tribromo-3,3-dimethylbutane are "split", as shown in the inserts containing expanded representations of the resonances. Each area contains two peaks called **doublets**. Multiple peaks are common in NMR spectroscopy. Other common multiplets include **triplets** and **quartets**, resonances that are split into three and four peaks, respectively. We will see that the number of peaks, or multiplicity, of a resonance helps us to determine structure by NMR spectroscopy.

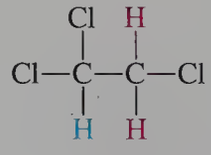
Multiple absorptions for a set of equivalent hydrogen atoms is known as **spin-spin splitting**. The splitting results from the interaction of the nuclear spin(s) of one or more nearby "neighboring" hydrogen atom(s) with a set of equivalent hydrogen atoms. The small magnetic field of nearby hydrogen atoms affects the magnetic field felt by other hydrogen atoms. This interaction depends only on the two interacting nuclei and the network of electrons between them. Consequently, the magnitude of the interaction is independent of the field strength of the NMR spectrometer. Spin-spin splitting occurs between geminal or vicinal nonequivalent nuclei. The coupling interaction is usually restricted to two or three bonds. Exceptions are noted in Section 15.16.

The resonance for the nine methyl hydrogen atoms of 1,1,2-tribromo-3,3-dimethylbutane is not "split" because the neighboring quaternary carbon atom has no hydrogen atoms. This is not the case for the hydrogen atom on the C-1 atom of 1,1,2-tribromo-3,3-dimethylbutane. There is a vicinal hydrogen atom at the C-2 atom that can spin in either of two directions. In those molecules, in which the hydrogen atom at the C-2 atom is spinning clockwise, the hydrogen atom at the C-1 atom experiences a small magnetic field that differs from that in molecules where the hydrogen atom at the C-1 atom is spinning counterclockwise. As a result, the C-1 hydrogen atoms in various molecules absorb electromagnetic radiation at two slightly different external magnetic fields. A doublet results. The same explanation accounts for the doublet for the hydrogen atom at the C-2 atom. In this case, the hydrogen atom at the C-1 atom is the neighboring atom, and its spin affects the magnetic field experienced by the hydrogen atom at the C-2 atom. Therefore, sets of hydrogen atoms on neighboring carbon atoms **couple** with each other. If hydrogen atom A couples and causes splitting of the resonance for hydrogen atom B, the resonance for hydrogen atom A is also split by hydrogen atom B. The spacing between adjacent peaks, expressed in Hz, is the **coupling constant** (J). Subscript descriptions are often used to designate coupling constants as in J_{vic} for vicinally coupled hydrogen atoms or J_{trans} for hydrogen atoms located trans to each other in an alkene.

Characteristics of Multiplets

A set of one or more hydrogen atoms with n equivalent neighboring hydrogen atoms has $n + 1$ peaks in the NMR spectrum. The appearance of multiplets resulting from $n = 1$ through $n = 4$ neighboring hydrogen atoms is shown in Figure 15.16 for some common structures. The areas of the component peaks of a doublet are equal, but the areas of the component peaks of other multiplets are not.

To understand the relative peak areas of multiplets resulting from more than one neighboring hydrogen atom, let's consider the spectrum of 1,1,2-trichloroethane (Figure 15.17).



1, 1, 2-trichloroethane

FIGURE 15.16 Common NMR Multiplets
The resonance of a common single hydrogen atom is shown. The number of equivalent neighboring hydrogen atoms is responsible for the multiplicity of the resonance.

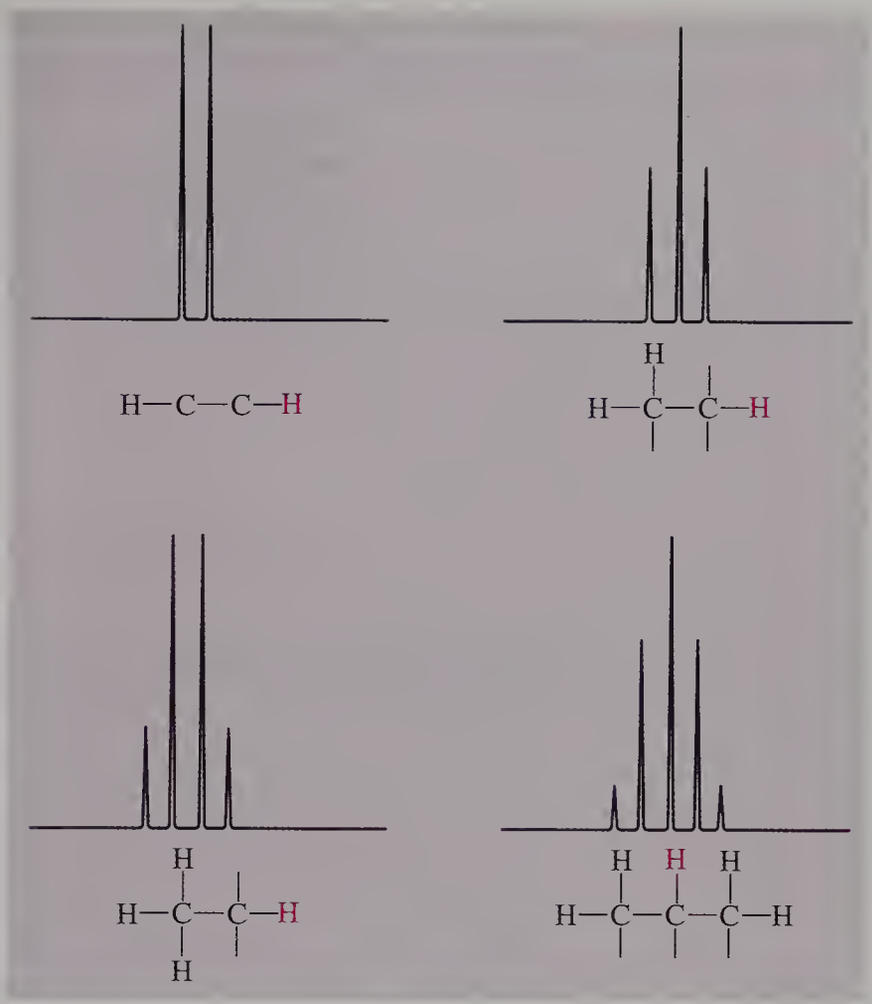
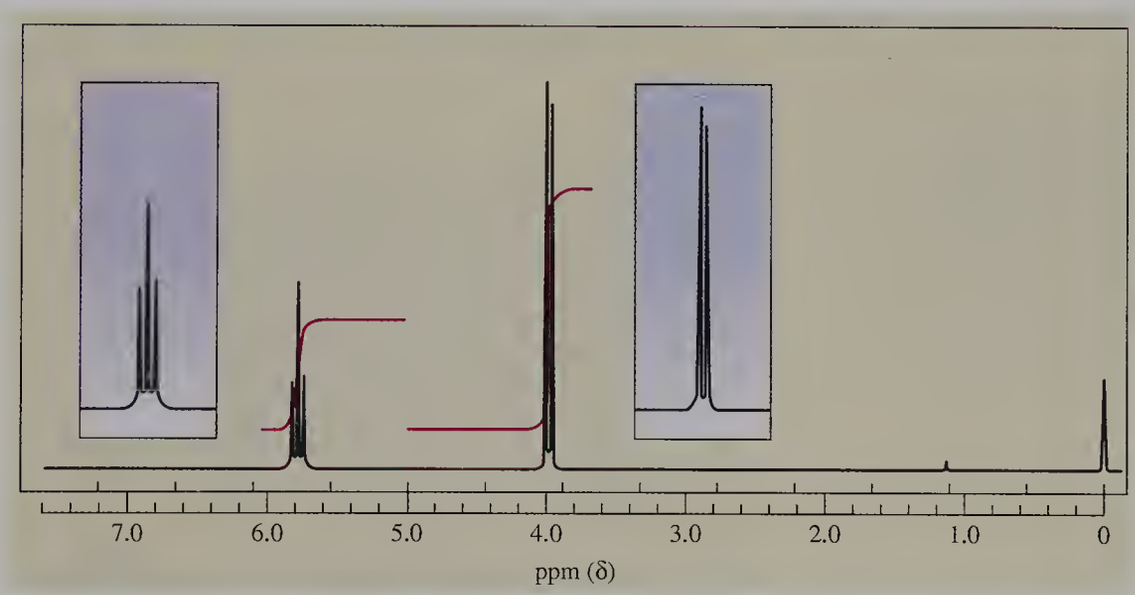


FIGURE 15.17 NMR Spectrum of 1,1,2-Trichloroethane
The inserts show the doublet for the 4.0 δ resonance of the hydrogen atoms bonded to the C-2 atom and the triplet at 5.7 δ of the hydrogen atom bonded to the C-1 atom. Note that the integrated intensities of the 4.0 and 5.7 δ resonances are in ratio of 2:1.



The doublet near 4 δ corresponds to the two hydrogen atoms bonded to the C-2 atom. These hydrogen atoms have one neighboring hydrogen atom, which can spin in either a clockwise or clockwise direction, which we can designate as α and β. As a consequence, the C-2 hydrogen atoms in various molecules experience two different magnetic fields, resulting in a doublet absorption. Now let's consider the triplet resonance for the C-1 hydrogen atom. The spins of the neighboring two hydrogen atoms at the C-2 atom can be αα, αβ, βα, and ββ. Because the magnetic fields generated by either αβ or βα sets of spins are equivalent, the hydrogen atom at the C-1 atom experiences three different magnetic fields in the ratio of 1:2:1. This ratio is the same as the ratio

of the observed triplet. Extension of the possible combinations of spins of n neighboring equivalent hydrogen atom accounts for the area ratios listed in Table 15.8.

Table 15.8
Number of Peaks of Multiplets and Area Ratios

Number of equivalent adjacent hydrogens	*Total number of peaks*	*Area ratios*
0	1	1
1	2	1:1
2	3	1:2:1
3	4	1:3:3:1
4	5	1:4:6:4:1
5	6	1:5:10:10:5:1
6	7	1:6:15:20:15:6:1

Splitting Patterns of the Ethyl Group and of the Isopropyl Group

Some splitting patterns are easily recognizable. For example, two coupled hydrogen atoms appear as two doublets. The separations of the components of each doublet are equal; that is, the coupling of each hydrogen atom with the other is the same.

Now let's consider systems containing many more hydrogen atoms. The analysis of an apparently complex spectrum is often made easier if we recognize characteristic patterns associated with a structural unit. One such pattern is due to the ethyl group (CH_3CH_2—). The pattern consists of a high-field triplet corresponding to the three hydrogen atoms of the methyl group. The resonance of the methylene group is at lower field because it is invariably bonded to a deshielding group. This group is a quartet with an integrated intensity of 2. Thus, the triplet–quartet pattern is characteristic of an ethyl group. The spectrum of ethyl iodide illustrates this pattern (Figure 15.18).

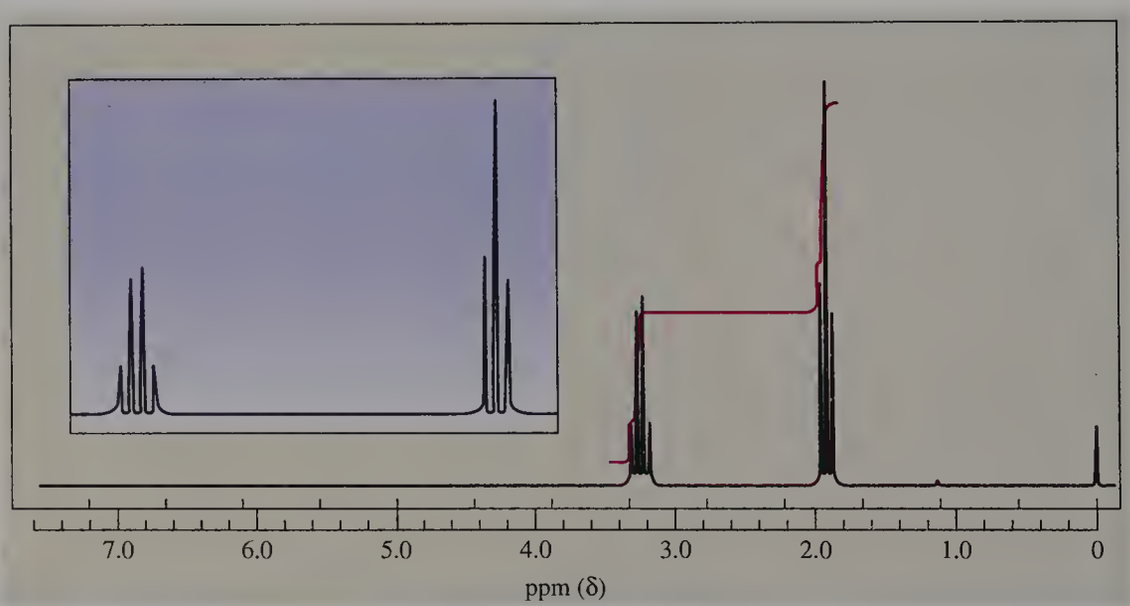


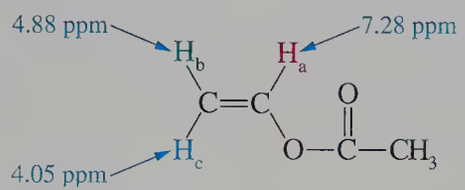
FIGURE 15.18
Characteristic Splitting Pattern of an Ethyl Group
The ethyl group consists of a three-proton triplet and a two-proton quartet.

Another common pattern occurs with isopropyl groups, $(CH_3)_2CH$—. The six equivalent methyl hydrogen atoms are split into a doublet by the methine proton. The methine hydrogen atom is split by all six of the methyl hydrogen atoms, and a heptet results. The doublet–heptet pattern identifies an isopropyl group. However, the

total intensity of the heptet is only one sixth that of the total intensity of the doublet. The entire heptet is not always visible because the outermost lines of the heptet have such a small intensity. As a result, the methine absorption may appear as a quintet.

Multiple Splitting: The Vinyl Group

Multiple splitting of a hydrogen atom occurs when it has more than one type of neighboring hydrogen atom. The vinyl group is an example.



The alkene hydrogen atoms have different chemical shifts. The hydrogen bonded to the carbon bonded to an oxygen atom (H_a) appears at lowest field. The assignment of the chemical shifts of H_b and H_c is based on their individual coupling patterns.

H_a, H_b, and H_c are all coupled and show the effects of interaction with each other. Thus, the resonance of each hydrogen atom is split separately by the other two. The magnitude of each coupling constant is characteristic of vinyl systems. Geminal coupling of the hydrogen atoms of the CH_2 unit is the smallest with J_{gem} (1–2 Hz). Vicinal couplings are larger, with J_{trans} (12–16 Hz) greater than J_{cis} (6–8 Hz). This relationship is further discussed in Section 15.16.

To analyze spectra with multiple coupling constants, we consider each hydrogen atom and split its resonance successively by each of the other hydrogen atoms coupled to it. This process leads to a **splitting diagram**. For the three-hydrogen vinyl system cited above, the H_a resonance is split into a doublet with J = 14 Hz by H_c, which is trans to it (Figure 15.19). Then each line of the doublet is further split into doublets with J = 7 Hz by H_b. A doublet of doublets results. Note that we could have constructed this splitting diagram by considering the coupling constants in reverse order. The result would be the same. However, it is usually simpler to apply the coupling constants in the order of decreasing value of J.

There is no doubt about the assignment of the doublet of doublets centered at 7.28 δ because the oxygen atom causes a substantial deshielding of this hydrogen atom. Now let's see how coupling constants are used to assign the chemical shifts of the remaining two vinyl protons.

The hydrogen atom labeled H_c shows the same large coupling constant as H_a because these atoms are situated trans to each other. The splitting of the resonance centered at 4.88 δ corresponds to J_{trans} (Figure 15.19). Each part of this doublet is further split into closely spaced doublets by the geminal hydrogen atom H_b (J_{gem} = 1.5 Hz). Thus, a second doublet of doublets results, but one of its two coupling constants is different than for the doublet of doublets of H_a.

Finally, the complete assignment of the vinyl resonances is confirmed by the splitting diagram of H_b (Figure 15.19). It has the same 7 Hz coupling constant associated with H_a because they are situated *cis* to each other. Each part of this doublet is further split into closely spaced doublets by the geminal hydrogen atom H_c. Yet another doublet of doublets results in the general area of that for H_c, but this one has evidence of J_{cis} rather than J_{trans}.

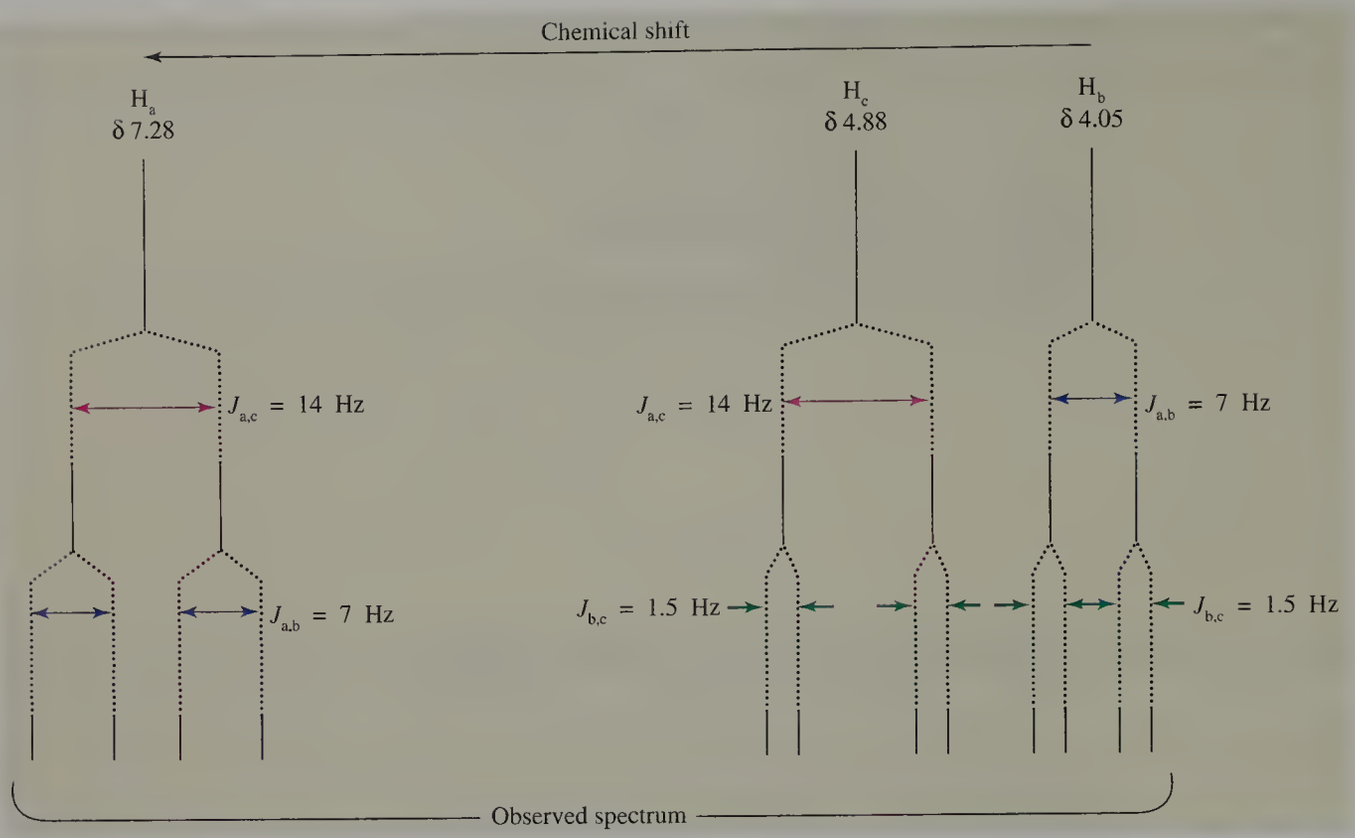


FIGURE 15.19 Splitting Pattern of Vinyl Group

Complex Splitting

The multiplicities and relative intensities of the components of multiplets are straightforward only if the magnitude of the coupling constant is small compared to the difference between the chemical shifts of the coupled protons. Such spectra are called "first order". In practice, the multiplicity "rules" are followed only if the ratio of the difference between chemical shifts (expressed in Hz) to the coupling constant is greater than 10.

$$\frac{\nu_{\text{sample}} - \nu_{\text{TMS}}}{J} = \frac{\Delta\nu}{J} > 10$$

If the ratio is smaller, the intensities of multiplet components change. For example, the intensities of the outermost peaks of two doublets of a H—C—C—H system decrease, and the intensities of the innermost peaks increase (Figure 15.20).

The changes in the intensity of a multiplet with a diminished ratio $\Delta\nu/J$ are commonly observed. However, it doesn't detract from the analysis of the spectrum and the establishment of a structure. As the ratio $\Delta\nu/J$ becomes smaller, the simple rules for predicting multiplicities do not apply. The resulting complex spectra are called "non-first order". They usually have many more peaks than predicted by the first order rules. The intensity and separation also have no obvious, simple relationship to each other. The analysis of the spectra of such compounds is beyond the scope of this text.

With the development of higher field NMR spectrometers, the spectra are more often first order. Higher field instruments produce higher radio frequencies to "flip" the nucleus. The chemical shift difference between two coupled hydrogen atoms expressed in ppm remains unchanged because $\Delta\nu$ is directly proportional to the magnetic field. However, the chemical shift difference corresponds to a large value expressed in Hz. Coupling constants are independent of field strength and remain constant. Hence, with higher field NMR spectrometers, the ratio $\Delta\nu/J$ increases, and a non-first order spectrum from a 60 MHz instrument may become a first order spectrum on a 360-MHz instrument.

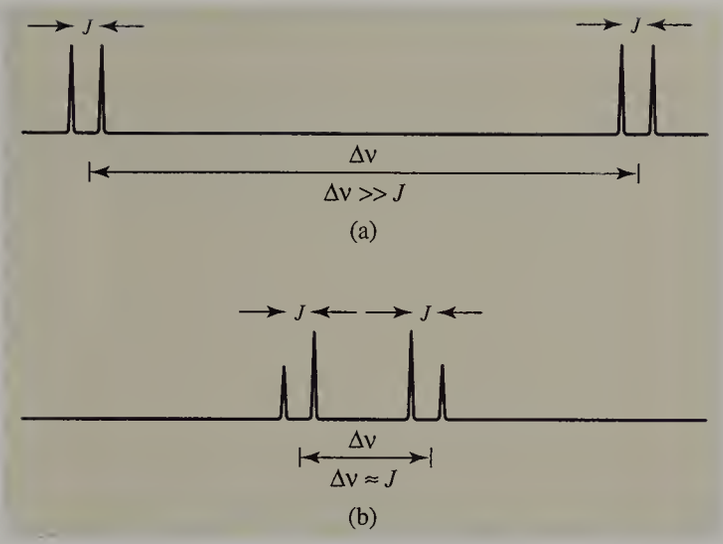


FIGURE 15.20 Effect of Chemical Shift and Coupling Constant on Spectra
The change from a first order to a non-first order spectrum is illustrated using a constant J (Hz) and hypothetical hydrogen atoms. The intensities of the components of the first order spectrum given in (a) are equal. The non-first order spectrum given in (b) has doublets whose components have changed to increase the intensity of the inner peaks and to decrease the intensity of the outer peaks.

Unfortunately, high-field NMR spectrometers are expensive and difficult to maintain. As a result, they are not widely available. Nevertheless, as with any developing technology, they are appearing in increasing numbers each year.

Problem 15.16

Describe the NMR spectrum of 1,3-dichloropropane.

Sample Solution

The methylene protons of the C-1 and C-3 atoms are equivalent and appear in the 3–4 δ region with a total intensity of 4. The methylene protons of the C-2 atom should appear at higher field with intensity 2. The low-field resonance should be a triplet because the protons at either the C-1 or C-3 atom are coupled with the two protons at C-2. The high-field resonance should be a quintet because the C-2 methylene protons are coupled to a total of four equivalent protons at C-1 and C-3.

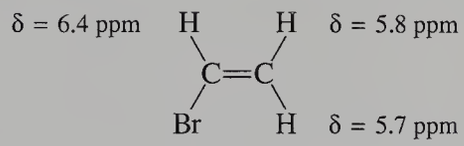
Problem 15.17

Describe the NMR spectrum of each of the following compounds.

(a) 2-chloropropane
(b) 1,1,1,2-tetrachloropropane
(c) 2,2-dibromobutane
(d) 1-bromo-1-chloroethene

Problem 15.18

Based on the indicated chemical shifts of 1-bromoethene, determine whether the spectrum of the compound obtained at 100 MHz is first order.

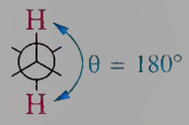


15.16 Structural Effects on Coupling Constants

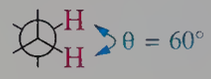
The coupling of two nuclei results from an interaction passed through the network of bonding electrons. This interaction is not like the flow of electricity though a wire. Instead, an orientation effect provides information about the geometry of the coupled nuclei in space. A few of the more important, well-established stereochemical contributions to the coupling constants are outlined below.

Saturated Compounds and Dihedral Angle

The stereochemistry of some saturated cyclic compounds can be established by determining some of the vicinal coupling constants. The value of J for vicinal hydrogen atoms depends on their dihedral angle, θ. We recall that trans periplanar arrangements have $\theta = 180°$, and gauche arrangements have $\theta = 60°$.



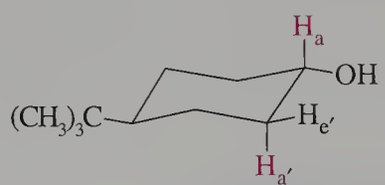
trans periplanar



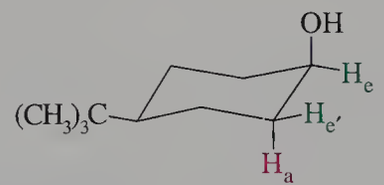
gauche

A theoretical relationship between the vicinal coupling constant and the dihedral angle, as predicted by M. Karplus, has been verified experimentally. The coupling constant maxima are for $\theta = 180°$ and $\theta = 0°$, with $J_{180°} > J_{0°}$. For $\theta = 90°$, the coupling constant is zero. For $\theta = 60°$, the coupling constant is 3–4 Hz.

Consider the two isomeric 4-*tert*-butylcyclohexanols. The trans isomer has an equatorial hydroxyl group. Thus, the hydrogen atom at C-1 is axial. It has a large coupling constant to the axial hydrogen atoms at C-2 and C-6 because $\theta = 180°$. It also is coupled to equatorial hydrogen atoms at C-2 and C-6 with $\theta = 60°$. The cis isomer has an equatorial hydrogen atom at C-1. It is coupled to axial and equatorial hydrogen atoms at C-2 and C-6. The dihedral angles are 60° for both sets of interacting protons. The sets of coupling constants for the cis isomer are therefore smaller than for the trans isomer.



$J_{aa'} = 11.1$ Hz
$J_{ae'} = 4.3$ Hz
trans-4-*tert*-butylcyclohexanol



$J_{ee'} = 2.7$ Hz
$J_{ea} = 3.0$ Hz
cis-4-*tert*-butylcyclohexanol

Geometric Isomerism in Alkenes

Although not directly related to the Karplus correlation cited above for saturated compounds, the vicinal coupling constants of alkenes have an angular dependence that is used to establish structure. The coupling constant for trans vicinal hydrogen atoms is about twice that for cis, vicinal hydrogen atoms. The NMR spectra of (*E*)- and (*Z*)-3-chloropropenenitrile are shown in Figure 15.21. Both spectra consist of two low-field doublets with similar δ values. However, the vicinal coupling constant for the trans isomer (14.0 Hz) is larger than that for the cis isomer (7.7 Hz).

Long-Range Coupling in Aromatic Compounds

The most common coupled systems characterized as J_{gem} and J_{vic} involve interactions across two and three bonds, respectively. Spin-spin coupling that results from interactions of nuclei across four or more bonds are termed **long range**. Although long-range coupling is observed in some stereochemically rigid structures with

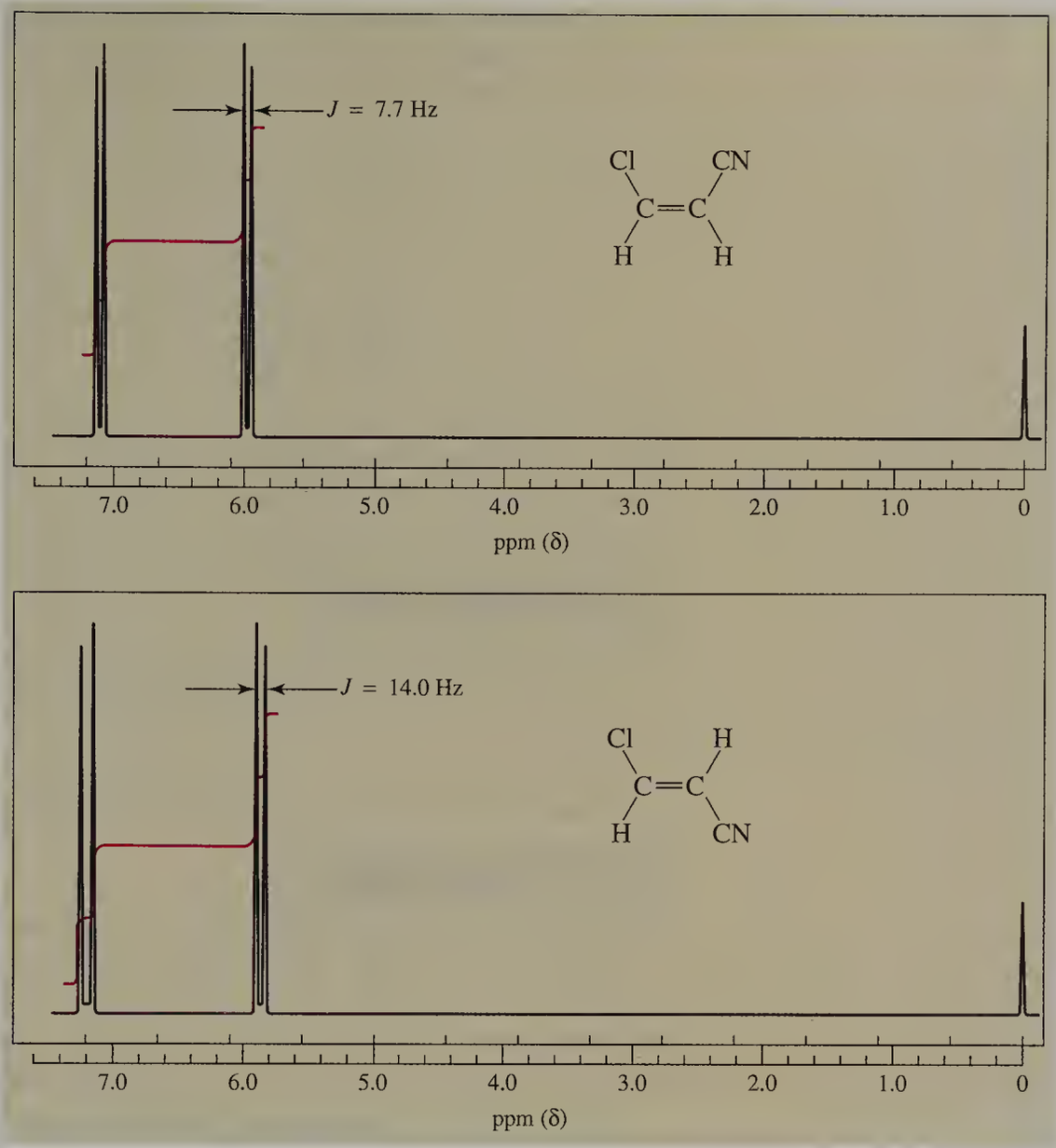
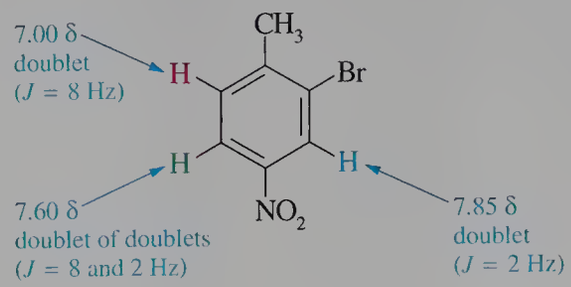


FIGURE 15.21 Effect of Stereochemistry on Coupling Constants of Alkenes
The coupling constant of trans hydrogen atoms is larger than the coupling of cis hydrogen atoms.

sp^3-hybridized carbon atoms, the more common examples are found in unsaturated compounds. Coupling occurs between ortho, meta, and para hydrogen atoms in aromatic compounds. The coupling between ortho hydrogen atoms is vicinal, and the coupling constant is in the 6–10 Hz range. Coupling between meta and para hydrogen atoms involves four and five bonds, respectively. The range of values are J_{meta} = 1–3 Hz and J_{para} = 0–1 Hz.

The determination of the structure of an aromatic compound by NMR is often possible by counting the number of different resonances that correspond to the number of nonequivalent hydrogen atoms. Assignment of each resonance can often be done using reference compounds that provide information about the effect of substituents on ortho hydrogen atoms. The assignment is confirmed from the multiplicity of each resonance. The largest coupling constant is for ortho hydrogen atoms. Smaller splitting occurs for coupling with a meta hydrogen atom. However, this analysis is often complicated by non-first order spectra because the chemical shifts of the aromatic hydrogen atoms are similar.

The spectral characteristics of 2-bromo-4-nitrotoluene are shown. The assignments are made using the knowledge that the deshielding effect of substituents on ortho hydrogen atoms is $NO_2 \gg Br > CH_3$.



The lowest field resonance is for the hydrogen atom at C-3, which is ortho to both the bromine atom and the nitro group. The resonance of the hydrogen atom at C-5 is close to the C-3 hydrogen resonance. However, it is a doublet of doublets due to coupling with the ortho hydrogen atom at C-6 and the meta hydrogen atom at C-3.

Problem 15.19

Explain why the isomeric 2,3,4-trichloroanisole and 2,3,6-trichloroanisole cannot be distinguished by the determination of coupling constants of the two doublets of each compound.

Sample Solution

Both compounds have two C—H bonds that are ortho to one another. The magnitude of the coupling constants should be similar and in the 6–10 Hz range.

Problem 15.20

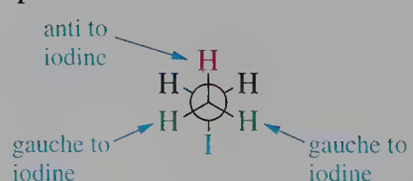
Explain how the identity of the isomeric 2,3,4-trichloroanisole, 2,3,5-trichloroanisole, and 2,4,5-trichloroanisole can be established using coupling constants of the two doublets of each compound.

15.17 Effect of Dynamic Processes

A specific hydrogen atom has a unique chemical shift because it maintains its "position" long enough to be "seen." If a rapid exchange process occurs, the NMR experiment "sees" a time average of all the species in equilibrium. To illustrate this principle as it applies to NMR spectroscopy, we will use the movement of an airplane propeller as an analogy. The appearance of the propeller as it moves is a useful model for understanding the role of dynamic processes in NMR. If the propeller is not moving, we can clearly see each blade. As the engine starts we still might be able to see each blade, but the images blur as the propeller accelerates, and we see the time average of the motion, which is a disk. Thus there is a relationship between the rate of the process and our ability to see that motion. Let's now apply that concept to NMR spectroscopy. The motion is that of conformational changes or chemical equilibrium. The "seeing" is related to the conditions under which the NMR spectrum is obtained.

Conformational Changes

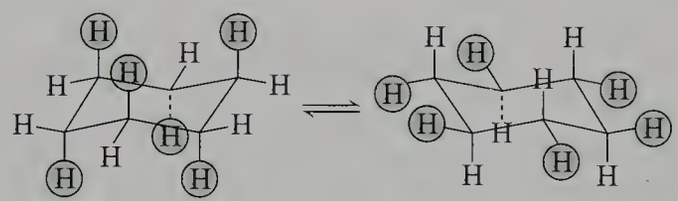
Consider the three hydrogen atoms of the methyl group of ethyl iodide in the Newman projection of the compound.



If this specific conformation of a single molecule could be "seen" by the NMR instrument, then the three methyl hydrogen atoms would not be equivalent. The two hydrogen atoms that are gauche to the iodide are equivalent, but different from the hydrogen atom that is anti to the iodide atom. As a result, the methyl group would appear as two chemical shifts, and more resonances would appear. However, we know that the methyl hydrogen atoms are equivalent. This equivalence results from a rapid rotation around the σ bond much like that of a propeller. Because the rotation is too fast for the NMR spectrometer to "see," the result is a time average, which appears as a single chemical shift.

A similar effect occurs for the observed coupling constant for the interaction between the methyl and methylene hydrogen atoms. Only a time average coupling constant appears. The protons that are anti to each other have J_{vic} in the 12–16 Hz range. Those that are gauche to each other have J_{vic} = 3–4 Hz. The time average coupling constant is 6–7 Hz because more gauche arrangements exist than anti arrangements.

Conformational changes of cyclic systems also lead to time-averaged chemical shifts. We know that the equatorial and axial hydrogen atoms of cyclohexane have different structural environments. However, we know that the cyclohexane ring undergoes a chair–chair interconversion and that the equatorial and axial hydrogen atoms exchange positions. This process is so rapid that the NMR cannot detect the individual conformations and the hydrogen atoms in the two different environments at room temperature. As a result, cyclohexane appears as a single resonance at 1.4 δ.



Hydroxyl Hydrogen Atoms

The resonance of a hydroxyl hydrogen atom is characterized by a variability of its chemical shift and the absence of any splitting. For example, the chemical shift of the hydroxyl hydrogen atom of ethanol "moves" depending on experimental conditions, but the chemical shift of the methylene and methyl hydrogen atoms remain unchanged.

The resonance of the hydroxyl hydrogen atom is a singlet rather than the triplet expected from coupling of this hydrogen atom with the methylene hydrogen atoms. Both of these features result from a fast chemical exchange process in which protons are transferred between hydrogen-bonded molecules.

The chemical shift varies with solvent, temperature, and concentration because as the degree of aggregation of the hydrogen-bonded species changes, the environment of the hydrogen atom changes. The chemical shift may vary from 4–5 δ in concentrated solutions to about 1 δ in dilute solutions.

The hydroxyl hydrogen atom is not split by neighboring hydrogen atoms like the methylene hydrogen atoms of ethanol. In addition, the methylene hydrogen atoms are not split by the hydroxyl hydrogen atom. The effects of coupled hydrogen atoms do not appear in the NMR because each individual hydroxyl hydrogen atom in the sample experiences a variety of spin arrangements as it rapidly changes sites. Because no single hydroxyl hydrogen atoms spends enough time at one site, the effect of different nuclear spins averages out, and no coupling appears.

15.18 ^{13}C NMR Spectroscopy

As ^{13}C has a nuclear spin of $\frac{1}{2}$, it can be detected in an NMR experiment. ^{13}C NMR allows us to detect the structural environment of carbon atoms. This is often an advantage, especially for carbon atoms that are not bonded to hydrogen atoms and thus cannot be detected by hydrogen NMR.

NMR spectra can be easily obtained for many isotopes with half integer spins, such as ^{19}F and ^{31}P, because their natural abundance is 100%. The detection of the isotope ^{13}C is more difficult because it has an abundance of only 1%. However, by using large samples and specialized instrumentation it is possible to obtain ^{13}C NMR spectra. At a field strength of approximately 58,700 gauss, the radio frequency required for resonance is 62.5 MHz.

Let's consider the location of the ^{13}C isotope in a compound such as 2-butanol. Most of the carbon atoms are ^{12}C, which has no nuclear spin. The probability is equal for the location of ^{13}C at any of the positions in a molecule. The probability of finding a ^{13}C at C-1 of a molecule is 1%. The probability of finding a ^{13}C at C-2 is also 1%, and so on. The probability of finding two or more ^{13}C in the same molecule and simultaneously bonded to each other is very low. For example, the probability of finding ^{13}C in the same molecule at both C-1 and C-2 is only 0.01%. As a result, a ^{13}C NMR spectrum shows a sum of the signals generated by individual atoms at all of the possible sites in a collection of isotopically substituted molecules. The observed spectrum therefore appears to indicate that ^{13}C is located at every position in a molecule. However, this is not the case because a molecule with ^{13}C at every position would show coupling between the ^{13}C isotopes.

Characteristics of ^{13}C Spectra

Table 15.9
Chemical Shifts of ^{13}C

Carbon atom	*Chemical shift (ppm)*
RCH_2CH_3	12–15
RCH_2CH_3	16–25
R_3CH	12–35
$CH_3\overset{O}{\overset{\|}{C}}R$	30
RCH_2Cl	40–45
RCH_2Br	27–35
RCH_2OH	50–65
$RCH{=}CH_2$	115–120
$RCH{=}CH_2$	125–140
$R\overset{O}{\overset{\|}{C}}OR$	170–175
$R\overset{O}{\overset{\|}{C}}H$	190–200
$R\overset{O}{\overset{\|}{C}}R$	205–220

The chemical shift value is for the carbon atom shown in boldface in the generalized structures.

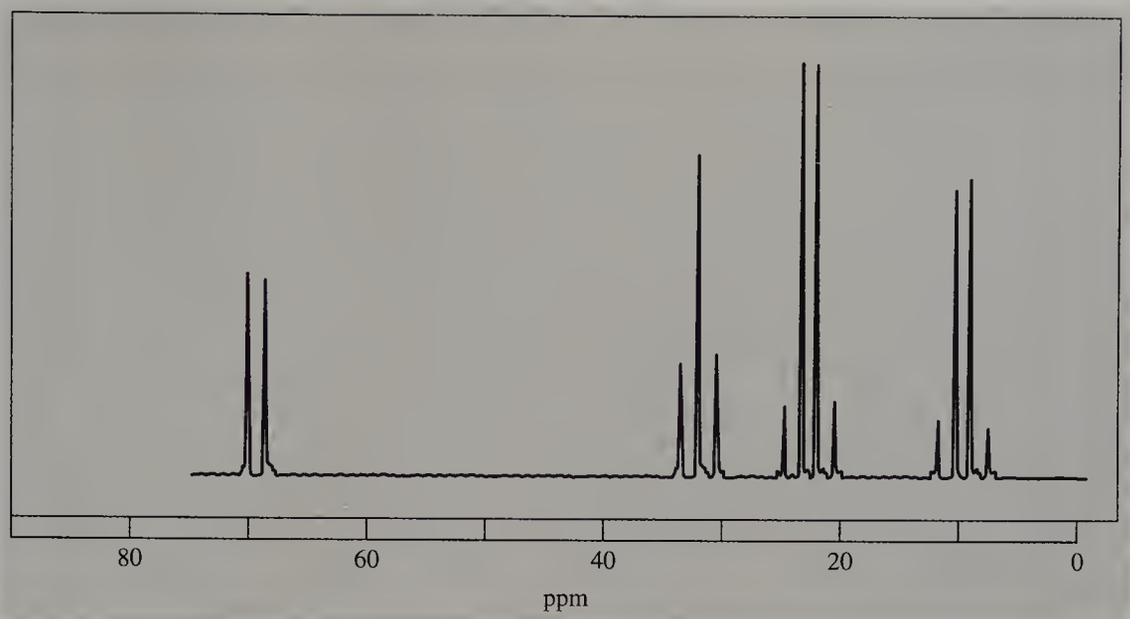
The ^{13}C spectra of organic compounds is shown using a δ scale relative to the resonance of ^{13}C in TMS. The chemical shift of ^{13}C shows many of the same trends as hydrogen chemical shifts. However, the range of chemical shifts for ^{13}C is very much larger, on the order of 200 ppm (Table 15.9). Thus, the chemical shifts are very sensitive to changes in structural environment. As a result, it is usually possible to "see" distinct signals for every nonequivalent ^{13}C in a molecule.

The resonances for ^{13}C are split by hydrogen atoms. The rules for the multiplicity of a ^{13}C resonance split by hydrogen are the same as for hydrogen coupled to hydrogen. The multiplicity is $n + 1$ for n equivalent neighboring hydrogen atoms. The largest coupling is observed for ^{13}C directly bonded to hydrogen—that is, a one-bond coupling. Coupling of ^{13}C with hydrogen atoms farther away is small. By using specialized experimental methods, all splitting by hydrogen atoms other than the one-bond coupling can be eliminated.

The ^{13}C spectrum of 2-butanol is shown in Figure 15.22. The four carbon atoms are clearly seen as four regions each consisting of multiplets. The signal at lowest field is assigned to C-2 because that atom is deshielded by an oxygen atom. This assignment is confirmed because the signal is a doublet that results from the coupling of the directly bonded hydrogen atom. The triplet at 32.3 δ is assigned to the C-3 atom because it has two hydrogen atoms bonded to it.

The two quartets in the spectrum of 2-butanol correspond to the C-1 and C-4 methyl groups. Each has three hydrogen atoms, which are responsible for the observed quartets. Assignment of the lower field quartet to C-1 is based on its proximity to the oxygen atom, which deshields that carbon by an inductive effect. The higher field quartet is due to the C-4 methyl group.

FIGURE 15.22 ^{13}C NMR Spectrum of 2-Butanol



Proton-Decoupled Spectra

The distinction between different resonances compared to components of a multiplet becomes a difficult task for more complex structures. A method that eliminates the multiplicity of all resonances and reduces the spectrum to singlets for each nonequivalent carbon atom makes it easier to determine structures using ^{13}C NMR.

The splitting of a resonance for a ^{13}C atom by hydrogen can be eliminated to generate a singlet by a technique called **proton decoupling**. The resulting spectrum is called a **proton-decoupled NMR spectrum**. While the spectrum of ^{13}C is being obtained at 58,700 gauss using 62.5 MHz, a high-intensity source of radio frequency at 250 MHz is simultaneously aimed at the sample. This combination of field and radio frequency causes changes in spin states of hydrogen nuclei. Because the intensity of the radio frequency is so high, the nuclei rapidly change their spin states. Hence, they do not spend sufficient time in specific arrangements to couple with the ^{13}C nucleus. As a result of this averaging phenomenon, no coupling is observed.

The proton-decoupled spectrum of 2-butanol is greatly simplified (Figure 15.23). It consists of four signals corresponding to the four nonequivalent carbon atoms. Consequently, we can eliminate the isomers 2-methyl-1-propanol and 2-methyl-2-propanol as possible structures because the spectra of these compounds would show three and two signals, respectively.

Counting Carbon Atoms

We note that the intensities of the four nonequivalent carbon atoms of 2-butanol are not equal. Unlike hydrogen NMR spectroscopy, the method used to obtain ^{13}C spectra gives peak intensities that are not proportional to the number of carbon atoms. The signals for carbon atoms bearing more hydrogen atoms tend to be larger than for carbon atoms bearing fewer hydrogen atoms. Carbon atoms without hydrogen atoms, such as quaternary carbon atoms and ketone carbonyl carbon atoms, have the lowest intensity. However, substituents also affect the intensity of the carbon atom. As a result we cannot accurately "count" the number of equivalent carbon atoms responsible for a resonance.

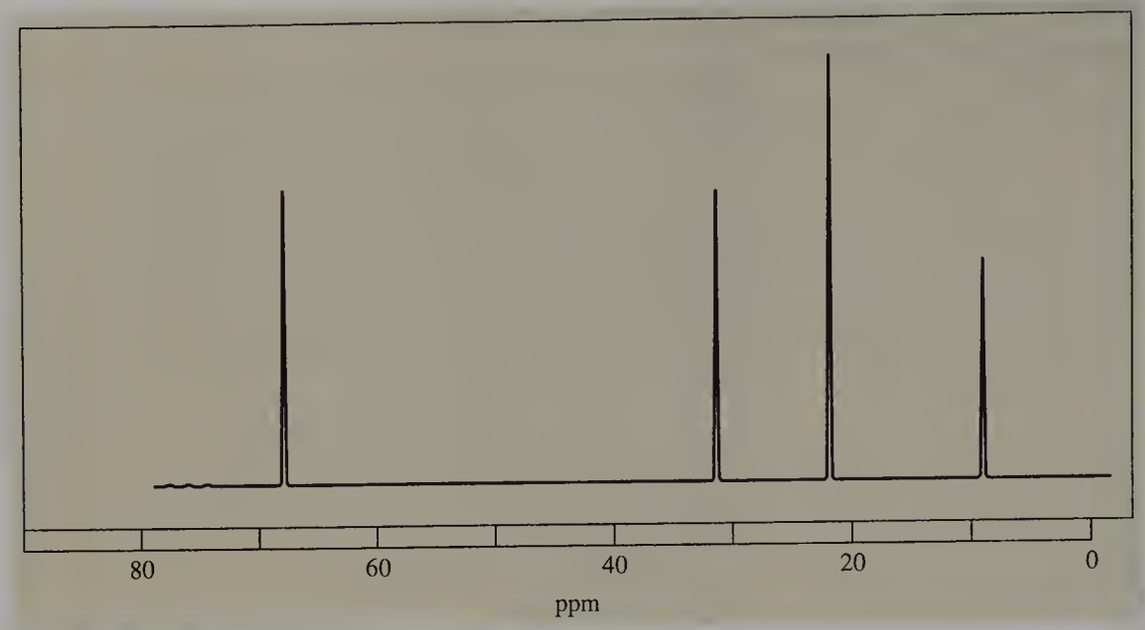
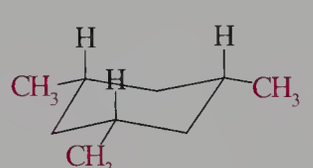


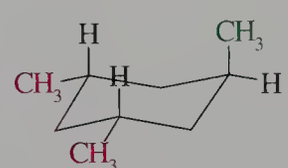
FIGURE 15.23 Proton-Decoupled ^{13}C Spectrum of 2-Butanol

The number of equivalent carbon atoms can be determined by comparing the number of signals in a ^{13}C spectrum with the number of carbon atoms in the molecular formula. If some of the carbon atoms in a molecule are equivalent, the number of signals is reduced. As a result, ^{13}C spectroscopy is quite useful in determining the symmetry of a molecule.

Consider the structures of the two diastereomeric 1,3,5-trimethylcyclohexanes. The isomer that has all-cis methyl groups is more symmetrical than its diastereomer with one trans methyl group.



1-*cis*,3-*cis*,5-trimethylcyclohexane



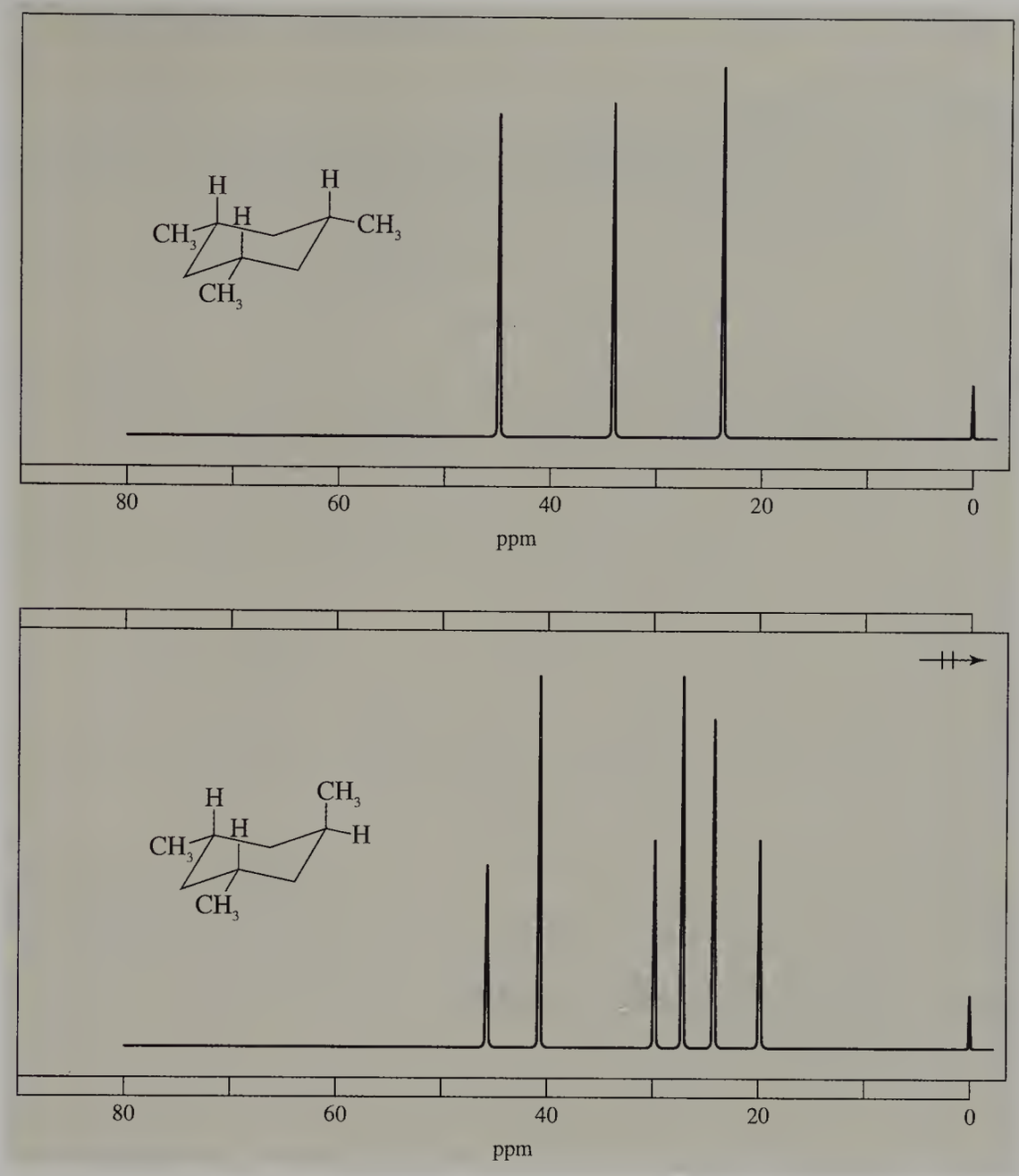
1-*cis*,3-*trans*,5-trimethylcyclohexane

The three methyl groups of the all-cis isomer are located in equatorial positions and are equivalent, so the methyl groups give one signal. The equivalence of the methyl groups is related to the equivalence of other sites in the structure. The three methine carbon atoms bonded to the methyl groups are also equivalent, as are the three methylene carbon atoms. Therefore, the nine carbon atoms of the molecule consist of three sets of three carbon atoms each. The spectrum consists of three resonances (Figure 15.24).

Now let's consider the expected spectrum of the diastereomeric 1,3,5-trimethylcyclohexane. The two equatorial methyl groups are equivalent, but different from the axial methyl group. Likewise, the two methine carbon atoms containing equatorial methyl groups are equivalent, but different from the methine carbon atom containing the axial methyl group. Finally, two methylene carbon atoms are equivalent and different from the third methylene carbon atom. Hence, the nine carbon atoms are divided into six groups. Three of the groups contain two carbon atoms each, and the other three groups contain one carbon atom each. The spectrum consists of six signals, of which three are approximately twice the intensity of the other three (Figure 15.24).

The determination of structure using ^{13}C depends on a one-to-one correspondence between the number of sets of equivalent carbon atoms and the number of sig-

FIGURE 15.24 Effect of Symmetry on ^{13}C NMR Spectra



nals in the spectrum. Although of rare occurrence, two nonequivalent carbon atoms can have the same chemical shift. For example, the ^{13}C spectrum of 1-octene contains only seven signals, even though there are eight nonequivalent carbon atoms.

Problem 15.21

How can a compound of molecular formula $C_4H_{10}O$ be established as an ether or an alcohol using ^{13}C NMR spectroscopy?

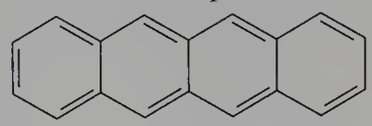
Problem 15.22

The isomeric alcohols 3-heptanol and 4-heptanol cannot be easily distinguished by hydrogen NMR spectroscopy. Describe how ^{13}C NMR spectroscopy can be used to distinguish between these isomers.

EXERCISES

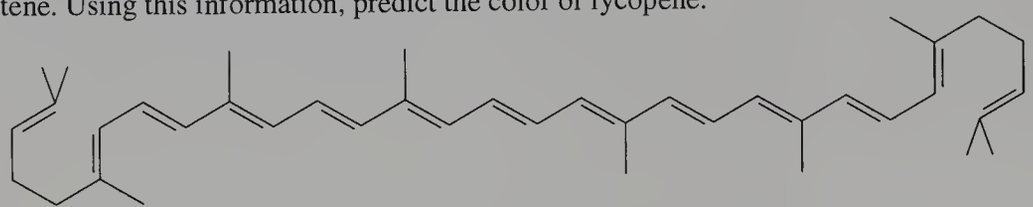
Ultraviolet Spectroscopy

15.1 The λ_{max} values of naphthalene, anthracene, and tetracene are 314, 380, and 480 nm, respectively. Suggest a reason for this order of the wavelength of maximum absorption. Are any of the compounds colored?

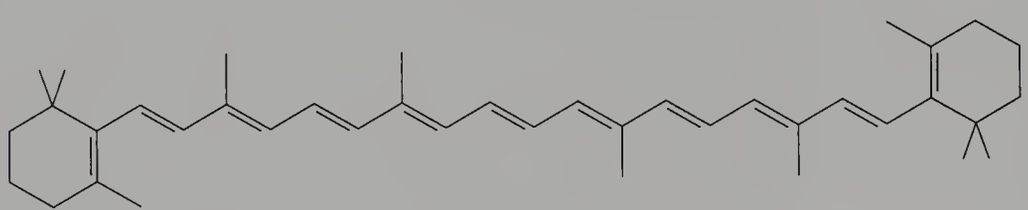


tetracene

15.2 How many conjugated double bonds are contained in lycopene? Compare the conjugation in this compound to that of β-carotene. Using this information, predict the color of lycopene.



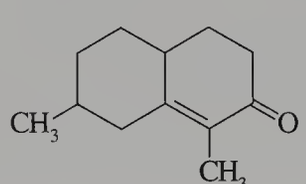
lycopene



β-carotene

15.3 How might 2,4-hexadiyne be distinguished from 2,5-hexadiyne by ultraviolet spectroscopy?

15.4 One of the following unsaturated ketones has λ_{max} at 225 nm and the other has λ_{max} at 252 nm. Assign each value to the proper structure.



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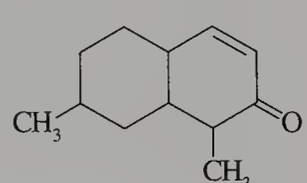
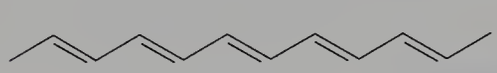


II

15.5 Rank the following polyenes in order of lengthening wavelengths of absorption in the ultraviolet spectrum.



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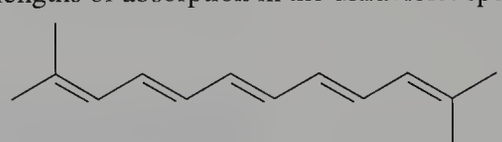
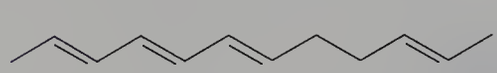
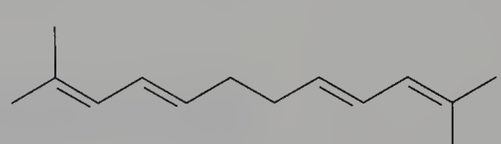


II



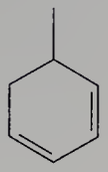
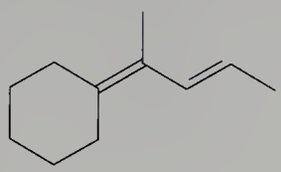
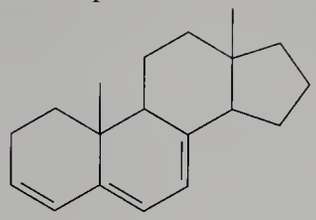
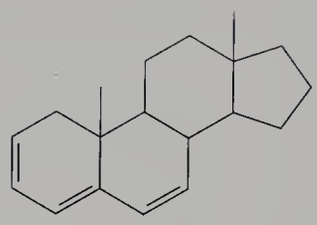
III



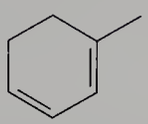
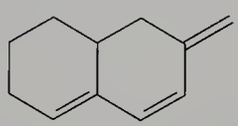
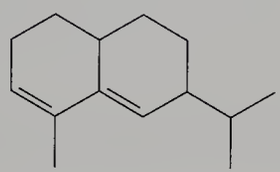
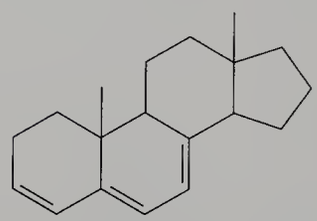
IV

15.6 The λ_{max} values of 2,4,6-octatriyne and 2,4,6,8-decatetrayne are 207 and 234 nm, respectively. Explain why these values differ.

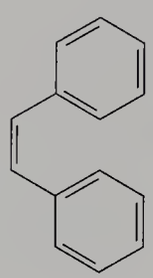
15.7 Calculate the λ_{max} of each of the following unsaturated compounds.

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

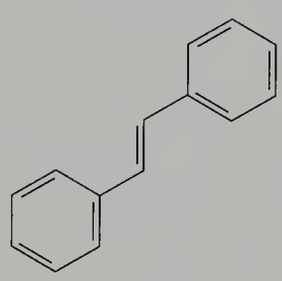
15.8 Calculate the λ_{max} of each of the following unsaturated compounds.

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

15.9 Explain why the λ_{max} values of *cis*- and *trans*-stilbenes are 280 and 295 nm, respectively.

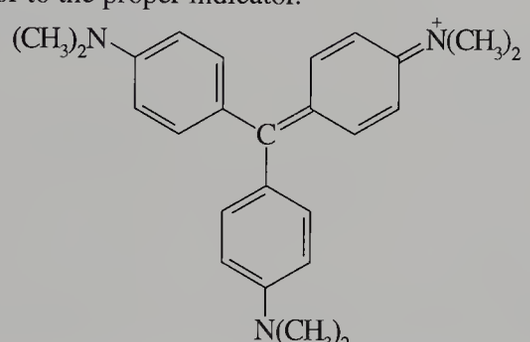


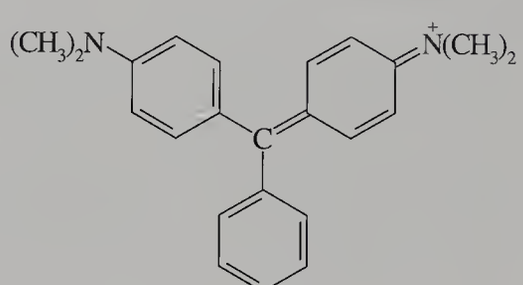
cis-stilbene



trans-stilbene

15.10 Each of the following compounds is an indicator. At pH 7, one appears violet and the other blue-green. Assign each color to the proper indicator.



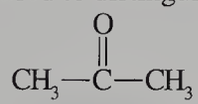


15.11 The λ_{max} of phenol is 210 nm in ethanol. Explain why addition of sodium hydroxide shifts this absorption to 235 nm.

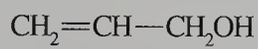
15.12 The λ_{max} values of benzene and *p*-methylaniline (*p*-toluidine) are 204 and 235 nm, respectively. However, when HCl is added, the λ_{max} of benzene is unchanged, whereas the λ_{max} of methylaniline changes to 207 nm. Explain the difference in the λ_{max} values for the two compounds and the effect of acid on the spectrum.

Infrared Spectroscopy

15.13 How can infrared spectroscopy be used to distinguish between propanone and 2-propen-1-ol?



propanone



2-propen-1-ol

15.14 How can infrared spectroscopy be used to distinguish between 1-pentyne and 2-pentyne?

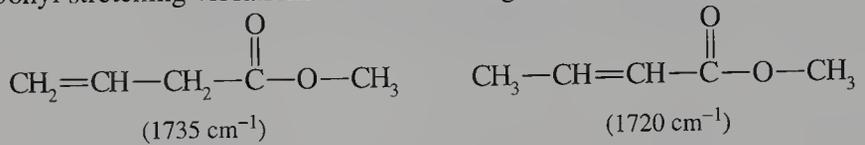
15.15 The carbonyl stretching vibration of ketones is at a longer wavelength than the carbonyl stretching vibration of aldehydes. Suggest a reason for this observation.

15.16 The carbonyl stretching vibrations of esters and amides occur at 1735 and 1670 cm^{-1}, respectively. Suggest a reason for this difference.

15.17 An infrared spectrum of a compound with molecular formula $C_4H_8O_2$ has an intense broad band between 3500 and 3000 cm^{-1} and an intense peak at 1710 cm^{-1}. Which of the following compounds best fits this data?

I: $CH_3CH_2CO_2CH_3$ II: $CH_3CO_2CH_2CH_3$ III: $CH_3CH_2CH_2CO_2H$

15.18 Explain why the carbonyl stretching vibrations of the following two esters differ.



(1735 cm^{-1}) (1720 cm^{-1})

15.19 Explain how the two isomeric nitration products of isopropylbenzene can be distinguished using infrared spectroscopy.

15.20 Explain how the structures of the three isomeric trimethylbenzenes can be established using infrared spectroscopy.

Calculation of Chemical Shift

15.21 The hydrogen NMR spectrum of $CHCl_3$, measured with a 60-MHz spectrometer, is a singlet that is 437 Hz downfield from TMS. Calculate δ.

15.22 The hydrogen NMR spectrum of CHI_3, measured with a 360-MHz spectrometer, is a singlet at 5.37 δ. Calculate the chemical shift in Hz relative to TMS.

Chemical Shifts and Structure

15.23 How many NMR signals should be observed for the hydrogen atoms in each of the following compounds?
(a) 2,2-dimethylpropane **(b)** 2-methyl-1-propene
(c) 1,3,5-trimethylbenzene **(d)** 2-methyl-2-butene

15.24 How many NMR signals should be observed for the hydrogen atoms in each of the following compounds?
(a) 1,1-dichloroethene **(b)** vinyl chloride
(c) allyl bromide **(d)** 1-bromo-1-chloroethene

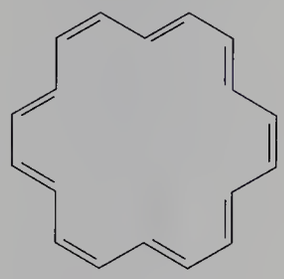
15.25 How can the compounds of each pair be distinguished using hydrogen NMR spectroscopy?
(a) isopropyl ethyl ether and *tert*-butyl methyl ether
(b) cyclohexane and *cis*-3-hexene
(c) 2,2-dimethyloxirane and *cis*-2,3-dimethyloxirane

15.26 How can the compounds of each pair be distinguished using hydrogen NMR spectroscopy?
(a) 1,3-dibromopropane and 2,2-dibromopropane
(b) 1,1-dichlorobutane and 1,4-dichlorobutane
(c) *cis*-2-butene and 2-methyl-1-propene

15.27 Draw the structure of each of the following hydrocarbons whose hydrogen NMR spectrum consists of a singlet with the indicated chemical shift.
(a) C_5H_{10}; δ = 1.5 **(b)** C_8H_{18}; δ = 0.9 **(c)** $C_{12}H_{18}$; δ = 2.2 **(d)** C_8H_8; δ = 5.8

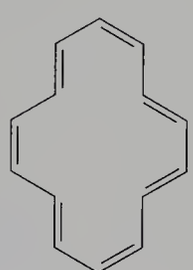
15.28 Draw the structure of each of the following halogen compounds whose hydrogen NMR spectrum consists of a singlet with the indicated chemical shift.
(a) $C_2H_3Cl_3$; δ = 2.7 **(b)** $C_2H_4Cl_2$; δ = 3.7 **(c)** C_4H_9Br; δ = 1.8 **(d)** $C_3H_6Br_2$; δ = 2.6

15.29 The hydrogen NMR spectrum of [18]annulene consists of signals at $\delta = 8.8$ ppm and $\delta = -1.9$ ppm. The negative value of δ corresponds to an "unusual" chemical shift that is upfield from TMS. The ratio of intensities of the 8.8-ppm to −1.9-ppm resonances is 2:1. Explain this data.



[18]annulene

15.30 The hydrogen NMR spectrum of [14]annulene consists of signals at $\delta = 7.8$ ppm and $\delta = -0.6$ ppm. Assign the resonances and predict the relative intensities of each.



[14]annulene

Multiplicity and Structure

15.31 Describe the multiplicity of each of the signals corresponding to a set of equivalent hydrogen atoms in each of the following ethers.
(a) $CH_3CH_2OCH_2CH_3$ **(b)** $CH_3OCH(CH_3)_2$ **(c)** $ClCH_2OCHClCH_3$ **(d)** $Cl_2CHOCHClCHCl_2$

15.32 Describe the multiplicity of the lowest field resonance of each of the following alkyl halides.
(a) 1-chloropentane **(b)** 1-chloro-2,2-dimethylpropane
(c) 3-chloropentane **(d)** 1-chloro-2-methyl-2-butene

15.33 Using a 100-MHz instrument, the chemical shifts of the C-1, C-2, and C-3 hydrogen atoms of 1,1,2-trichloropropane are 5.82, 4.40, and 1.78 ppm. The coupling constant of the C-2 and C-3 hydrogen atoms is 6.0 Hz and that of the C-2 and C-1 hydrogen atoms is 3.5 Hz. Draw the splitting diagram for the C-2 hydrogen atom.

15.34 Assume that the coupling constants for three nonequivalent hydrogen identified as H_a, H_b, and H_c are $J_{a,b} = 6$ Hz, $J_{a,c} = 2$ Hz, and $J_{b,c} = 6$ Hz. Draw the splitting diagram for H_b. What is the appearance of this resonance?

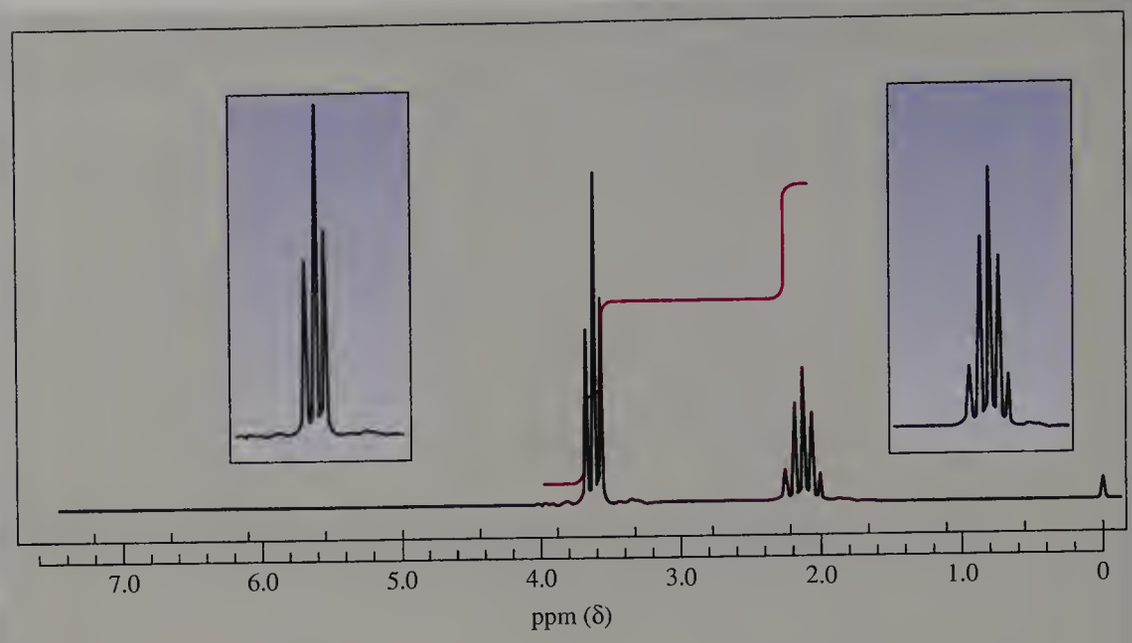
15.35 Hydrogen bromide adds to 3-bromopropene under certain experimental conditions to give a compound whose NMR is a quintet at 2.10 δ and a triplet at 3.60 δ. The ratio of the total intensity of the quintet to that of the triplet is 1:2. What is the structure of the compound?

15.36 The spectrum of a compound with molecular formula $C_3H_3Cl_5$ consists of a triplet at 4.5 δ and a doublet at 6.0 δ. The intensity ratio of the high-field to low-field signal is 1:2. What is the structure of the compound?

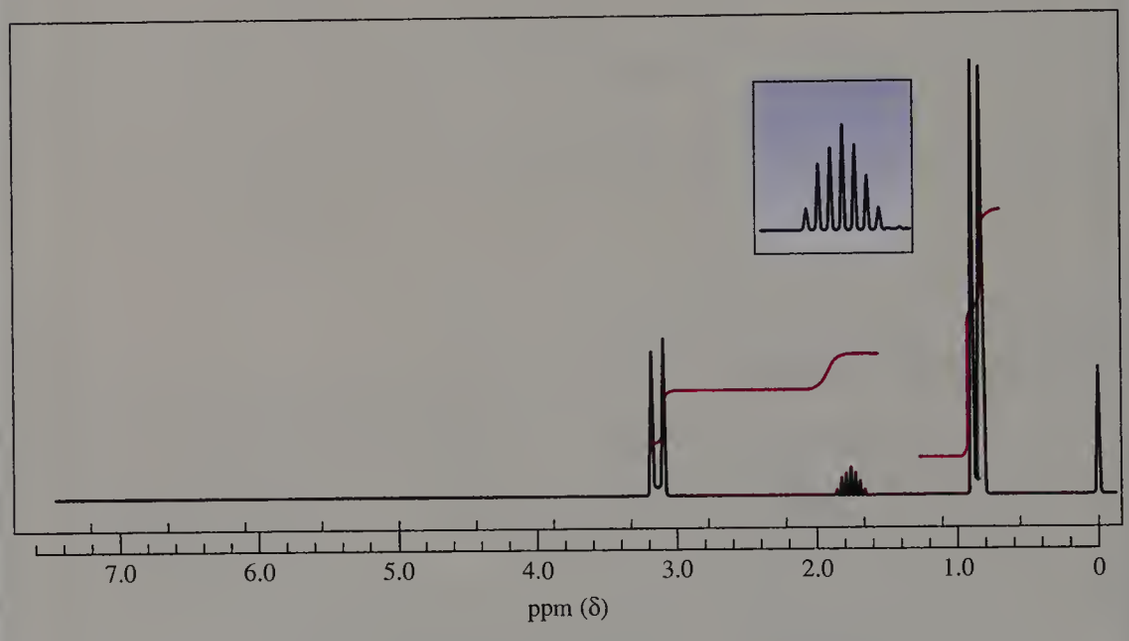
Analysis of Spectra

15.37 Determine the structure of the compound corresponding to each of the following hydrogen NMR spectra.

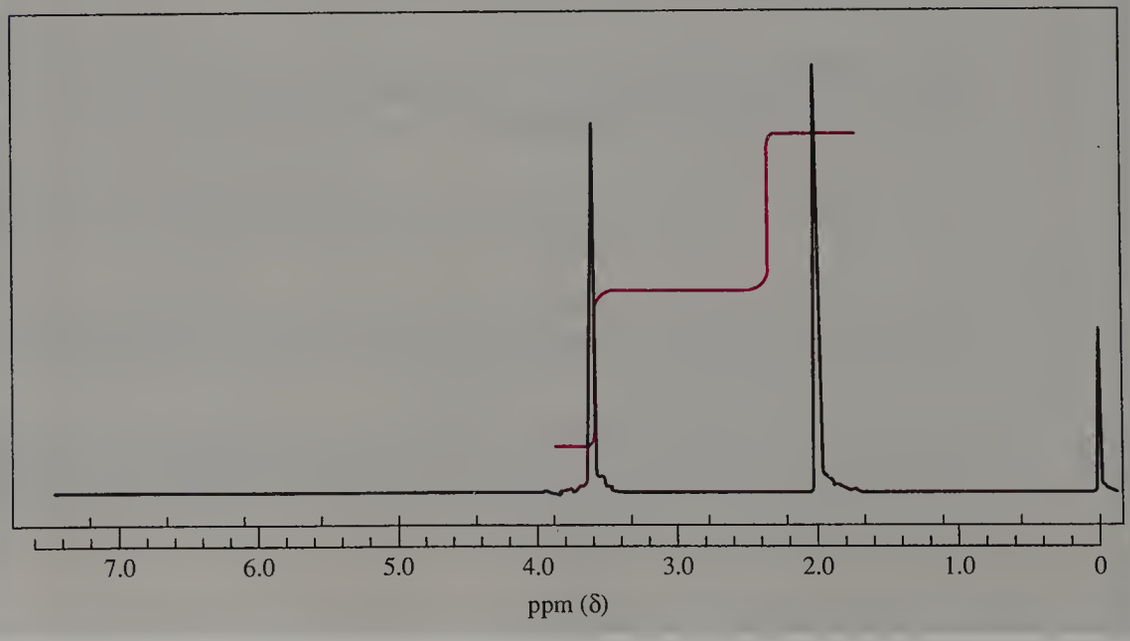
(a) $C_3H_6Cl_2$



(b) C_4H_9Cl

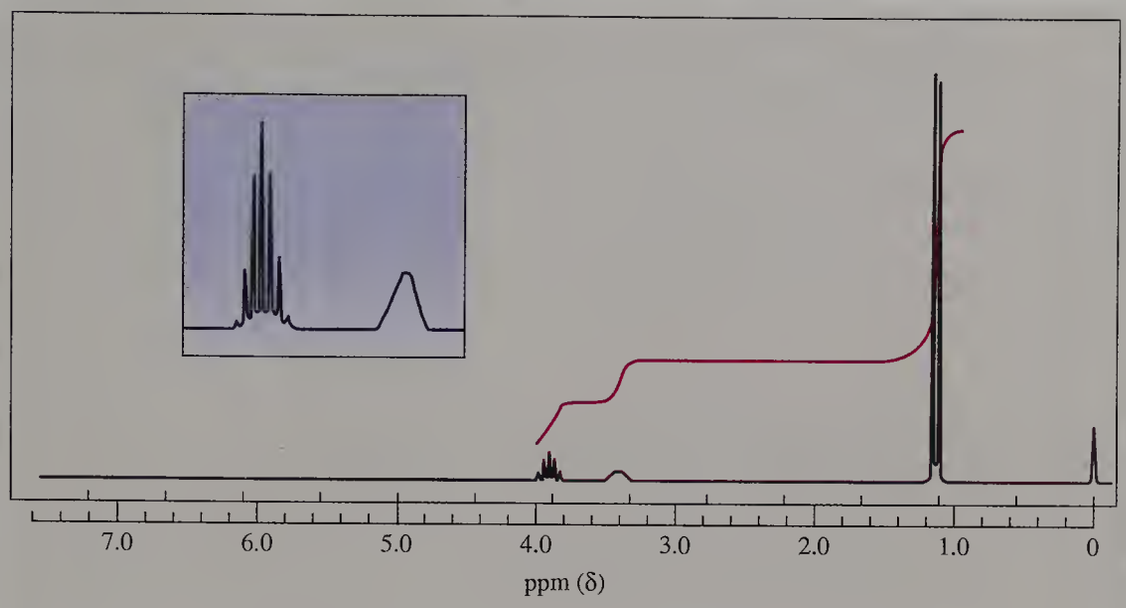


(c) C_4H_8O

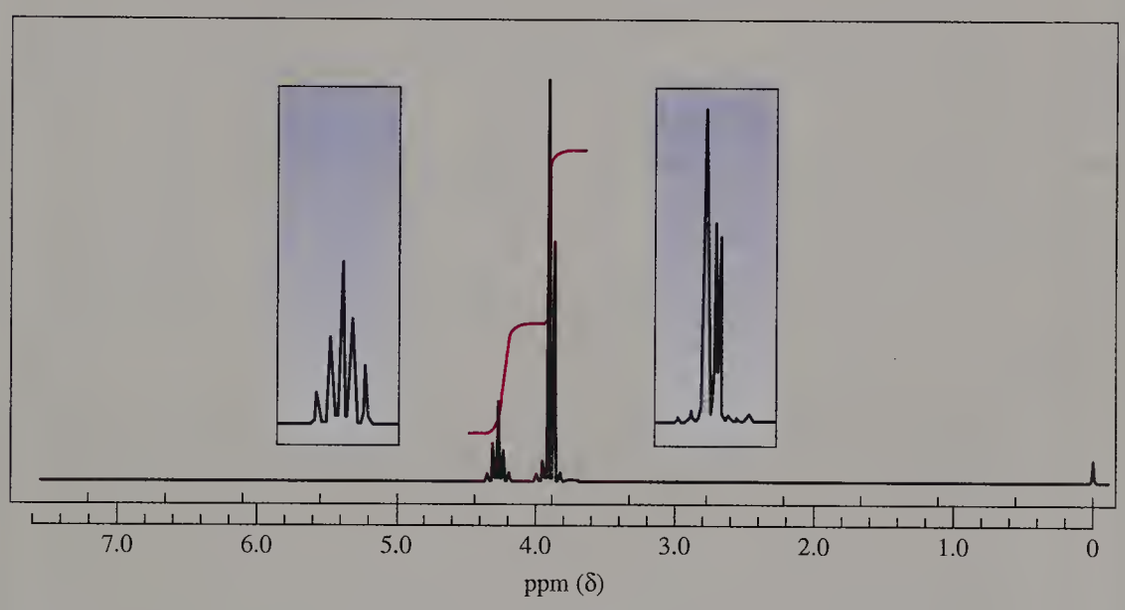


15.38 Determine the structure of the compound corresponding to each of the following hydrogen NMR spectra.

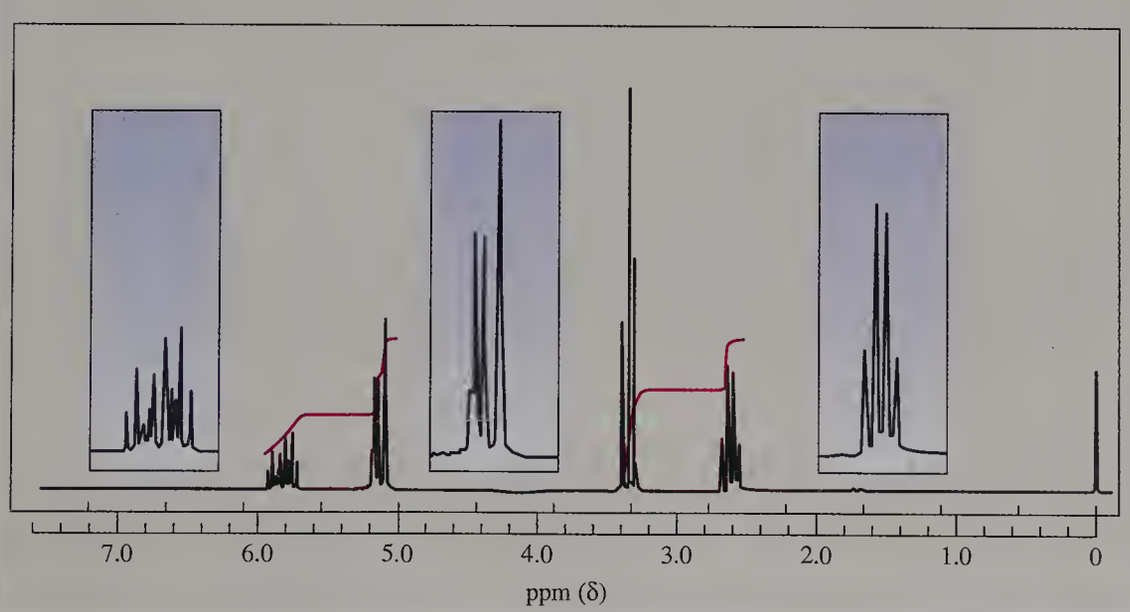
(a) C_3H_8O



(b) $C_3H_5Cl_3$



(c) C_4H_7Br



15.39 Determine the number of signals in the ^{13}C NMR spectrum of each of the following aromatic compounds.

(a) naphthalene **(b)** 1,2,3-trimethylbenzene
(c) 1,3,5-trimethylbenzene **(d)** 1,4-dimethylbenzene

15.40 Determine the number of signals in the ^{13}C NMR spectrum of each of the following ketones.

(a) $CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_2-CH_3$ **(b)** $CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_3$ **(c)** $CH_3-CH_2-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{CH}-CH_3$

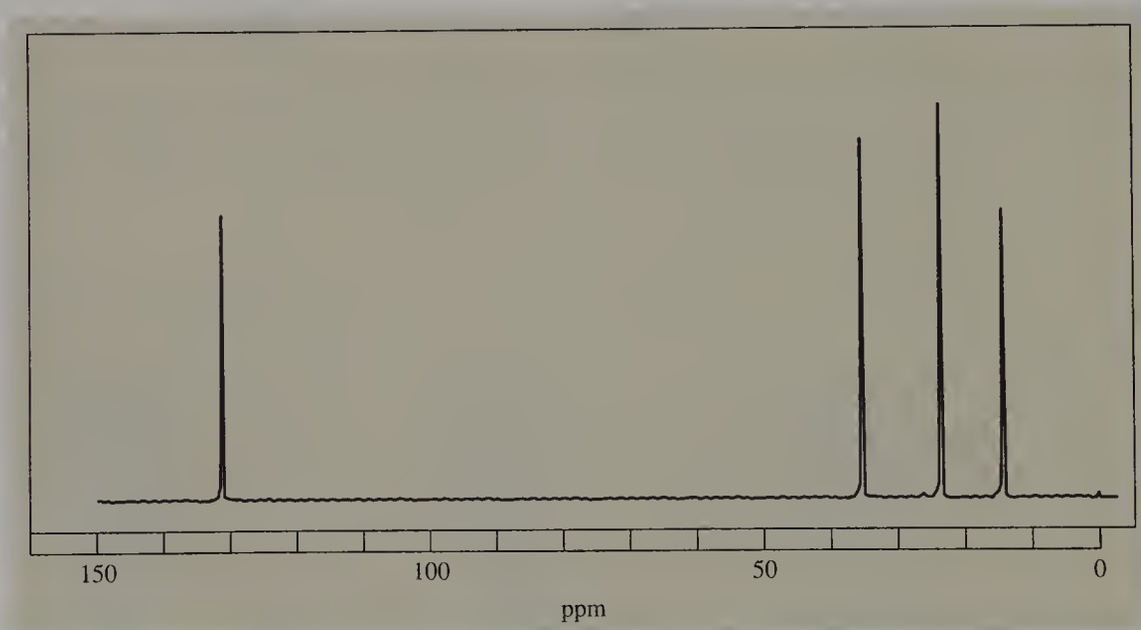
15.41 The ^{13}C NMR spectrum of a hydrocarbon with molecular formula C_4H_6 consists of a triplet at 30.2 δ and a doublet at 136 δ. What is the structure?

15.42 The ^{13}C NMR spectrum of a hydrocarbon with molecular formula C_6H_{14} consists of a quartet at 19.1 δ. and a doublet at 33.9 δ. What is the structure?

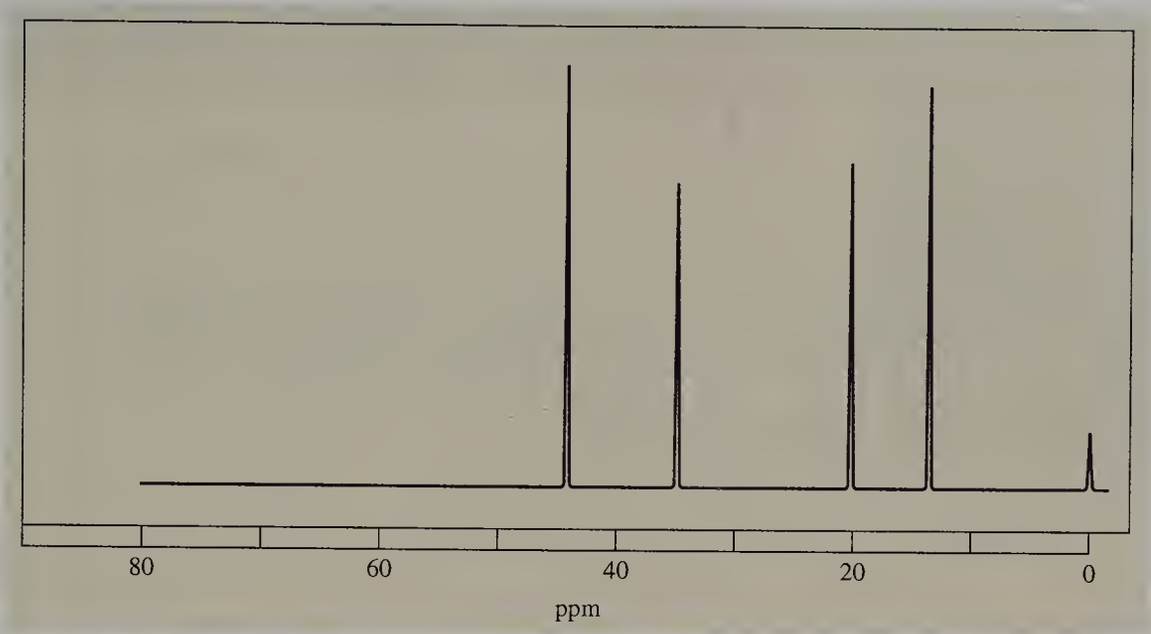
15.43 The ^{13}C NMR spectra of both 3-methylpentane and 2,2-dimethylbutane consist of four resonances. Explain how the two compounds can be distinguished based on the multiplicity of the signals.

15.44 The ^{13}C NMR spectra of both 1-butanol and 2-butanol consist of four resonances. Explain how the two compounds can be distinguished based on the multiplicity of the signals.

15.45 The proton-decoupled ^{13}C NMR spectrum of a compound with molecular formula C_8H_{16} is shown. What structures are consistent with this spectrum? Could a proton-coupled ^{13}C spectrum distinguish between these possibilities?



15.46 The proton-decoupled ^{13}C NMR spectrum of a compound with molecular formula C_4H_9Cl is shown. What structures are consistent with this spectrum? Explain how the proton-coupled ^{13}C spectrum could distinguish between these possibilities.



NMR of Other Nuclei

15.47 The naturally occurring isotope ^{19}F has a nuclear spin of $\frac{1}{2}$ and NMR spectrometers can be adjusted to detect the resonance of this isotope. What will be the multiplicity of the ^{19}F resonance of each of the following compounds?
(a) methyl fluoride **(b)** benzyl fluoride **(c)** trifluoromethane

15.48 The naturally occurring isotope ^{19}F has a nuclear spin of $\frac{1}{2}$. What will be the multiplicity of the ^{1}H resonance of each of the following compounds?
(a) methyl fluoride **(b)** difluoromethane **(c)** 1-chloro-1,2-difluoroethene

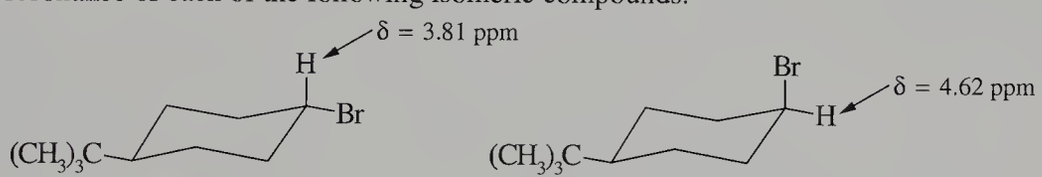
15.49 The naturally occurring isotope ^{31}P has a nuclear spin of $\frac{1}{2}$. Explain why the methyl hydrogen atoms of trimethyl phosphite, $(CH_3O)_3P$, appear as a doublet in the ^{1}H NMR spectrum.

15.50 NMR spectrometers can be adjusted to detect the resonance of the ^{31}P isotope. Based on the information given in Exercise 15.49, predict the multiplicity of the ^{31}P spectrum of trimethyl phosphite.

Dynamic Processes

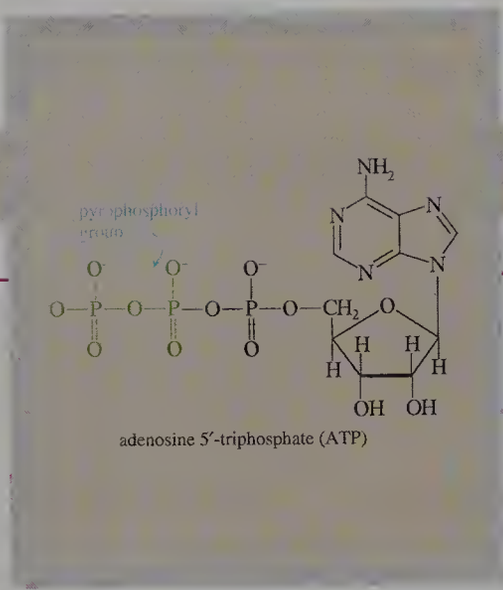
15.51 Explain why the ^{13}C NMR spectrum of *trans*-1,4-dimethylcyclohexane shows only one methyl resonance.

15.52 Bromocyclohexane has a one-proton resonance at 3.95 δ. Explain the origin of this resonance taking into account the indicated resonance of each of the following isomeric compounds.



15.53 The hydrogen NMR of 2,2,3,3-tetrachlorobutane is a singlet at 25 °C. Decreasing the temperature to –50 °C yields a spectrum with two singlets of unequal intensity. What structures account for the spectrum at the lower temperature?

15.54 Explain how the observed vicinal coupling of 1,1-dibromo-2,2-dichloroethane reflects the percentages of the two conformations that are in rapid equilibrium.



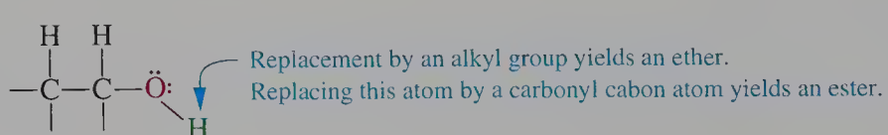
16

Alcohols: Reactions and Synthesis

16.1 Overview of Alcohol Reactions

Alcohols can be converted into an array of other classes of oxygen–containing compounds including ethers, esters, aldehydes, ketones, and carboxylic acids. In addition, they can be converted into haloalkanes by substitution reactions, and into alkenes by elimination reactions.

We classify reactions of alcohols according to the different bonds that are broken. Considering only the bonds of the hydroxyl oxygen atom, two types of reactions occur, those involving the O—H bond and those involving the C—O bond. We have already considered the loss of a proton from the O—H bond in acid–base reactions. These are not synthetic reactions. However, replacing the hydrogen atom of the O—H bond by a carbon-containing group is a synthetic procedure used to form more complex structures.

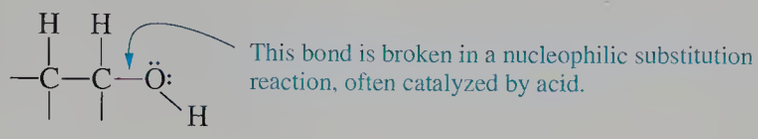


The reaction of the oxygen atom with the electrophilic center of alkyl groups bonded to good leaving groups yields ethers. The formation of ethers will be considered in Chapter 17. Many of the reactions of alcohols yield an ester either as a reaction intermediate or as a stable product. Ester formation is therefore a useful unifying concept to present some of the chemistry of alcohols. Ester-forming reactions fall into three broad classes:

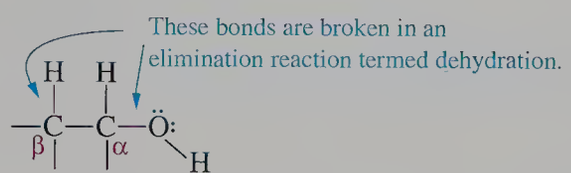
1. The synthesis of esters of inorganic or organic acids
2. The formation of ester intermediates that contain a transition metal.
3. The formation of ester intermediates in the conversion of alcohols into alkyl halides.

The conversion of alcohols into alkyl halides, initially presented in Chapter 8, will be reviewed in this chapter. Conversion to alkyl chlorides and alkyl bromides is

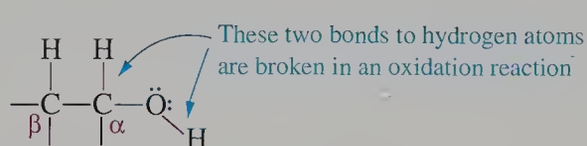
accomplished using thionyl chloride and phosphorus tribromide, respectively. The C—O bond breaks in these nucleophilic substitution reactions.



In some reactions in which either the C—O or the O—H bond breaks, a C—H bond also breaks. That C—H bond may be on the β carbon atom or on the carbon atom bearing the hydroxyl group. The dehydration reaction of alcohols results in cleavage of both the C—O bond and the C—H bond of the β carbon atom. This process, a β-elimination reaction, was discussed in Section 8.20 and is not considered in this chapter.

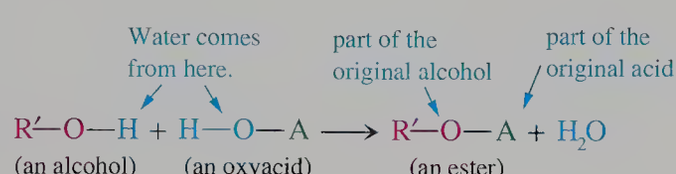


Breaking both the O—H bond and the C—H bond at the carbon atom bearing the hydroxyl group is an oxidation reaction. We will consider this α-elimination reaction in detail in this chapter. The oxidation reactions convert alcohols into aldehydes and ketones or, by further oxidation, into carboxylic acids.



16.2 Conversion of Alcohols into Esters

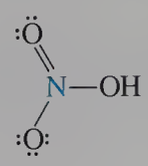
An ester can form from the reaction of an oxyacid, represented as HOA, with an alcohol. The ester forms by the nucleophilic attack of the alcohol's oxygen atom on the central atom of the oxyacid bearing the —OH group. Thus, the ester contains the oxygen atom of the alcohol.



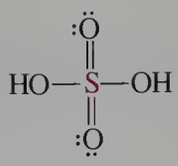
Esters of Inorganic Oxyacids

The structures of several inorganic mono- and polyprotic oxyacids are shown below with the "A" component emphasized. Note that the polyprotic acids, sulfuric acid and phosphoric acid, contain two and three —OH groups, respectively. Thus,

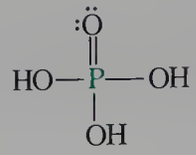
mono-esters and diesters can form from sulfuric acid and mono-, di-, and triesters from phosphoric acid.



nitric acid

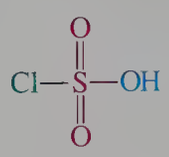


sulfuric acid

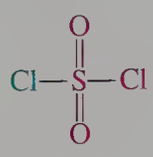


phosphoric acid

Although esters can be formed by direct reaction of an acid with an alcohol, they are more commonly formed using a derivative of an acid called an acid chloride. For sulfuric acid, there are two acid chlorides, chlorosulfonic acid and sulfuryl chloride, used to prepare monoesters and diesters, respectively.

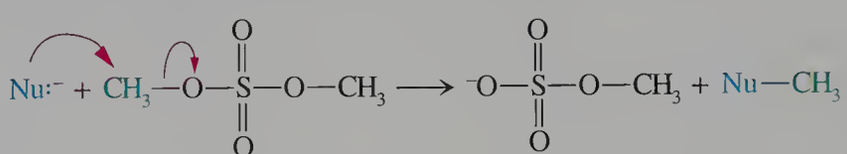


chlorosulfonic acid

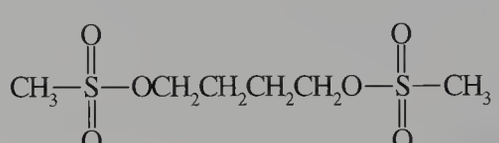


sulfuryl chloride

Dimethyl sulfate, a diester of sulfuric acid, is a commercially available liquid used as a methylating agent. Nucleophiles readily attack the electrophilic methyl carbon atom by an S_N2 process to give methylated products. The methyl sulfate ion is an excellent leaving group because it is resonance stabilized and only weakly basic.

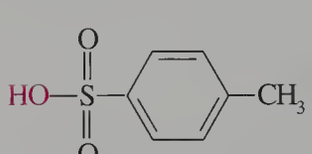


Highly active methylating agents such as dimethyl sulfate must be used with great care because they react with our biological molecules, which all contain nucleophilic sites. Some alkylating agents act as antineoplastic agents, slowing the growth of some cancers. For example, myleran is used in the treatment of myelogenous leukemia.

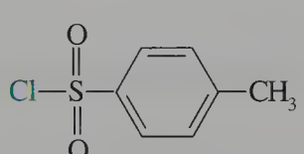


myleran

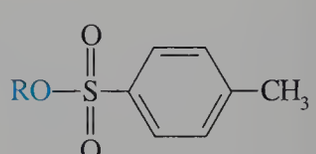
We recall that alcohols react with sulfonyl chlorides—the acid chlorides of sulfonic acids—to form sulfonates (Section 10.3). We now recognize that these alcohol derivatives are esters of an organic analog of sulfuric acid.



p-toluenesulfonic acid

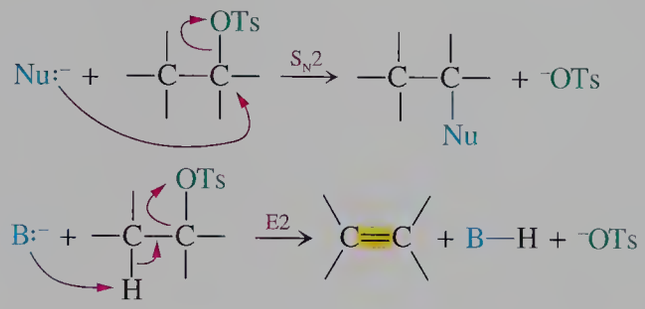


p-toluenesulfonyl chloride
(tosyl chloride)



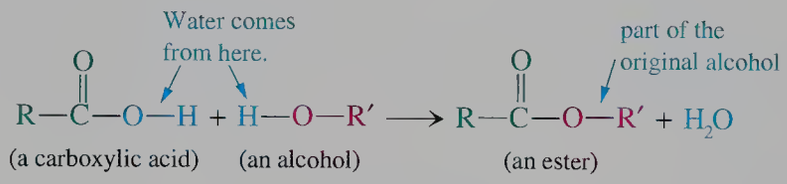
alkyl *p*-toluenesulfonate
(alkyl tosylate)

Alcohols react with *p*-toluenesulfonyl chloride to give useful synthetic intermediates called *p*-toluenesulfonates. The *p*-toluenesulfonate ion, a weak base, is an excellent leaving group. Methyl, primary, and secondary tosylates undergo S_N2 displacement reactions with nucleophiles. They also react with strong bases in E2 reactions.

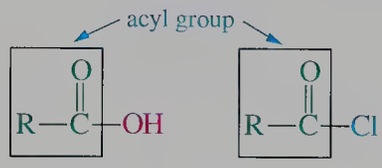


Esters of Carboxylic Acids

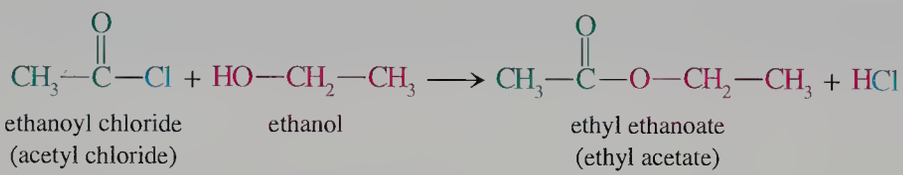
Esters of carboxylic acids most often result from attack of the alcohol's nucleophilic oxygen atom on the carbonyl carbon atom of the carboxylic acid. The ester therefore contains the oxygen atom of the alcohol.

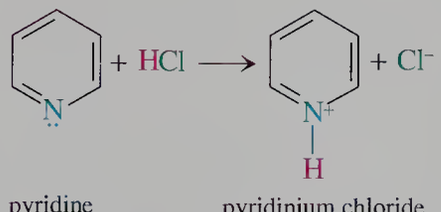


As in the case of inorganic acids, a derivative of a carboxylic acid called an **acid chloride** or **acyl chloride** is often the preferred reagent to form esters. Isolating the acyl group within the boxes shown below emphasizes the relationship between carboxylic acids and acid chlorides.



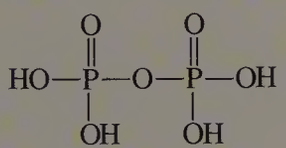
Organic esters are conveniently made by reacting an alcohol with an acid chloride. A base such as pyridine neutralizes the HCl released.



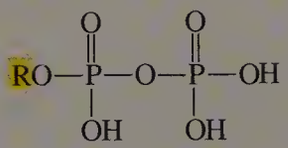


Phosphate and Pyrophosphate Esters

Many of the reactions that occur in cells require displacement of a hydroxyl group by a nucleophile. Although the hydroxyl group of an alcohol is not a good leaving group, it can be converted into a phosphate or pyrophosphate ester. Both phosphoric and pyrophosphoric acids are stronger acids than water. Thus, the related conjugate bases—phosphate ion and pyrophosphate ion—are weaker bases than the hydroxide ion. Both conjugate bases are then excellent leaving groups. Let's focus on the pyrophosphates and pyrophosphoric acid.

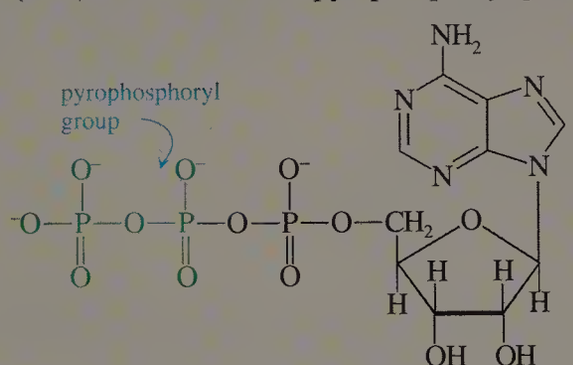


pyrophosphoric acid



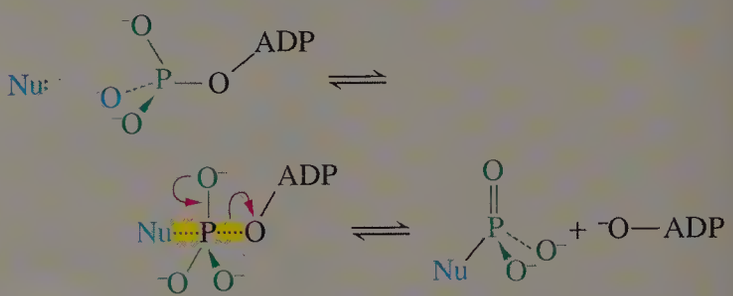
(a pyrophosphate)

The concentration of pyrophosphate ion in cells is very low, and the conversion of alcohols to pyrophosphates almost never occurs by itself. So, how are alcohols converted to pyrophosphates in cells? The answer is that the source of pyrophosphate is not the pyrophosphate ion or phosphoric acid, but a molecule called adenosine 5′-triphosphate (ATP) which contains a pyrophosphoryl group.



adenosine 5′-triphosphate (ATP)

The phosphorus atoms are very susceptible to attack by nucleophiles because of the inductive electron withdrawal by oxygen atoms. The leaving group is a phosphate or diphosphate derivative, depending on which phosphorus atom the nucleophile attacks. For example, attack at the terminal phosphorus would release ADP as the leaving group.



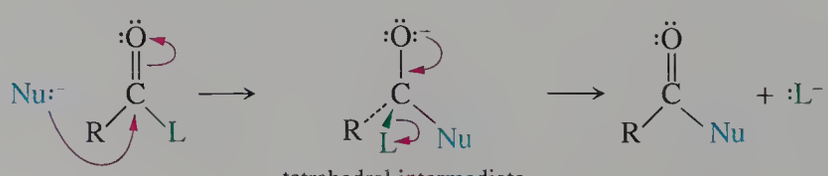
The hydrolysis of ATP is one example of nucleophilic attack at phosphorus. Either of the P—O—P bonds of adenosine triphosphate can be hydrolyzed. Nucleophilic attack by water at a terminal phosphorus atom displaces adenosine 5′-diphosphate (ADP). Attack at the internal phosphorus atom displaces adenosine 5′-monophosphate (AMP) and forms pyrophosphate. The ΔG°_{rxn} for both hydrolysis reactions is negative, as indicated by the following equations using the ionic forms of all species as they exist in biological systems.

$$ATP^{4-} + H_2O \longrightarrow ADP^{3-} + HPO_4^{2-} + H^+ \qquad \Delta G^\circ = -34.2 \text{ kJ mole}^{-1}$$

$$ATP^{4-} + H_2O \longrightarrow AMP^{2-} + HP_2O_7^{3-} + H^+ \qquad \Delta G^\circ = -35.0 \text{ kJ mole}^{-1}$$

The large negative free energy of hydrolysis is in part a reflection of the release of electrostatic repulsion among the negatively charged oxygen atoms on neighboring

This reaction, in which a halide ion is formally replaced by an alkoxy group, is an example of nucleophilic acyl substitution. A general representation of this mechanism using Nu:⁻ as the nucleophile and L:⁻ as the leaving group is given below.



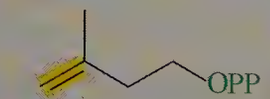
tetrahedral intermediate

phosphorus atoms. The better solvation of the separated product ions compared to the solvation of ATP also favors the reaction.

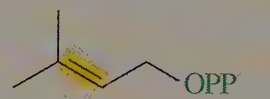
Phosphate and pyrophosphate esters of alcohols form when a phosphorus-containing group transfers from ATP to oxygen. The reaction occurs by nucleophilic attack on phosphorus by the hydroxyl group's oxygen atom. The net enzyme-catalyzed reaction for formation of a pyrophosphoryl group is shown below. For simplicity, charges have been left out, and —OPP used to represent the covalently bonded pyrophosphoryl group.

$$ROH + ATP \longrightarrow R{-}OPP + AMP$$

Pyrophosphate derivatives of alcohols participate in the biosynthesis of many molecules, including cholesterol and steroid hormones. The biosynthesis of these molecules begins with a nucleophilic substitution reaction between two five-carbon isoprenoid pyrophosphates called isopentenyl pyrophosphate and dimethylallyl pyrophosphate. An enzyme-catalyzed reaction interconverts the two isomers.



isopentenyl pyrophosphate

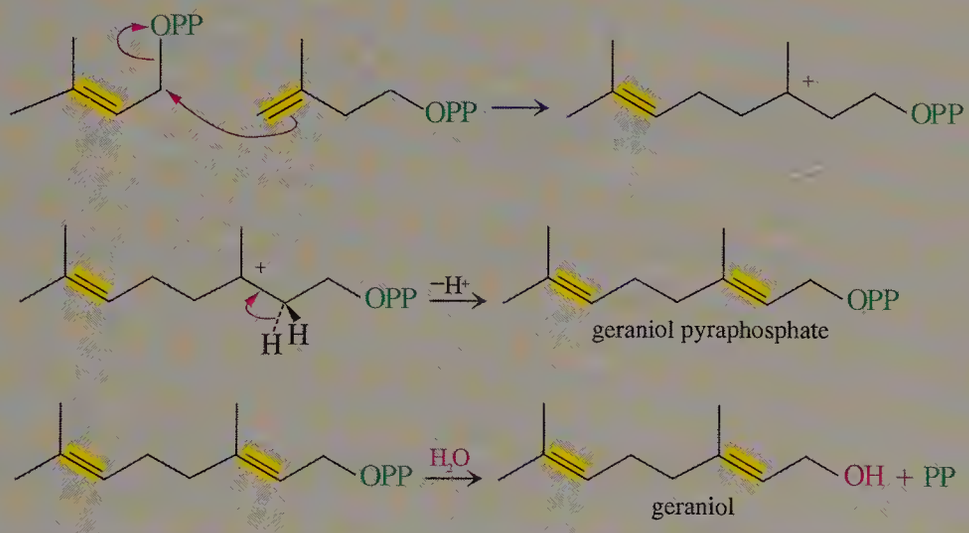


dimethylallyl pyrophosphate

They combine in a nucleophilic substitution reaction in which the π electrons of isopentenyl pyrophosphate act as a nucleophilic center to displace a pyrophosphoryl group from dimethylallyl pyrophosphate.

The nucleophilic substitution reaction produces a new carbon–carbon bond, leaving a carbocation in the isopentenyl group. Loss of a proton at the C-2 atom yields geraniol pyrophosphate. This product then reacts with water, which displaces the pyrophosphate group and produces a terpene alcohol, geraniol.

Although the processes become more complicated, the mechanisms for the formation of other terpenes, both cyclic and acyclic, are similar.



The net result is a substitution reaction in which the stoichiometry resembles that of an S_N2 substitution reaction of haloalkanes. However, an S_N2 reaction occurs in a single step in which the nucleophile bonds to the carbon atom as the leaving group leaves. Nucleophilic acyl substitution occurs in two steps, and the rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. The loss of the leaving group occurs in a second, faster step. Chapter 22 contains additional details of nucleophilic acyl substitution.

We recall that the size of the nucleophile strongly affects the rate of an S_N2 process. Thus, *tert*-butoxide is a poorer nucleophile than ethoxide ion (Section 10.1).

For the same steric reasons, the order of reactivity of an alcohol with an acyl chloride (or carboxylic acid) decreases in the order primary > secondary > tertiary.

The chemistry of organic esters differs substantially from that of inorganic esters. The conjugate base of a carboxylic acid—the carboxylate ion—is a stronger base than the conjugate bases of inorganic acids. Hence, a carboxylate ion is not a good leaving group, and the alkyl carbon atom is not nearly as susceptible to nucleophilic substitution reactions. Also, the carbonyl carbon atom of the ester is much more susceptible to attack by a nucleophile (Chapter 22).

Problem 16.1

Write the Lewis structure of phosphorus oxychloride ($POCl_3$) the acid chloride of phosphoric acid. Write the structure of the product formed when excess methanol reacts with phosphorus oxychloride.

Problem 16.2

Write the structure of the product formed in the reaction of chlorosulfonic acid with (*S*)-2-butanol. What is the configuration of this product?

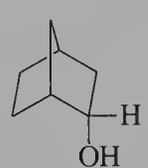
Problem 16.3

Silicic esters, $(RO)_4Si$, form in the reaction of alcohols with $SiCl_4$. They react with water to form silica and an alcohol. Mechanisms for the hydrolysis can be written that involve S_N2 attack of water on silicon or at the carbon atom of the R group. Suggest an experiment using isotopes that would distinguish between these two possible mechanisms.

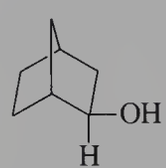
$$(RO)_4Si + 4\ H_2O \longrightarrow 4\ ROH + Si(OH)_4$$

Problem 16.4

The rates of reaction of ethanoyl chloride (CH_3COCl, acetyl chloride) with *exo*- and *endo*-bicyclo[2.2.1]heptan-2-ol are different even though both are secondary alcohols. Examine molecular models of these compounds to determine why. Which compound reacts at the faster rate?



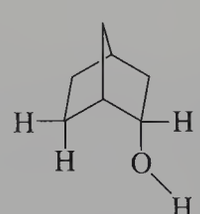
endo-bicyclo[2.2.1]heptan-2-ol



exo-bicyclo[2.2.1]heptan-2-ol

Sample Solution

The hydroxyl group of the endo compound is in a more sterically crowded environment. There are 1,3 diaxial interactions, much like those in the axial position of a cyclohexane ring.



We recall that the rate of reaction of nucleophiles decreases with increased steric size of the nucleophile (Section 10.1). Thus the endo compound should react at a slower rate than the exo compound.

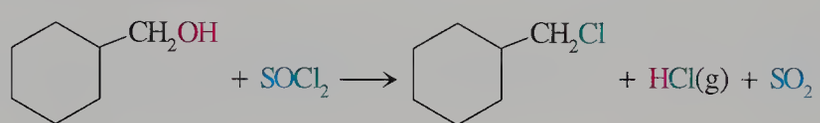
16.3 Conversion of Alcohols into Alkyl Halides

As discussed in Section 8.14, the conversion of alcohols into alkyl chlorides or bromides requires HCl and HBr, respectively. The reactions occur by way of the conjugate acid of the alcohol, which is protonated by the strongly acidic hydrogen halide. We recall that the negatively charged hydroxide ion, a strong base, is a poor leaving group. However, protonation of the alcohol converts the —OH group into a good leaving group, water. Substitution of water by chloride or bromide ion occurs by an S_N2 process for primary and secondary alcohols and an S_N1 process for tertiary alcohols. The order of reactions rates for alcohols is $3° > 2° > 1°$.

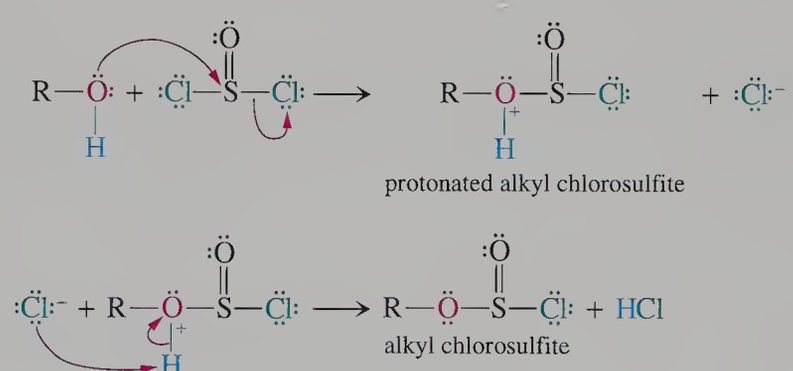
Formation of Alkyl Chlorides Using Thionyl Chloride

Thionyl chloride and phosphorus tribromide also convert either secondary or primary alcohols into alkyl chlorides and alkyl bromides, respectively. Both of these reagents transform the hydroxyl group into a good leaving group, which a halide ion can then displace.

The reaction of an alcohol with thionyl chloride to give an alkyl chloride produces two gaseous products, hydrogen chloride and sulfur dioxide, both released from the reaction mixture. The alkyl chloride remains in solution.

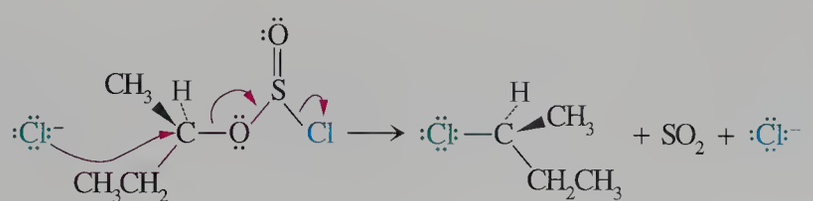


The reaction mechanism occurs in several steps. First, a nucleophilic oxygen atom of the alcohol displaces a chloride ion from thionyl chloride to form an a protonated alkyl chlorosulfite intermediate. Subsequent deprotonation of this intermediate by a base yields the alkyl chlorosulfite, an inorganic ester.

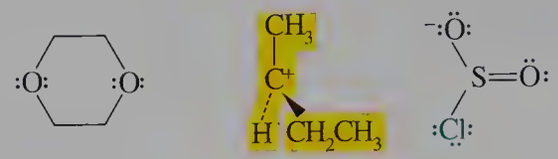


The next step of the reaction may occur by either of two mechanisms, depending on the reaction conditions.

1. If a base such as pyridine is present to neutralize the HCl generated in the steps leading to the alkyl chlorosulfite, a substitution reaction occurs with inversion of configuration.

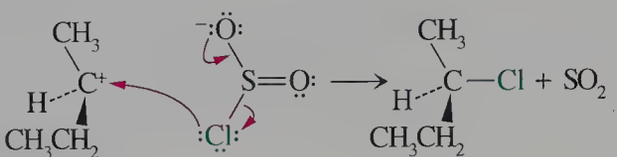


2. In dioxane as solvent, the substitution process occurs with net retention of configuration. The alkyl chlorosulfite undergoes heterolytic cleavage of its C—O bond to give a pair of oppositely charged ions. These ions, a carbocation and chlorosulfite, remain together as an **ion pair**. Dioxane may solvate the carbocation on the side opposite the chlorosulfite.



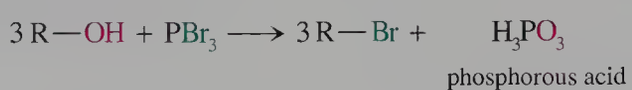
solvated ion pair

The ion pair can react by transfer of chloride ion to the same face of the carbocation as the original C—O bond. The process is called **internal return**, and the mechanism is called S_Ni, where the i of the notation refers to internal.

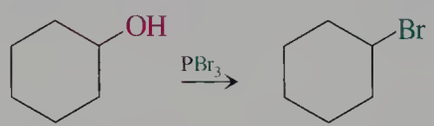


Formation of Alkyl Bromides Using Phosphorus Tribromide

The reaction of an alcohol with phosphorus tribromide produces an alkyl bromide and phosphorous acid, which has a high boiling point and is water soluble. Consequently, the bromoalkane can be separated from the reaction mixture by distillation or by adding water.

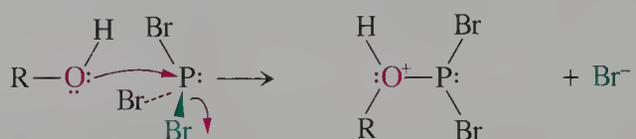


phosphorous acid



cyclohexanol bromocyclohexane

In the first step of this reaction, the nucleophilic oxygen atom of the alcohol displaces a bromide ion from the phosphorus tribromide to form the conjugate acid of a phosphite ester, $ROPBr_2$.

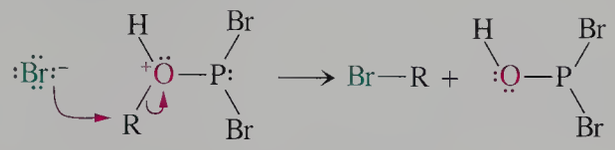


protonated phosphite ester

Continued reaction, and successive displacement of bromide ion on the $ROPBr_2$ intermediate, yields esters having the general formulas $(RO)_2PBr$ and $(RO)_3P$. These esters react with bromide ion to form the alkyl bromide product. For the sake of simplicity, we consider only the reaction of the $ROPBr_2$ intermediate. The driving force

for the reaction is the formation of a P—O bond, which has a large bond dissociation energy.

In the second step of the reaction, the C—O bond of the phosphite ester breaks, with predominant inversion of configuration.



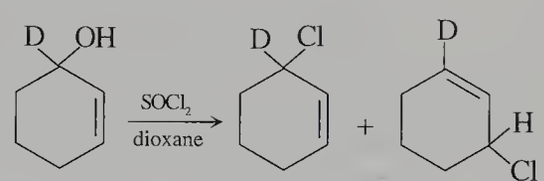
Some loss of optical activity and a small amount of rearrangement may occur. For example, 2-bromobutane formed from optically active 2-butanol is about 80% optically pure. About 2% of the product is 2-bromo-2-methylpropane.

Problem 16.5

Reaction of 3-pentanol with phosphorus tribromide yields a mixture of 3-bromopentane and 2-bromopentane in approximately a 9:1 ratio. Explain the source of each product.

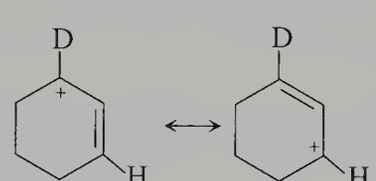
Problem 16.6

Reaction of 1-deuterio-2-cyclohexen-1-ol with thionyl chloride in dioxane as solvent yields a mixture of two isomeric 3-chlorocyclohexenes with the deuterium distributed as indicated. Suggest a mechanism that accounts for the formation of the two products. Predict the ratio of the two products formed.



Sample Solution

The chlorosulfite derived from the alcohol is an allyl derivative that is prone to react by an S_N1 mechanism. Two resonance forms can be written for the carbocation, which are equal in energy, but nonequivalent because of the deuterium atom.

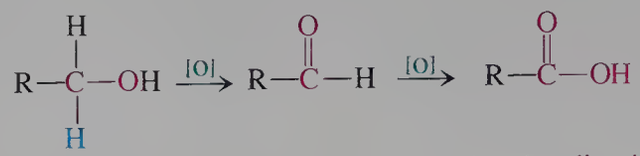


Capture of the carbocation by a chloride ion can occur at either of two sites, giving two isomeric 3-chlorocyclohexenes in equal amounts.

16.4 Oxidation of Alcohols

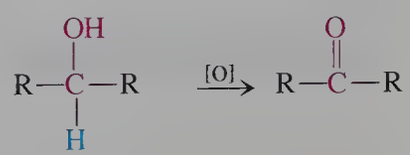
A variety of chemical reagents can oxidize primary and secondary alcohols, which react differently with oxidizing agents. Primary alcohols (general formula RCH_2OH) can be oxidized to aldehydes (general formula RCHO). Note that this oxidation occurs with the loss of two hydrogen atoms. Aldehydes are easily oxidized, and may react to produce carboxylic acids (RCOOH). When an aldehyde is oxidized to a car-

boxylic acid, the oxidized carbon atom gains an oxygen atom. The [O] shown above the reaction arrow represents an unspecified oxidizing agent.

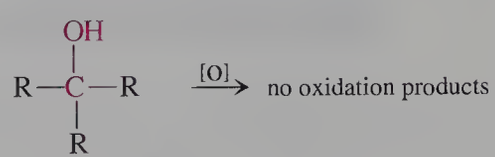


(an aldehyde) (a carboxylic acid)

Secondary alcohols are oxidized to form ketones (RCOR) which are not easily oxidized because there is no hydrogen atom on the carbonyl carbon atom of the ketone. Tertiary alcohols are not oxidized because the carbon atom bearing the —OH group has no hydrogen atom.



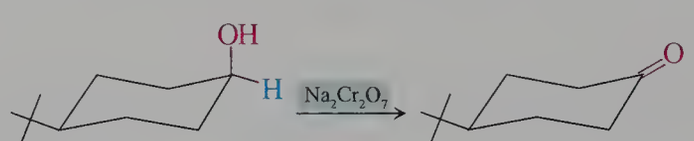
(a secondary alcohol) (a ketone)



(a tertiary alcohol)

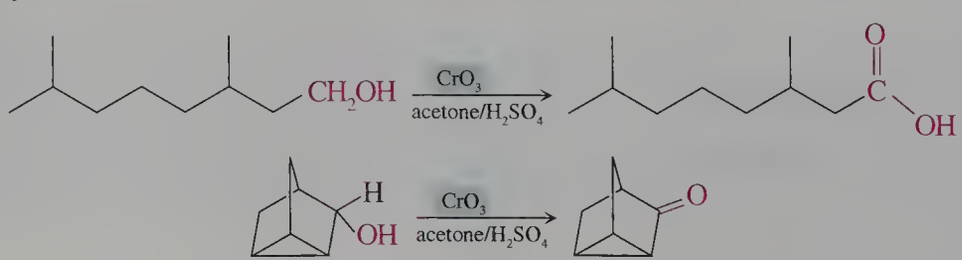
Oxidizing Agents for Alcohols

Alcohols are usually oxidized using chromium(VI) compounds. When the alcohol is oxidized, Cr(VI) is reduced in several steps to Cr(III). The specific Cr(VI) species used depends on the scale of the process, cost of reagents, and limitations that result from the presence of other functional groups in the reactant. For example, sodium dichromate is an inexpensive reagent. It is used in aqueous acetic acid for large-scale reactions. This reagent oxidizes secondary alcohols to ketones. It oxidizes primary alcohols to aldehydes and then to carboxylic acids unless the intermediate aldehyde has a low molecular weight and can be distilled out of the reaction mixture to prevent its further oxidation.



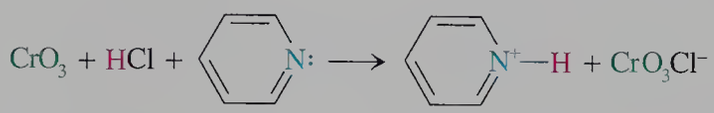
cis-4-*tert*-butylcyclohexanol 4-*tert*-butylcyclohexanone

In small-scale reactions, the Jones reagent is used to oxidize alcohols. The **Jones reagent** consists of chromium trioxide (CrO_3) in a solution of aqueous acetone and sulfuric acid. The Jones reagent oxidizes primary alcohols to aldehydes, then immediately oxidizes the aldehydes to carboxylic acids. This reagent also converts secondary alcohols to ketones.

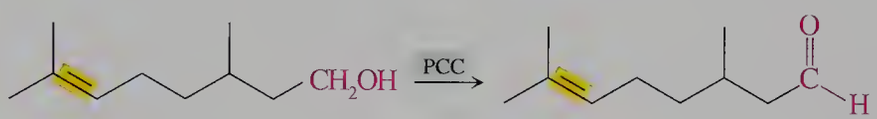


Oxidation by the Jones reagent occurs rapidly at or below room temperature. A simple alcohol with no other functional groups is easily oxidized to give a good yield of oxidized product. However, the yield of the desired oxidation product may diminish if functional groups that are sensitive to acid are present. For example, oxidation of a carbon–carbon double bond in an unsaturated alcohol may occur.

Alcohols are also oxidized with a milder oxidizing agent consisting of pyridinium chlorochromate (PCC) in methylene chloride (CH_2Cl_2) as solvent. The PCC reagent is made by dissolving CrO_3 in HCl and then adding pyridine to obtain a solid, which is isolated and then dissolved in methylene chloride. The reagent is anhydrous.

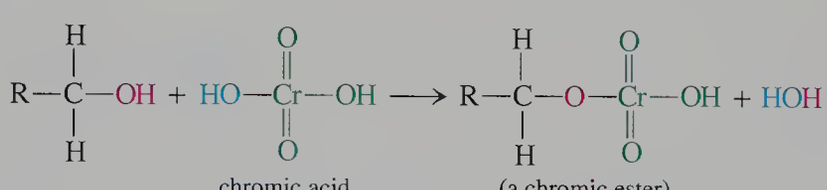


Because the reaction occurs under basic conditions, functional groups such as carbon–carbon double bonds are unaffected during the time required for oxidation of the alcohol. But the principal advantage of PCC is that primary alcohols are converted to aldehydes without continued oxidation to carboxylic acids.

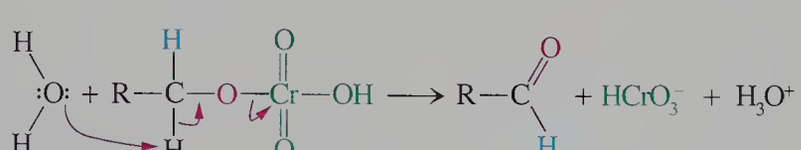


Mechanism of Oxidation by Chromium(VI)

Chromic acid (H_2CrO_4) can oxidize alcohols both in aqueous solutions of sodium dichromate and in the Jones reagent. It reacts with alcohols to form a chromic ester in which the alcohol oxygen atom bridges the carbon and chromium atoms. Thus, the ester forms by nucleophilic attack of the alcohol's oxygen atom on the chromium atom.



In the second step, the chromic ester undergoes an α-elimination reaction. Most of the elimination processes discussed in prior chapters have been β-elimination reactions, which form a carbon–carbon double bond. In this oxidation step, a carbon–oxygen double bond forms.

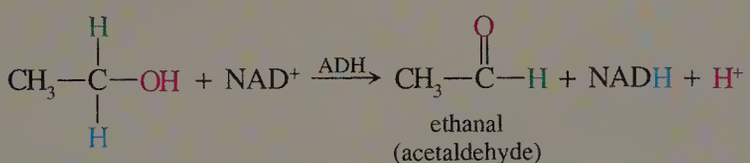


Note that if we regard the chromium atom as equivalent to the β hydrogen atom in a β elimination, then the oxidation reaction occurs by a concerted E2 process. Although the chromium species formed contains chromium(IV), a series of disproportionation steps occurs. These generate higher oxidation states, which continue the oxidation, and chromium(III), the final reduced form in the reaction. The exact steps in this sequence are unimportant to our understanding of the oxidation of the alcohol.

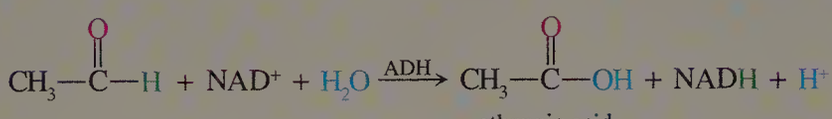
Toxicity of Alcohols

Methanol is highly toxic. Drinking as little as 15 mL of pure methanol can cause blindness; 30 mL will cause death. Prolonged breathing of methanol vapor is also a serious health hazard.

Although ethanol is the least toxic of the simple alcohols, it is still a poisonous substance and must be oxidized in the body to prevent high blood alcohol levels, which can "poison" the brain. The liver enzyme alcohol dehydrogenase (ADH) oxidizes alcohol. ADH requires a coenzyme, nicotinamide adenine dinucleotide (NAD^+), as an oxidizing agent. The coenzyme can exist in an oxidized form, NAD^+, and a reduced form, NADH. NAD^+-dependent liver ADH oxidizes ethanol to ethanal (acetaldehyde). Subsequent oxidation of ethanal yields ethanoic acid (acetic acid), which is nontoxic in small concentrations.

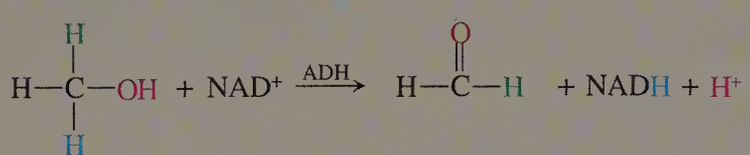


ethanal
(acetaldehyde)

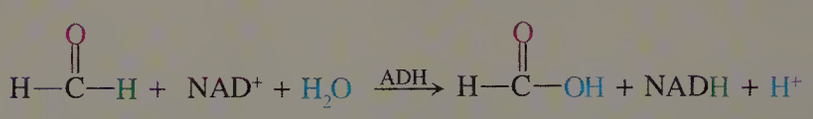


ethanoic acid
(acetic acid)

The oxidation products of some other alcohols are toxic. In the case of methanol, oxidation catalyzed by ADH gives methanal (formaldehyde) and then methanoic acid (formic acid).



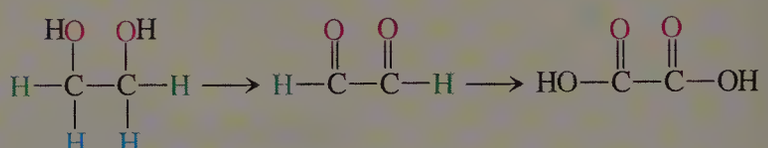
methanal
(formaldehyde)



methanoic acid
(formic acid)

Formaldehyde travels in the blood throughout the body and reacts with proteins, destroying their biological function. Methanol causes blindness because formaldehyde destroys an important visual protein. Formaldehyde reacts with an amine functional group of the amino acid lysine in a protein, called rhodopsin. Formaldehyde also reacts with amino groups in other proteins, including many enzymes, and the loss of the function of these biological catalysts causes death.

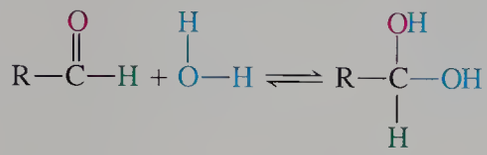
Ethylene glycol is also toxic. This sweet-tasting substance is the primary component of antifreeze. Dogs sometimes ingest the poisonous antifreeze left in open containers. Oxidation occurs to give oxalic acid, which causes kidney failure.



ethylene glycol glyoxal oxalic acid

Physicians treat methanol or ethylene glycol poisoning with intravenous injections of ethanol before substantial oxidation has occurred. ADH binds more tightly to ethanol than to methanol or ethylene glycol, and the rate of oxidation of ethanol is about six times as fast as that of methanol. The ethanol concentration can be kept higher because it is directly injected. As a result, neither methanol nor ethylene glycol is competitively oxidized to toxic products and the kidneys can slowly excrete them.

Aldehydes are oxidized because they form **gem diols**, also known as **hydrates**. Gem diols result from an addition reaction to the carbonyl group, a process that we will discuss in Chapter 18.



(a gem diol)

The gem diol is an alcohol. One of its hydroxyl groups is oxidized by way of a chromic half ester in the same manner as alcohols. The resulting compound retains the hydroxyl group of the original chromic half ester and is a carboxylic acid.

chromic acid half ester of a gem diol

The gem diols form in low concentration in equilibrium with the aldehyde. However, as they are converted into chromic acid half esters and oxidized, they continue to form from the aldehyde until the oxidation is complete. When a primary alcohol is oxidized by PCC, water is absent. So, a gem diol cannot form, and the aldehyde is not further oxidized.

Problem 16.7

Which of the isomeric $C_4H_{10}O$ alcohols reacts with the Jones reagent to produce the ketone C_4H_8O?

Problem 16.8

Potassium permanganate ($KMnO_4$) oxidizes alcohols but is a less selective reagent than chromium(VI) reagents. Write a reasonable multistep mechanism involving a manganate ester that accounts for the oxidation of a secondary alcohol to a ketone.

Problem 16.9

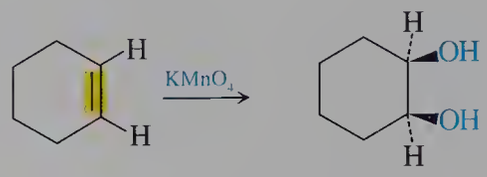
The Jones reagent oxidizes isomeric alcohols at different rates. For example, *cis*-4-*tert*-butylcyclohexanol reacts faster than the trans isomer. Considering the anticipated steric effect on each step of the mechanism, predict which step determines the reaction rate.

Sample Solution

The formation of a chromic ester should be sensitive to the steric environment of the oxygen atom, which acts as a nucleophile in forming the Cr—O bond. Because an axial hydroxyl group is in a more hindered position than an equatorial hydroxyl group, we would expect the cis isomer to react more slowly than the trans isomer if ester formation were the rate-determining step. The second step involves removal of a hydrogen atom at the α carbon atom. In the cis isomer the carbon–hydrogen bond is equatorial, a position that is more sterically accessible to base than is the axial carbon-hydrogen bond of the trans isomer. Thus, this order of reactivity observed is consistent with this step as the rate-determining step.

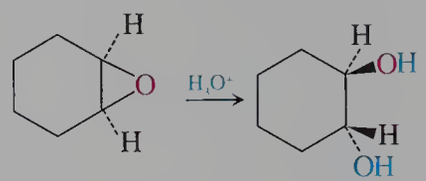
16.5 Reactions of Vicinal Diols

Vicinal diols can be prepared from alkenes using potassium permanganate or osmium tetraoxide (Section 7.9). We recall that these reactions occur by syn addition to give cis 1,2-diols.



cis-1,2-cyclohexanediol

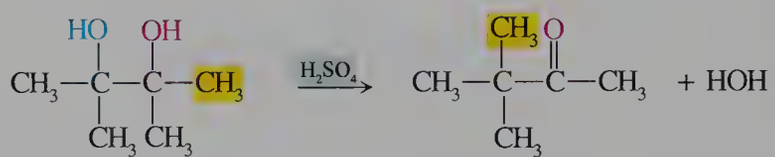
Vicinal diols also occur in which the OH groups are trans. Net anti dihydroxylation occurs in a multistep process with an epoxide intermediate (Section 7.8). The acid-catalyzed hydrolysis of epoxides yields a ring-opened product by S_N2 attack of the nucleophilic water molecule on the protonated epoxide.



trans-1,2-cyclohexanediol

The Pinacol Rearrangement

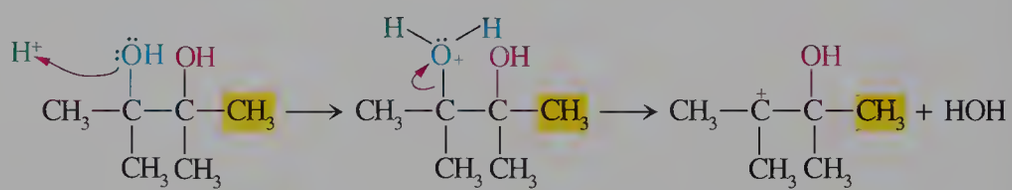
A vicinal diol reacts with sulfuric acid to give a rearranged dehydration product. The reaction of 2,3-dimethyl-2,3-butanediol (pinacol) to 3,3-dimethyl-2-butanone (pinacolone) is an example of this process, generally known as the **pinacol rearrangement**.



2,3-dimethyl-2,3-butanediol (pinacol)

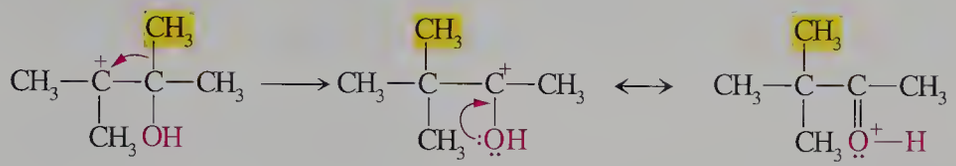
3,3-dimethyl-2-butanone (pinacolone)

The first step of the pinacol rearrangement is protonation of one of the two hydroxyl oxygen atoms. Then water leaves, yielding a tertiary carbocation.



In the dehydration of alcohols, we recall that a methyl group can migrate to an adjacent electron-deficient center if a more stable carbocation results (Section 8.20). In this case, the rearrangement of a methyl group yields a carbocation that is formally a secondary ion. However, it is a stabilized **hydroxy carbocation**.

The nonbonded electron pair on the oxygen atom is delocalized to the positive carbon atom.

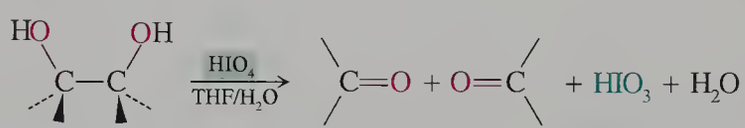


hydroxy carbocation

Because the oxonium ion resonance form has an octet of electrons around each of the atoms, it is the most important contributor. The resultant stabilization of the ion compared to a typical carbocation is part of the reason for the rearrangement reaction. (We recall that the cyclohexadienyl cation intermediates formed in aromatic substitution reactions are also stabilized by the resonance donation of electrons from the oxygen atom of phenols and anisoles.) Loss of the hydrogen atom bonded to oxygen from the resonance-stabilized cation yields the final product, pinacolone.

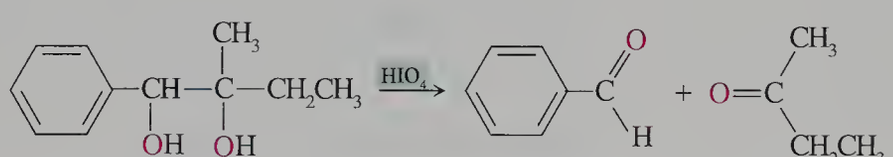
Oxidative Cleavage of Vicinal Diols

Vicinal diols are cleaved by periodic acid to yield aldehydes or ketones, depending on the number of substituents on the carbon atoms bearing the hydroxyl groups. The periodic acid is reduced to iodic acid (HIO_3).

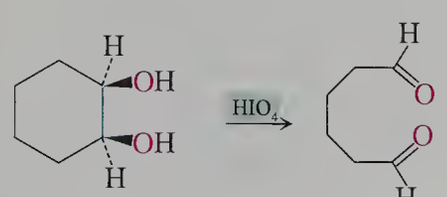


Because vicinal diols are obtained from alkenes, the combination of dihydroxylation followed by oxidative cleavage of a diol provides an alternative method to ozonolysis of alkenes to yield the same products. We can deduce the structure of the starting diol from the structures of the carbonyl compounds.

If the vicinal diol is contained in an acyclic portion of a molecule, two carbonyl compounds result—unless the vicinal diol is a symmetrical molecule, in which case it yields two equivalents of a carbonyl compound. If the two hydroxyl groups are both on a ring, a ring-opened product containing two carbonyl groups forms.

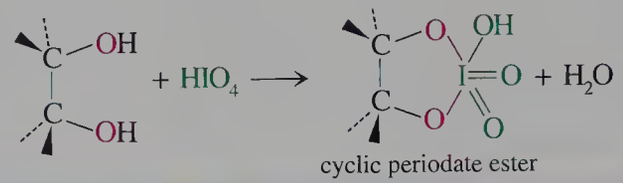


2-methyl-1-phenyl-1,2-butanediol — benzaldehyde — 2-butanone



cis-1,2-cyclohexanediol — 6-oxohexanal

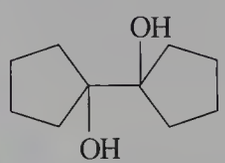
The cleavage reaction occurs by way of a cyclic periodate intermediate, which may formally be considered a diester of an inorganic acid. The cyclic ester forms more easily for cis diols than for trans diols, so the rate of cleavage of cis diols is faster than the rate of cleavage of trans diols.



cyclic periodate ester

Problem 16.10

Reaction of the following diol with sulfuric acid yields a ketone with the molecular formula $C_{10}H_{16}O$. Write the strucure of the product.



Problem 16.11

A compound with molecular formula $C_{12}H_{22}O_2$ reacts with periodic acid to give cyclohexanone. Write the structure of the reactant.

16.6 Synthesis of Alcohols

Alcohols are important synthetic intermediates because they can be transformed into many other functional groups. Fortunately, they can also be synthesized from several classes of compounds, some of which contain oxygen and some of which do not. We will find that each method for the synthesis of alcohols has certain limitations that determine the scope of the reaction. Thus, it is important to learn what can and cannot be done with each set of reagents.

To synthesize an alcohol (or any other compound) conditions must be chosen that produce only the correct compound with a minimum of by-products in the smallest number of steps. As the number of steps in a synthetic sequence increases, the chance of obtaining a high yield of the end product decreases.

The selection of a given reaction to synthesize an alcohol is often based on a knowledge of the mechanisms of the various potential reactions. For that reason, we have to understand how differences in molecular structure can affect the final yield of product. We can't simply select a reagent because it works for some other compound. We must always ask whether the reaction will occur in good yield for the selected compound.

Synthetic Methods: A Review

We learned in Chapter 8 that an alcohol can be obtained by substituting a halide ion in an alkyl halide with hydroxide ion. However, we discussed in Chapter 9 that a competing elimination reaction diminishes the yield in the substitution reaction because the nucleophilic hydroxide ion is also a strong base. In Section 16.7, we will examine an alternative substitution reaction that takes into account this potential competing reaction.

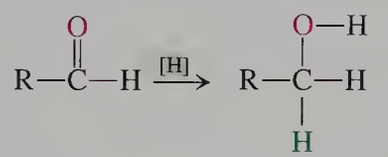
We have previously discussed the hydration of alkenes as a method for the synthesis of alcohols (Section 7.5). The reaction is easily reversible, and poor yields of product may result. Furthermore, even if the reaction is "pushed" by the selection of optimal reaction conditions, there is a competing reaction. Hydration is an elec-

trophilic addition reaction that occurs by way of a carbocation and can yield rearranged products. Therefore direct hydration is not the preferred method of synthesis of most alcohols. In Section 16.8, we will examine alternate addition reactions that have no competing rearrangement reactions and give good yields of alcohols.

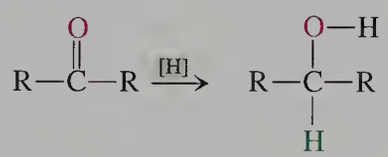
Reductive Synthetic Methods

Both the nucleophilic substitution of halide by an oxygen nucleophile and the hydration of alkenes start with substrates that do not contain oxygen. However, the synthesis of alcohols from compounds with functional groups that already contain oxygen has an obvious advantage. The presence of oxygen in a functional group at the very site where the hydroxyl group is desired is a synthetic opportunity of immense value.

Carbonyl compounds such as aldehydes and ketones contain a carbon–oxygen double bond that can be reduced to yield an alcohol.



aldehyde primary alcohol

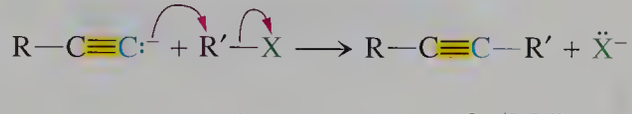


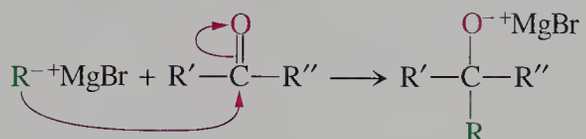
ketone secondary alcohol

In Section 16.9, we will consider reducing agents and their regioselectivity. The reduction of carbonyl groups is sometimes accompanied by reduction of other functional groups. We will find that many synthetic variations are possible because several reducing agents with different reactivities and regioselectivities have been developed.

Alkylation Synthetic Methods

Organic synthetic methods must be able to accomplish more than just functional group transformations. We also need methods that form carbon–carbon bonds so that complex structures can be made from simpler structures. One example of this method is the formation of complex alkynes by alkylation of alkyl halides using alkynide ions. We recall that the reaction occurs by nucleophilic attack of the alkynide ion at the electrophilic carbon atom of the alkyl halide (Section 11.8). The carbanion available from a Grignard reagent reacts with certain electrophilic carbon atoms, such as a carbonyl carbon atom of either an aldehyde or a ketone. A new carbon–carbon bond results, and an alcohol forms. We will see that this use of Grignard reagents to form alcohols is one of the powerful synthetic methods in organic chemistry.

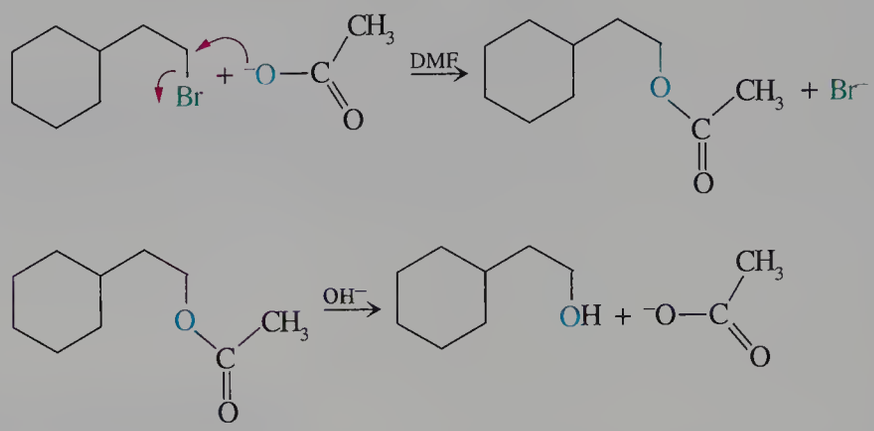




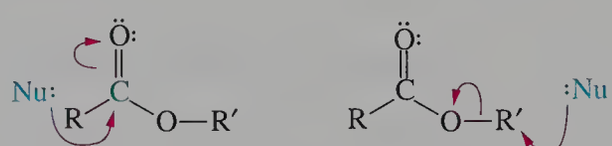
alkoxide ion
(can be neutralized
to form an alcohol)

16.7 Synthesis of Alcohols from Haloalkanes

To avoid competition between substitution and elimination, we can select a nucleophilic oxygen source that is not a strong base. One such source is the ethanoate ion (acetate ion). It is a weaker base than the hydroxide ion because ethanoic acid (acetic acid) is a stronger acid than water. It will displace a halide such as bromide ion in an S_N2 process. The resulting ester can then be cleaved by aqueous base in a process called saponification to give the desired alcohol.



We will discuss the details of the mechanism of this second reaction, a nucleophilic acyl substitution, in Chapter 22. At present, you need only remember that the nucleophilic hydroxide ion cleaves the carbonyl carbon–oxygen bond and that a competing elimination reaction does not occur. Although the equation may look like a typical nucleophilic substitution reaction in which hydroxide ion displaces the ethanoate ion, the reaction does not occur by way of an S_N2 mechanism. The oxygen atom bridging the sp^3-hybridized carbon atom and the carbonyl carbon atom remains bonded to the alkyl group. In general, attack of nucleophiles on esters occurs at the carbonyl carbon atom, not at the sp^3-hybridized carbon atom of the alkyl group.

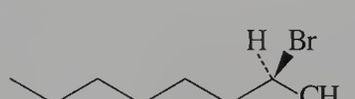


favored reaction site | less favored reaction site

What are the limitations of this two-step procedure to produce alcohols from alkyl halides? First, of course, we need an appropriate alkyl halide. Second, the displacement of halide ion by acetate occurs by way of an S_N2 process, which is efficient for primary alkyl halides, but occurs at a slower rate for secondary alkyl halides. The process fails for tertiary alkyl halides, which are too sterically hindered to react.

Problem 16.12

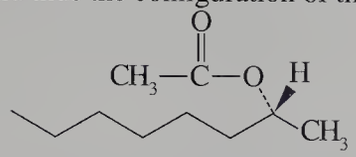
Write the structures of the products of the reaction of (*S*)-2-bromooctane with sodium acetate followed by hydrolysis with hydroxide ion. What is the configuration of each compound?



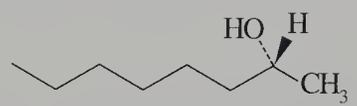
(*S*)-2-bromooctane

Sample Solution

An S_N2 reaction gives a product with inverted configuration with respect to the reactant. The ester formed has the *R* configuration. The hydrolysis reaction does not occur at the chiral center, and thus the configuration of the alcohol is the same as for the ester.



(an *R* ester)



(an *R* alcohol)

Problem 16.13

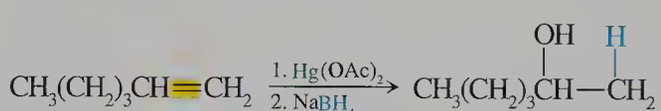
Which of the two compounds should react faster with sodium acetate in DMF, *cis*- or *trans*-4-methyl-1-chlorocyclohexane?

16.8 Indirect Hydration Methods

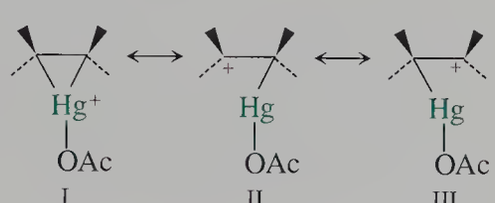
We can bypass the problems encountered in the hydration of alkenes by using either of two indirect hydration reactions. The discovery and development of these two complementary synthetic procedures are examples of the sophistication of modern synthetic methods, which allow the selective formation of desired products. The two methods use reagents that react by way of mechanisms that produce intermediates that do not rearrange. The reagents have different regioselectivities. One method, called the oxymercuration–demercuration method, indirectly gives net Markovnikov addition of water. The second method, called the hydroboration–oxidation method, gives net anti-Markovnikov addition of water.

Oxymercuration–Demercuration

In an oxymercuration–demercuration reaction, an alkene is treated with mercuric acetate, $Hg(OAc)_2$, and the product is treated with sodium borohydride. The net result is a Markovnikov addition product in which the OH group bonds to the more substituted carbon atom of the alkene.

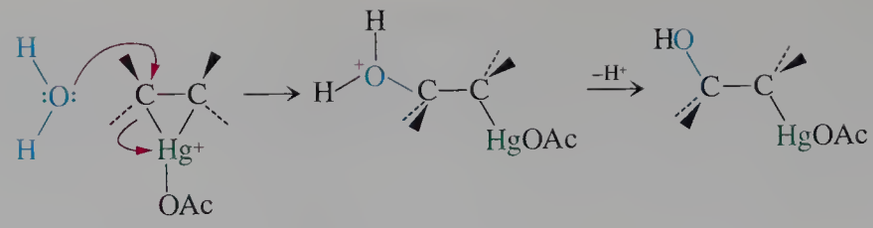


In the first step, an electrophilic $HgOAc^+$ ion adds to the double bond to give a mercurinium ion whose structure is similar to the structure of the bromonium ion (Section 11.6). Like the bromonium ion, the mercurinium ion is a hybrid of three contributing resonance structures.

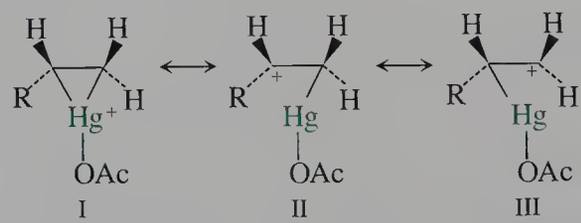


resonance contributors of a mercurinium ion

This species subsequently reacts with a nucleophilic water molecule. This results in the bonding of —HgOAc and a hydroxyl group on adjacent carbon atoms, with net anti addition.

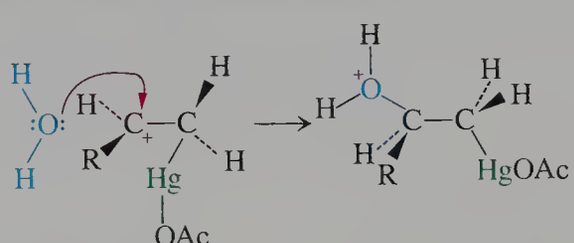


Why does Markovnikov addition occur as a result of the attack of water on the mercurinium ion? If the alkene is not symmetric, then neither is the mercurinium ion. In the most important resonance contributor to the ion, the mercury atom has the positive charge. Of the other two contributors, the one with the charge on the more substituted carbon atom is more stable. That is, resonance structure II is more stable than structure III.



mercurinium ion of a terminal monosubstituted alkene

The structure of the transition state for nucleophilic attack of water on the mercurinium ion is closely related to the structure of this intermediate. Thus the energy barrier is lower for attack of water at the more positive carbon atom of the intermediate. For a mercurinium ion of a terminal monosubstituted alkene such as 1-hexene, attack occurs at the C-2 atom, the more substituted site.



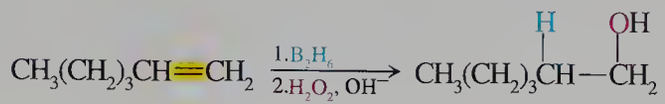
The organomercury compound is reduced with sodium borohydride, and the —HgOAc group is replaced by a hydrogen atom. The mechanism is not well established, but is thought to involve free radicals. Thus, the reaction is not necessarily stereospecific. Only the location of the hydroxyl group can be predicted from knowledge of the formation of the mercurinium ion and the direction of attack of water on that ion.

Oxymercuration–demercuration gives the product that would result from direct hydration of an alkene. However, the reactions occur with a higher yield than the direct hydration reaction because the competing reverse reaction, dehydration, does not occur. Because most of the positive charge in the mercurinium ion is on the mercury atom, the mercurinium ion has little carbocation character, and rearrangement reactions do not occur.

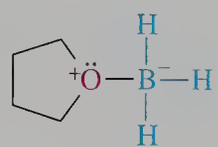
Hydroboration–Oxidation

Hydroboration–oxidation of alkenes, developed by the American chemist H. C. Brown, of Purdue Univeristy, also requires two steps. The sequence of reactions adds

the hydrogen and hydroxyl of water to a double bond to give a product that corresponds to anti-Markovnikov addition.

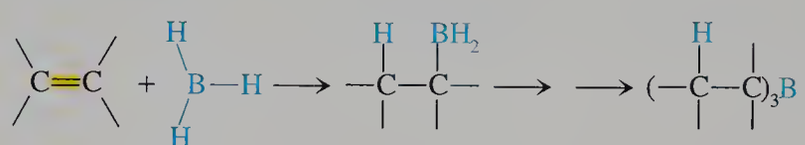


In the first step, hydroboration, an alkene is treated with diborane $(BH_3)_2$ or B_2H_6. Diborane acts as if it were the monomeric species called borane, (BH_3). The boron reagent is usually prepared in an ether solvent such as diethyl ether or tetrahydrofuran.

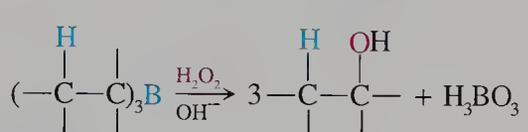


BH_3–tetrahydrofuran complex

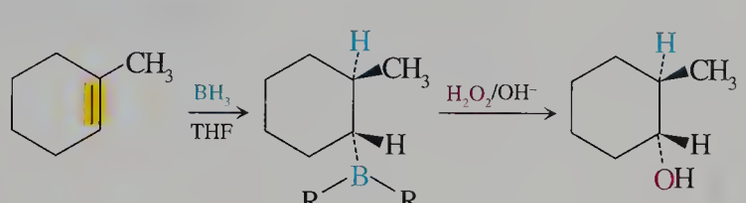
Borane adds to the carbon–carbon double bond of one alkene and then adds successively to two more alkenes, producing a trialkylborane, R_3B. These steps are hydroboration reactions.



In the oxidation step, the trialkylborane is treated with hydrogen peroxide and base to oxidize the organoborane to an alcohol.



Let's consider the result of the hydroboration–oxidation of 1-methylcyclohexene. The overall addition of water is anti-Markovnikov. That is, the hydrogen atom adds to the more substituted carbon atom, and the hydroxyl group to the less substituted carbon atom. The hydrogen atom and hydroxyl group are introduced from the same side of the double bond. In the oxidation step, a hydroxyl group replaces the boron with retention of configuration. Therefore, the net addition of water is syn.



This mode of addition occurs because hydroboration is a concerted syn process (Figure 16.1). That is, the carbon–boron and carbon–hydrogen bonds form at the same time that the boron–hydrogen bond breaks. Borane reacts with alkenes for two reasons. First, the boron atom in borane is an electron-deficient species with only six

electrons. Thus, the boron atom has a vacant 2p orbital and is an electrophilic Lewis acid. Because boron is electrophilic, it bonds to the least substituted carbon atom much like a proton. Second, boron is more electropositive than hydrogen. Therefore, the hydrogen atom of the boron–hydrogen bond has a partial negative charge. This hydrogen atom behaves like a hydride ion, not like a proton.

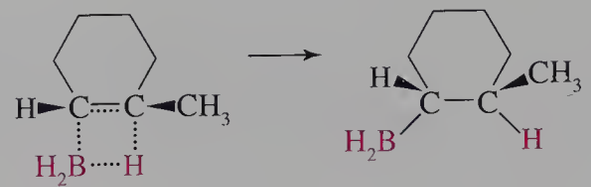
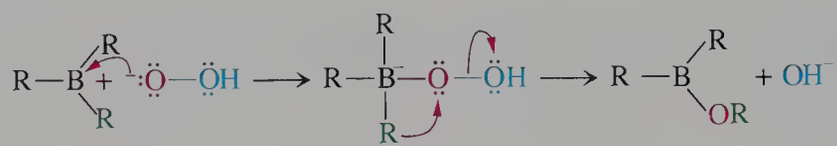


FIGURE 16.1
Mechanism of Borane Addition to a Double Bond
The boron and hydrogen atom add to the same face of the double bond. The resulting product has the groups cis to each other. The dotted lines represent bonds formed and broken in the transition state of the concerted reaction.

In summation, two properties of BH_3, the electrophilic character of the boron atom and the hydride character of the hydrogen atom, account for anti-Markovnikov addition of BH_3 to alkenes. In addition, the regioselectivity probably also reflects some steric control in which the boron adds to the less substituted carbon atom.

Now let's consider the mechanism for the oxidation of the intermediate borane with hydrogen peroxide and base, in which a hydroxyl group replaces boron with retention of configuration. The nucleophilic hydroperoxide ion attacks the electron-deficient borane to give an intermediate with a weak O—O bond. Although the hydroxide ion is a poor leaving group, a concerted intramolecular migration of an alkyl group occurs.



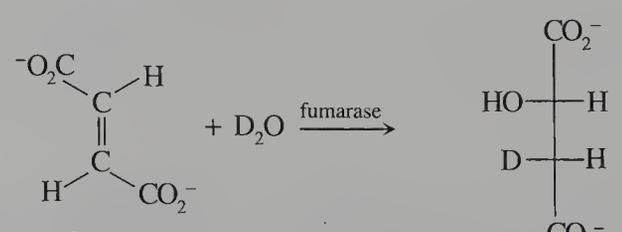
This migration resembles those we described for the migrations of hydrogen and alkyl groups in carbocations. In both cases, the group moves with its bonding electron pair in a concerted process to an adjacent site. The configuration of the alkyl group is retained in this transfer process.

The initial product formed from the migration of an alkyl group has the formula R_2BOR. It continues to react with hydroperoxide ion to give $RB(OR)_2$, and eventually the trialkyl borate, $(RO)_3B$. Subsequent hydrolysis of the borate in basic solution gives the alcohol and sodium borate.

$$(RO)_3B + 3\ NaOH \longrightarrow 3\ ROH + Na_3BO_3$$

Problem 16.14

Hydration of alkenes occurs stereospecifically in biological systems. Hydration of fumarate by D_2O catalyzed by fumarase yields (2*S*,3*R*)-3-deuteriomalate. Determine the stereochemistry of addition.

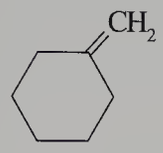


fumarate

(2*S*,3*R*)-3-deuteriomalate

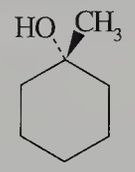
Problem 16.15

What product forms from the following methylenecyclohexane by oxymercuration–demercuration? What product forms in hydroboration–oxidation?

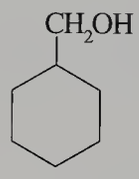


Sample Solution

Both alkyl groups of this disubstituted alkene are part of the ring and are bonded to the same carbon atom. The CH_2 unit has the less substituted carbon atom. An oxymercuration–demercuration reaction places a hydrogen atom at the CH_2 site and a hydroxyl group on the ring carbon atom. This product is the predicted Markovnikov product of indirect hydration of an alkene.



The hydroboration–oxidation product has a hydroxyl group at the CH_2 site and a hydrogen atom at the ring carbon atom. This process is equivalent to anti-Markovnikov addition of water to an alkene.

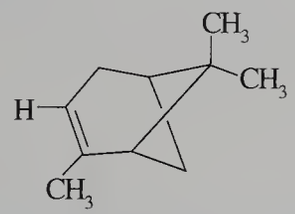


Problem 16.16

Write the structure of the product of oxymercuration–demercuration of 3,3-dimethyl-1-butene. Is this product the same as would be obtained by the acid-catalyzed hydration of the alkene?

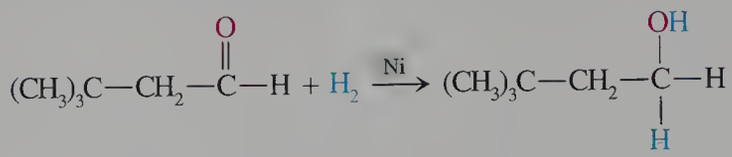
Problem 16.17

Write the structure, showing the stereochemistry, of the product of hydroboration–oxidation of 2,6,6-trimethyl-2-bicyclo[3.1.1]heptene (α-pinene).

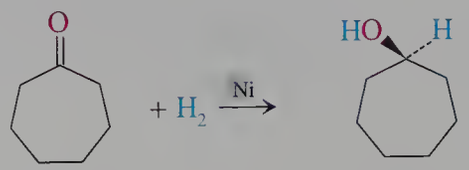


16.9 Reduction of Carbonyl Compounds

Alcohols can be made by reducing the carbonyl group of aldehydes and ketones with hydrogen gas in the presence of a metal catalyst such as palladium, platinum, or Raney nickel. Aldehydes yield primary alcohols; ketones yield secondary alcohols.

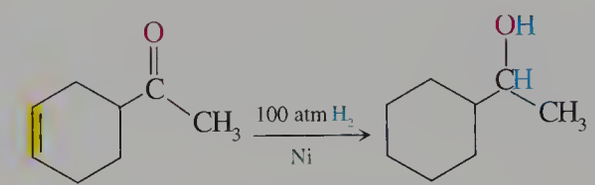


3,3-dimethylbutanal (an aldehyde) — 3,3-dimethylbutanol (a primary alcohol)



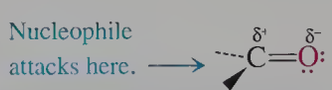
cycloheptanone (a ketone) — cycloheptanol (a secondary alcohol)

The reduction reaction occurs by the transfer of hydrogen atoms bound to the surface of the metal catalyst to the carbonyl oxygen and carbon atoms. We recall that the same types of catalysts are used for the hydrogenation of alkenes, a much faster reaction. Alkenes can be reduced at room temperature under 1 atm pressure of hydrogen gas. Carbonyl compounds require higher temperatures and pressures as high as 100 atm. Therefore, transition-metal-catalyzed reduction of carbonyl compounds that also have a carbon–carbon double bond results in reduction of both functional groups.

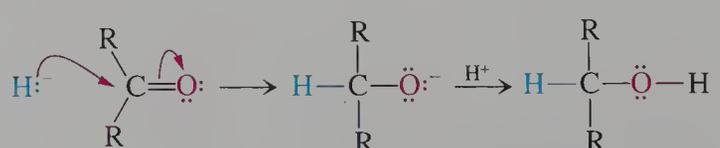


Reduction by Metal Hydrides

The carbonyl group is highly polarized. The carbonyl carbon atom has a partial positive charge that tends to react with nucleophiles.

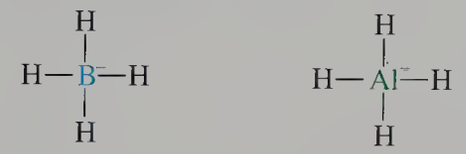


Hence, a nucleophilic form of hydrogen, the hydride ion, is a possible reagent for the reduction of a carbonyl compound. After the hydride ion attacks the carbonyl carbon atom in the first step, protonation of the resulting alkoxide ion in a second step yields an alcohol.



(a ketone) (an alkoxide ion) (a secondary alcohol)

Although hydride ion is an excellent nucleophile, it also is an extremely strong base, which reacts with far too many other functional groups to be a useful reagent for the reduction of carbonyl compounds. However, the basicity of the hydride ion is greatly diminished in two covalently bonded hydridic compounds called sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). The two hydride-containing anions have four hydrogen atoms covalently bonded to a tetrahedral central boron and aluminum atom, respectively.

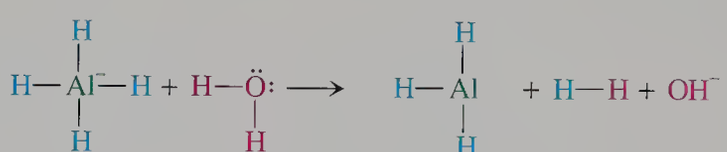


borohydride ion

aluminum hydride ion

Selection of Solvents for Hydride Reagents

The hydrogen atoms of the B—H and Al—H bonds have a partial negative charge because hydrogen is more electronegative than either boron or aluminum. The hydrogen atom therefore behaves as a hydride ion, but is less basic than a hydride ion in sodium hydride. Both polyatomic ions react with proton sources. Lithium aluminum hydride reacts violently with water to form hydrogen gas, which may burn explosively because of the heat generated in the reaction.



(also hydridic)

In continued rapid reactions, the aluminum hydride and other intermediate aluminum compounds react to give lithium aluminate. Therefore, lithium aluminum hydride can only be used in aprotic solvents such as diethyl ether.

$$LiAlH_4 + 4\,H_2O \longrightarrow Li^+\,Al(OH)_4^- + 4\,H_2$$

The borohydride ion is less reactive toward protic substances. It can be used in water at pH near or greater than 7. However, it reacts rapidly in acidic solutions. Sodium borohydride can be used in water or ethanol as the solvent. It reacts with these solvents at a much slower rate than with an aldehyde or ketone. Lithium aluminum hydride reacts more rapidly with alcohols than with carbonyl compounds.

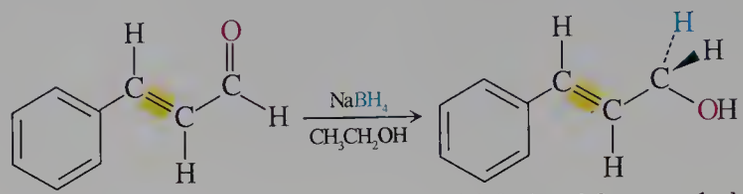
$$NaBH_4 + 4\,CH_3CH_2OH \xrightarrow{\text{slow}} Na^+\,{}^-B(OCH_2CH_3)_4 + 4\,H_2$$

$$LiAlH_4 + 4\,CH_3CH_2OH \xrightarrow{\text{rapid}} Li^+\,{}^-Al(OCH_2CH_3)_4 + 4\,H_2$$

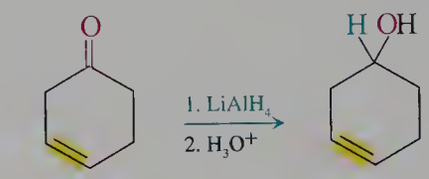
Regioselectivity of Hydrides

The carbon–carbon double bond of alkenes is not polar and does not react with nucleophiles. This difference in reactivity accounts for the regioselectivity of sodium

borohydride or lithium aluminum hydride. Neither reagent reduces alkenes; both reduce aldehydes and ketones.

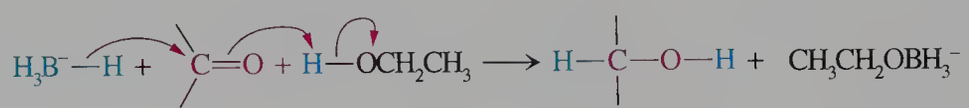


(*E*)-3-phenyl-2-propenal (*E*)-3-phenyl-2-propen-1-ol



3-cyclohexenone 3-cyclohexenol

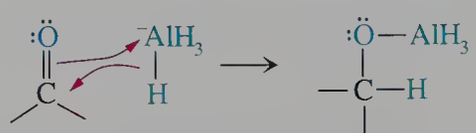
In reduction by sodium borohydride, a hydride ion of the borohydride ion (BH_4^-), is transferred to the carbonyl carbon atom, and the carbonyl oxygen atom is protonated by the ethanol.



ethoxyborohydride

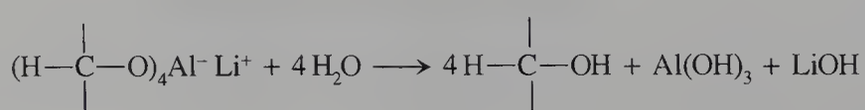
The ethoxyborohydride product in the above reaction has three remaining hydride ions available for further reduction reactions, and the ultimate boron product is tetraethoxyborohydride, $(RO)_4B^-$. As a result, one mole of $NaBH_4$ reduces four moles of a carbonyl compound. A dilute solution of acid is used to destroy any excess reagent as part of the standard workup procedure.

When lithium aluminum hydride is used to reduce carbonyl compounds, an ether, such as diethyl ether, $(CH_3CH_2)_2O$, is used as the solvent. The reduction of a carbonyl group by lithium aluminum hydride occurs by transfer of a hydride anion from AlH_4^- to the carbonyl carbon atom. The carbonyl oxygen atom forms an alkoxyaluminate salt.



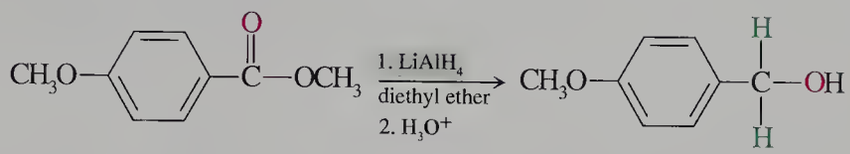
(an alkoxyaluminate)

The initial alkoxyaluminate has three remaining hydride ions available for further reduction reactions, and the ultimate aluminum product is tetraalkoxyaluminate, $(RO)_4Al^-$. Consequently, one mole of $LiAlH_4$ reduces four moles of a carbonyl compound. The tetraalkoxyaluminate is hydrolyzed with aqueous acid in a separate, second step.



Reduction of Other Carbonyl Compounds

Many carbonyl compounds, including aldehydes and ketones, acids, esters, acid halides, and amides, can be reduced with lithium aluminum hydride. For example, lithium aluminum hydride reduces esters to primary alcohols.



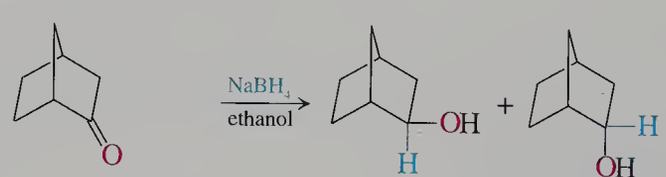
methyl *p*-methoxybenzoate

p-methoxybenzyl alcohol

Sodium borohydride is less reactive. It reduces only aldehyde or ketones. Therefore, if both a ketone and an ester functional group are present in a molecule and the goal is to reduce just the ketone, only sodium borohydride gives the required result.

Stereoselectivity

Both sodium borohydride and lithium aluminum hydride have only moderate stereoselectivity. The anions tend to attack sterically hindered compounds from the least sterically hindered side. For example, reduction of bicyclo[2.2.1]heptan-2-one yields a mixture of two alcohols in which the endo compound predominates. The exo face of the carbonyl group is more open to attack by the nucleophilic hydride reagent, and as a result the endo alcohol is the major product.



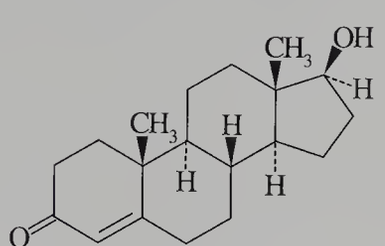
bicyclo[2.2.1]heptan-2-one

exo (14%) endo (86%)

bicyclo[2.2.1]heptan-2-ol

Problem 16.18

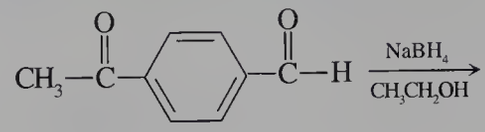
Under conditions of high pressure, two moles of hydrogen gas react with testosterone. Write the structure of the major product of the reaction taking into account the steric accessibility of the α and β faces of the A ring of the steroid.

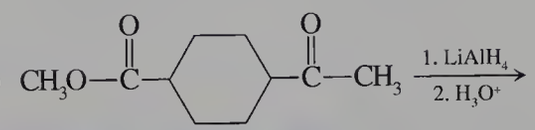


testosterone

Problem 16.19

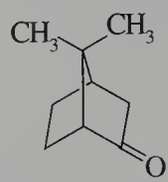
Write the structure of the product of each of the following reactions, assuming an excess of each metal hydride.

(a) 

(b) 

Problem 16.20

Reduction of 7,7-dimethylbicyclo[2.2.1]heptan-2-one with sodium borohydride yields two isomeric alcohols in a 6:1 ratio. Considering the effect of the methyl groups, write the structures of the products.



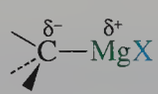
7,7-dimethylbicyclo[2.2.1]heptan-2-one

16.10 Synthesis of Alcohols Using Grignard Reagents

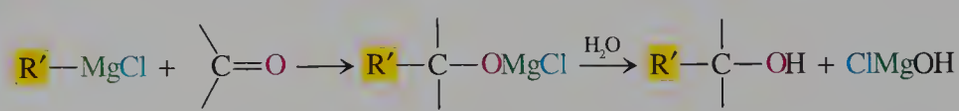
In Section 8.8, we discussed the reaction of haloalkanes with magnesium to produce **organometallic compounds** called **Grignard reagents**.

$$R{-}X \xrightarrow[\text{ether}]{Mg} R{-}Mg{-}X$$

Grignard reagents are very reactive and versatile reactants used to form carbon–carbon bonds in the synthesis of complex molecules from simpler molecules. Grignard reagents contain a strongly polarized carbon–magnesium bond in which the carbon atom has a partial negative charge.



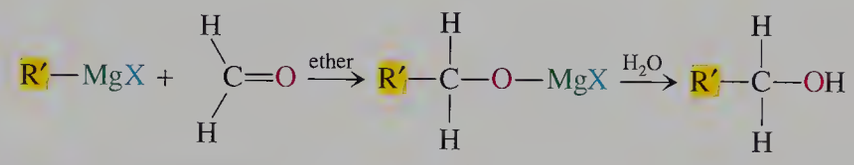
The carbon atom of the Grignard reagent resembles a carbanion. It reacts as a nucleophile and adds to the electrophilic carbon atom of a carbonyl group in an aldehyde or ketone. The magnesium ion forms a salt with the negatively charged oxygen atom. This product, a magnesium alkoxide, is subsequently hydrolyzed to obtain an alcohol.

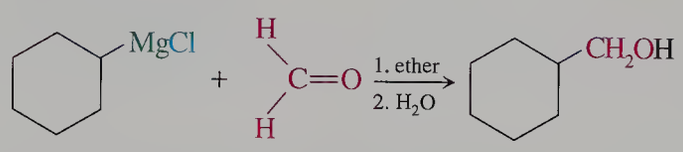


(a magnesium alkoxide)

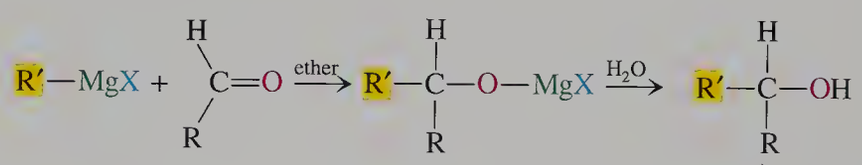
Grignard reagents do not add to carbon–carbon double bonds because these carbon atoms are not as electrophilic as the polarized carbonyl group. That's why Grignard reagents can add regiospecifically to a carbonyl group in a compound having other units of unsaturation.

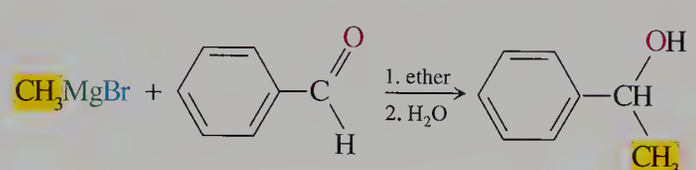
Grignard reagents add to various types of carbonyl compounds to give primary, secondary, and tertiary alcohols. A primary alcohol is synthesized by reacting the Grignard reagent, R′—MgX, with formaldehyde.



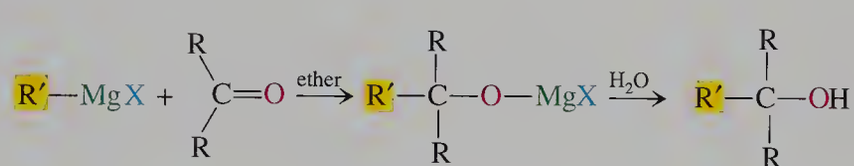


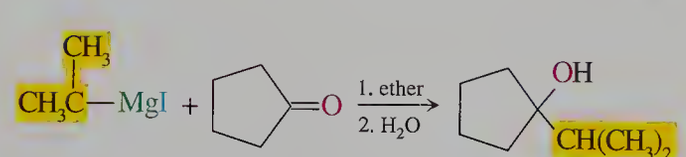
A secondary alcohol is produced by reacting the Grignard reagent (R′—MgX) with an aldehyde R—CHO. Note that the carbon atom bearing the hydroxyl group is bonded to the alkyl groups of the Grignard reagent and the aldehyde.





A tertiary alcohol is made by reacting the Grignard reagent, (R′—MgX) with a ketone. Two of the alkyl groups bonded to the carbon atom bearing the hydroxyl group were part of the ketone; one alkyl group is provided from the Grignard reagent.



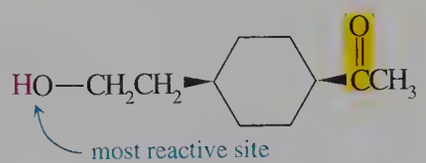


Limitations of the Grignard Reaction

We recall that Grignard reagents cannot be made if acidic functional groups are also present in the halogen compound. The Grignard reagent is destroyed by reaction with acidic hydrogen atoms of water, alcohols, phenols, or carboxylic acid groups (—COOH).

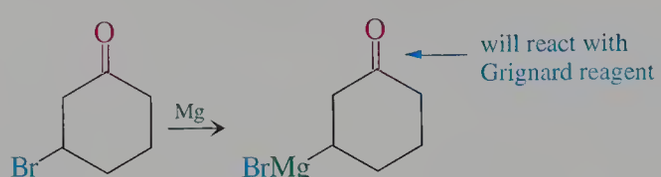
$$R{-}OH + R'{-}MgBr \longrightarrow R{-}O^{-}MgBr^{+} + R'{-}H$$

For the same reason, we must consider the structure of the carbonyl compound selected for reaction with a Grignard reagent. If the carbonyl compound also contains a hydroxyl group, the fastest reaction will be the destruction of the added Grignard reagent by protonation.



However, if two equivalents of the Grignard are added, then the second equivalent would be available for reaction with the carbonyl group.

Finally, it is impossible to prepare a Grignard reagent if there is a functional group contained within the molecule that would react with the Grignard reagent as it forms. The following bromine-substituted ketone is such a case.

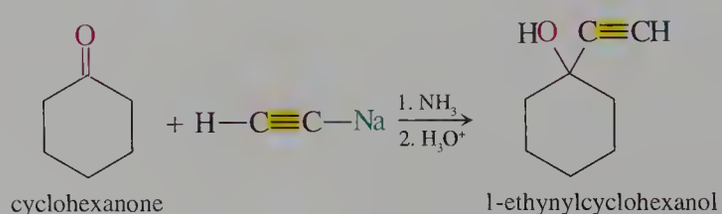


In Chapter 18, we will learn how to "protect" the carbonyl group by converting it into a functional group that does not react with Grignard reagents. After a reaction of the Grignard reagent with another carbonyl compound to give an alcohol, the "protecting group" is then transformed back to the original carbonyl group.

Acetylenic Alcohols

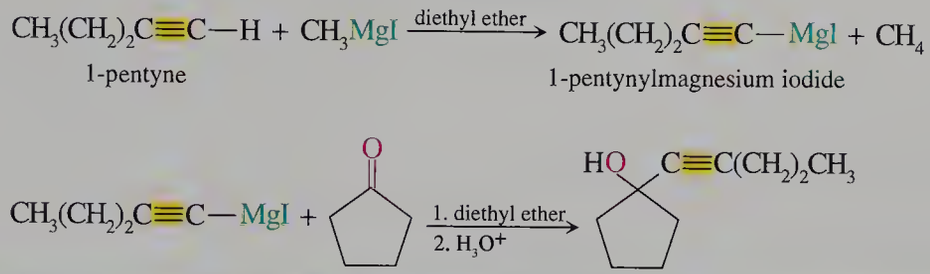
Alkynide ions react with carbonyl groups in much the same way as Grignard reagents do. We recall that these ions are effective nucleophiles that will displace a halide ion from an alkyl halide to give an alkylated alkyne. The alkynides are prepared in an acid–base reaction with acetylene or a terminal alkyne using sodium amide in ammonia. If a carbonyl compound is then added to the reagent, an alcohol forms after acid workup. If the alkynide is derived from acetylene, an acetylenic alcohol forms.

$$H{-}C{\equiv}C{-}H + NaNH_2 \xrightarrow[-33\ ^\circ C]{NH_3} H{-}C{\equiv}C{-}Na + NH_3$$



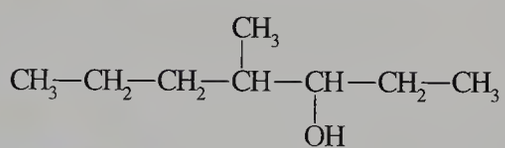
cyclohexanone 1-ethynylcyclohexanol

We can also produce alkynides without using liquid ammonia. We recall that alkynes are more acidic than alkanes. Therefore, the acid–base reaction of an alkyne with a readily available Grignard reagent gives a Grignard of the alkyne. This alkynide ion of the Grignard reagent reacts with carbonyl compounds.



Problem 16.21

The European bark beetle produces a pheromone that causes beetles to congregate. Describe two ways that the compound could be synthesized in the laboratory by a Grignard reagent.

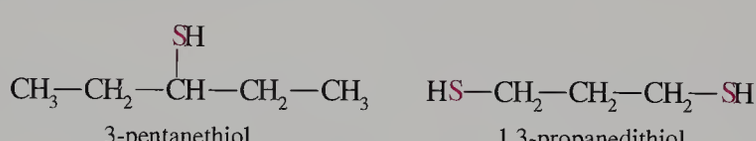


Problem 16.22

Write the structures of the two products obtained by reaction of 4-*tert*-butylcyclohexanone with sodium acetylide. Predict which one is obtained in the larger amount.

16.11 Sulfur Compounds

Sulfur is in the same group of the periodic table as oxygen and forms compounds structurally similar to alcohols. Compounds containing an —SH group, called the **sulfhydryl group**, are named **mercaptans** or **thiols**. The nomenclature of these compounds resembles that of alcohols, except that the suffix *-thiol* replaces the suffix *-ol* and the *-e* of the alkane name is retained.



Physical Properties

Alcohols and thiols resemble each other in many ways, but they also differ in some significant respects. For example, thiols have lower boiling points than corresponding alcohols because sulfur does not form hydrogen bonds. We recall from Chapter 2 that only nitrogen, oxygen, and fluorine form hydrogen bonds.

Some alcohols have rather sweet odors, but one of the distinguishing properties of thiols is their strong, disagreeable odor. The odor of the striped skunk (*Mem-*

phitis mephitis) is due to 3-methyl-1-butanethiol. The human nose can detect thiols at a few parts per billion in air. Small amounts of thiols are added to natural gas to aid in easy detection of leaks.

Reactions of Thiols

Although thiols are weak acids, they are far stronger than alcohols.

$$\text{R—S—H} + \text{H}_2\text{O} \rightleftharpoons \text{R—S}^- + \text{H}_3\text{O}^+ \qquad pK_a = 8$$
$$\text{R—O—H} + \text{H}_2\text{O} \rightleftharpoons \text{R—O}^- + \text{H}_3\text{O}^+ \qquad pK_a = 17$$

The sulfhydryl group reacts with hydroxide ions to form thiolate ions, which are excellent nucleophiles.

$$\text{R—S—H} + \text{NaOH} \longrightarrow \underset{\text{(a thiolate)}}{\text{R—S}^-} + \text{Na}^+ + \text{H}_2\text{O}$$

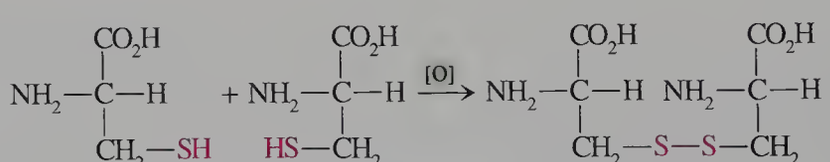
The oxidation of alcohols occurs at the carbon atom bonded to the oxygen atom and gives compounds with carbon-oxygen multiple bonds. The oxidation of thiols is very different. Although sulfur analogs of aldehydes (or ketones) and acids are known, they are not obtained by direct oxidation of thiols.

$$\text{R—CH}_2\text{—SH} \xrightarrow{[O]} \text{R—C(=S)—H} \xrightarrow{[O]} \text{R—C(=S)—OH}$$

Thiols are easily oxidized, but oxidation occurs at the sulfur atom rather than at the carbon atom. Mild oxidizing agents such as bromine or iodine convert thiols into disulfides. In the following equation, the symbol [O] represents an unspecified oxidizing agent that removes the hydrogen atoms.

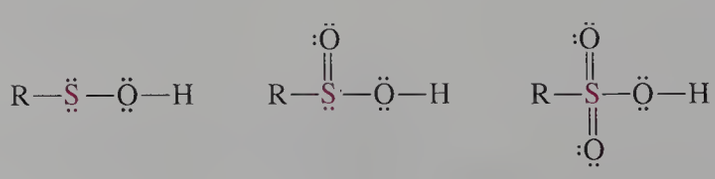
$$2\,\text{R—S—H} \xrightarrow{[O]} \underset{\text{(a disulfide)}}{\text{R—S—S—R}}$$

This reaction is of great biological importance because many proteins contain the amino acid cysteine. Oxidation of the —SH group of cysteine gives a disulfide bond in cystine.



In some cases, the sulfhydryl groups in an enzyme must remain in the reduced state for proper biological function. If an essential cysteine sulfhydryl group is oxidized, the enzyme becomes inactive.

Oxidation with stronger oxidizing agents converts thiols to a series of acids with oxygen atoms bonded to sulfur.



Sulfonic acids, the ultimate oxidation product of thiols, are obtained by vigorous oxidation by concentrated nitric acid.

$$CH_3(CH_2)_4CH_2{-}SH \xrightarrow{HNO_3} CH_3(CH_2)_4CH_2{-}SO_3H$$

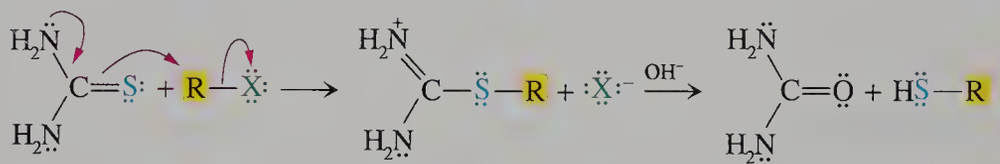
Synthesis of Thiols

Thiols can be obtained from haloalkanes by nucleophilic displacement of halide ion with the sulfhydryl ion (HS^-), an excellent nucleophile. Because thiolates are also excellent nucleophiles, the product can react to give a thioether. To limit the competitive second reaction, a large excess of HS^- must be used. The fact that H_2S is extremely poisonous also dictates against the general use of this method.

$$R{-}Br + HS^- \longrightarrow R{-}SH + Br^-$$

$$R{-}Br + R'S^- \longrightarrow \underset{\text{(a thioether)}}{R'{-}S{-}R} + Br^-$$

The sulfur atom in thiourea provides a better method of producing thiols. It displaces a halide ion from an alkyl halide to give an isothiouronium salt. Subsequent hydrolysis of the isothiouronium salt in the same reaction vessel yields a thiol.



thiourea isothiouronium salt urea

The overall driving force for the reaction is the instability of the C=S bond, which is lost when the isothiouronium salt forms. The second step readily occurs because the C=O is a very stable bond.

EXERCISES

Formation of Esters

16.1 The ΔH°_{rxn} and ΔG°_{rxn} for the formation of methyl acetate from methanol and acetic acid in the gas phase are both −16 kJ mole^{-1}. Explain why the values are equal.

$$CH_3CO_2H + CH_3OH \longrightarrow CH_3CO_2CH_3 + H_2O$$

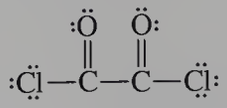
16.2 The equilibrium constant for the formation of ethyl acetate in the liquid phase is 4. What is ΔG°_{rxn}?

$$CH_3CO_2H + CH_3CH_2OH \rightleftharpoons CH_3CO_2CH_2CH_3 + H_2O$$

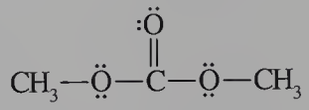
16.3 Write the structural formula of each of the following esters.
(a) ethyl sulfate **(b)** dimethyl phosphate
(c) propyl nitrate **(d)** 2-propyl methanesulfonate

16.4 Write the structural formula of each of the following esters.
(a) trimethyl phosphate **(b)** dipropyl sulfate
(c) 2-propyl nitrate **(d)** 1-butyl *p*-toluenesulfonate

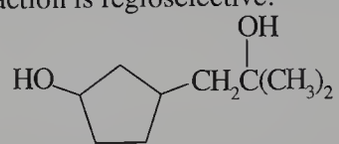
16.5 Oxalyl chloride is a diacid chloride having the following structure. Draw the structure of the related diacid. Draw the structure of the product from reaction of one equivalent of benzyl alcohol with oxalyl chloride. Draw the structure of the product from reaction of two equivalents of methyl alcohol with oxalyl chloride.



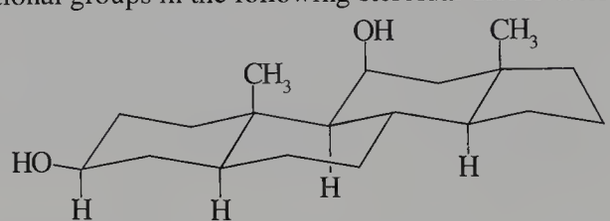
16.6 What acid is contained in the following diester? Write the structure of an acid chloride that could be used to synthesize the diester.



16.7 The following diol reacts with one equivalent of tosyl chloride to give a single ester in good yield. Write the structure of the ester. Explain why the reaction is regioselective.



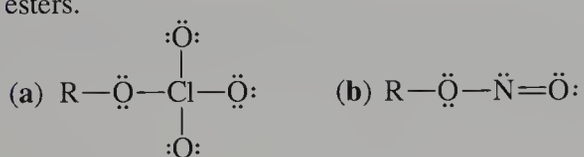
16.8 Which of the two alcohol functional groups in the following steroidal diol is esterified at the faster rate?



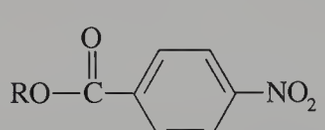
Reactivity of Esters

16.9 Are alkyl esters of trifluoromethylsulfonic acid expected to be more or less reactive in S_N1 reactions than alkyl esters of methanesulfonic acid?

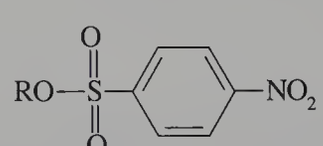
16.10 Describe the expected reactivity of the following compounds in S_N2 reactions compared to methanesulfonate esters.



16.11 The relative reactivities of alkyl *p*-nitrobenzoates and alkyl *p*-nitrobenzenesulfonates in S_N2 reactions relative to the reactivity of alkyl chlorides are 10^{-5} and 10^5, respectively. Explain the difference in the relative rates of reaction of the two esters.



(an alkyl *p*-nitrobenzoate)



(an alkyl *p*-nitrobenzenesulfonate)

16.12 Predict whether *p*-bromobenzenesulfonate is a better or worse leaving group than *p*-toluenesulfonate.

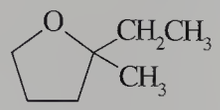
Reaction of Alcohols with Acid

16.13 Explain why (*R*)-2-butanol in aqueous acid gradually loses its optical activity.

16.14 Explain why 1-phenyl-2-propen-1-ol rearranges to an isomer in the presence of a catalytic amount of H_2SO_4.

16.15 *cis*-2-Buten-1-ol isomerizes to form a mixture containing two additional isomeric alcohols when treated with dilute sulfuric acid. Write the structures of these alcohols.

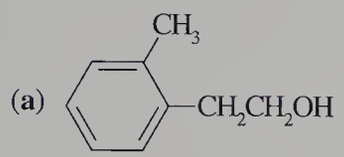
16.16 When (*S*)-4-methyl-1,4-hexanediol is heated with acid, optically inactive 2-ethyl-2-methyltetrahydrofuran results. Write a mechanism for the reaction that accounts for the formation of the product and its lack of optical activity.

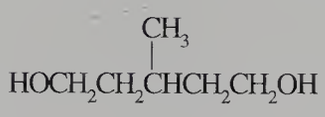


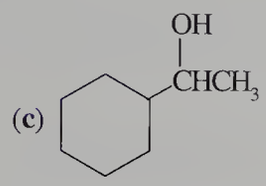
2-ethyl-2-methyltetrahydrofuran

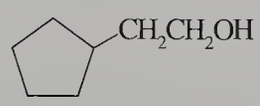
Formation of Alkyl Halides

16.17 Draw the structure of the product of reaction for each of the following compounds with PBr_3

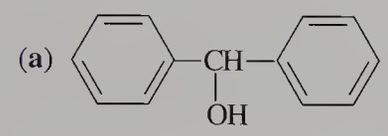


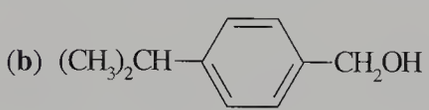


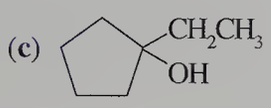


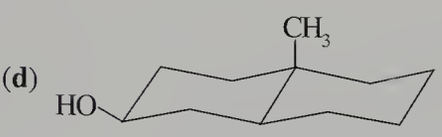


16.18 Draw the structure of the product of the reaction for each of the following compounds with $SOCl_2$ and pyridine.









16.19 Both 2-methyl-2-buten-1-ol and 3-methyl-2-buten-1-ol are converted to chlorides using concentrated HCl. Which compound reacts at the faster rate?

16.20 3-Methyl-2-cyclopentenol reacts with aqueous HBr to yield a mixture of two isomeric bromo compounds. Draw the structures of the two products. Predict the major isomer, assuming the reaction is not reversible. How might the data be different if the products can equilibrate?

16.21 The yields of alkyl bromides obtained by reaction of an alcohol with PBr_3 are reduced if some of the HBr formed escapes from the reaction. In what alternate product would the alkyl groups be found under these conditions?

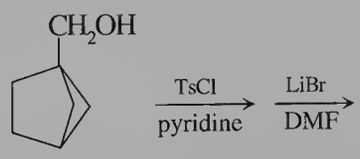
16.22 The yields of alkyl bromides in the reaction of alcohols with PBr_3 are increased if "extra" HBr is bubbled into the reaction vessel after the PBr_3 and alcohol are mixed. Explain why.

16.23 How could *trans*-4-*tert*-butylcyclohexanol be converted into *trans*-4-chloro-1-*tert*-butylcyclohexane? How could *trans*-4-*tert*-butylcyclohexanol be converted into *cis*-4-chloro-1-*tert*-butylcyclohexane?

16.24 What is the product of the reaction of (*R*)-2-octanol with thionyl chloride in pyridine? What is the product in diethyl ether, $(CH_3CH_2)_2O$, as solvent?

16.25 Draw the structure of the product of the following series of reactions. What product would result if the alcohol reacted with HCl?

16.26 Draw the structure of the product of the following series of reactions. What product would result if the alcohol reacted with HBr?

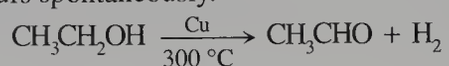


16.27 Sterically hindered alcohols react with phosphorus tribromide, but tend to give large quantities of rearranged product. The product mixture obtained from 2,2-dimethyl-1-propanol (neopentyl alcohol) contains 63% 1-bromo-2,2-dimethylpropane, 26% 2-bromo-2-methylbutane, and 11% 2-bromo-3-methylbutane. Explain the origin of the products. Why are sterically hindered alcohols more prone to give rearranged products?

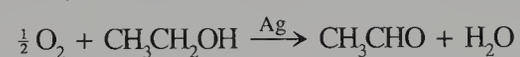
16.28 Both 2-chloropentane and 3-chloropentane are converted to a mixture of the two compounds in a concentrated HCl solution containing zinc chloride. The ratio of the 2-chloro to the 3-chloro compound is 2:1. Write a mechanism utilizing the zinc chloride that accounts for the equilibration process. Why does the observed ratio occur?

Oxidation of Alcohols

16.29 Ethanol can be converted commercially into ethanal by the following reaction, even though the $\Delta H^\circ_{rxn} = +63$ kJ mole^{-1}. Explain why the reaction occurs spontaneously.

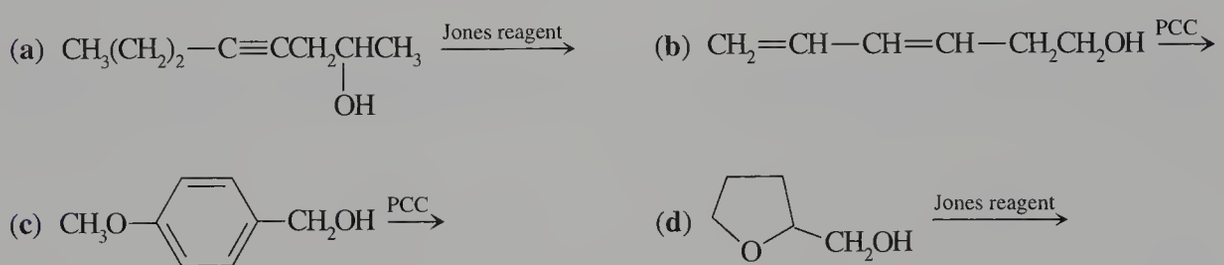


16.30 Ethanol can be converted commercially into ethanal by the following reaction. The $\Delta H^\circ_{rxn} = -180$ kJ mole^{-1}. Explain why this reaction is exothermic, whereas the reaction in Exercise 16.29 is endothermic.



16.31 Both 1-octanol and 2-octanol react with aqueous basic potassium permanganate ($KMnO_4$). The product of the reaction of 2-octanol is insoluble in aqueous base, but the product of reaction of 1-octanol is soluble. What are the products? Explain the difference in solubility.

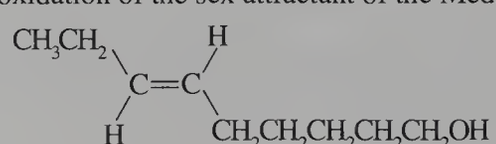
16.32 Draw the structure of the product of each of the following reactions.



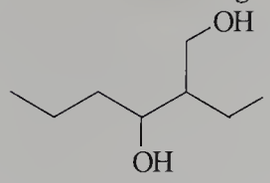
16.33 Write the product formed from the oxidation of each of the compounds in Exercise 16.17 using PCC.

16.34 Write the product formed from the oxidation of each of the compounds in Exercise 16.18 by the Jones reagent.

16.35 Write the product formed from the oxidation of the sex attractant of the Mediterranean fruit fly by PCC.



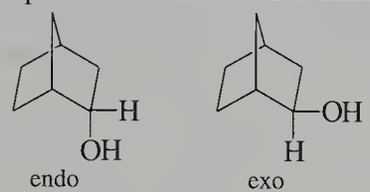
16.36 Write the product formed by oxidation with PCC of the following mosquito repellent.



16.37 Consider the relative rates of oxidation of the following three compounds by chromium(VI) and determine the rate-determining step of the reaction.

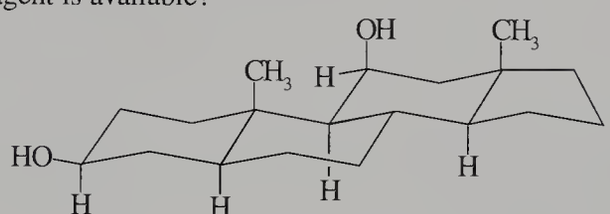
$CH_3CH(OH)CH_3$	$CH_3CD(OH)CH_3$	$CD_3CH(OH)CH_3$
1.0	0.16	1.0

16.38 The rate of oxidation of *endo*-bicyclo[2.2.1]heptan-2-ol is faster than the rate of oxidation of the exo isomer. What does this fact indicate about which step in the mechanism determines the reaction rate?



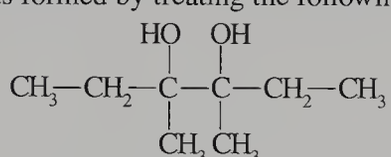
16.39 Write a mechanism for the oxidation of an alcohol by chromium(VI) that uses only an intramolecular process for the abstraction of the α hydrogen atom. Considering the size of the ring in the cyclic process, how likely is it that this process will occur?

16.40 Which of the two sites within the following structure will be oxidized at the faster rate when only one equivalent of a chromium(VI) oxidizing agent is available?

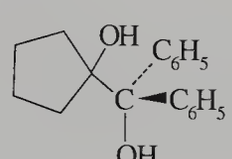


Reactions of Vicinal Diols

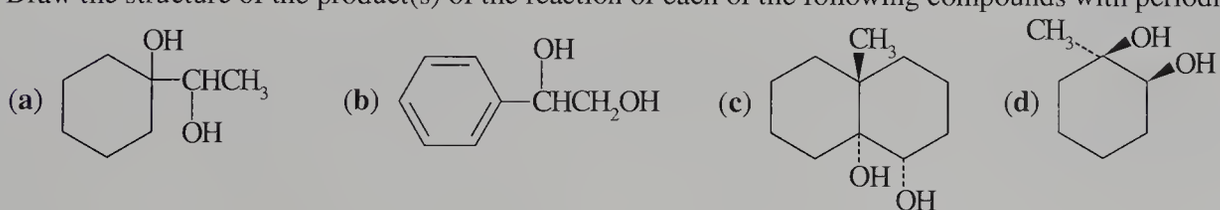
16.41 Draw two possible structures of products formed by treating the following vicinal diol with sulfuric acid.



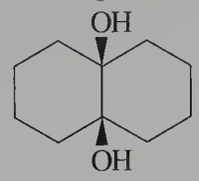
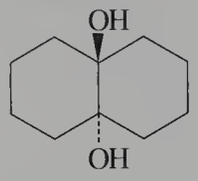
16.42 Only one product is formed by treating the following vicinal diol with sulfuric acid. Draw its structure. Why is it formed in preference to an isomeric product?

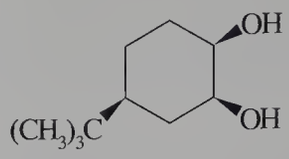
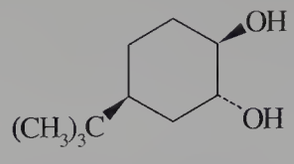


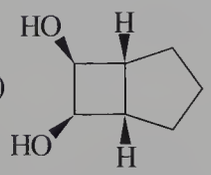
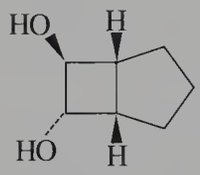
16.43 Draw the structure of the product(s) of the reaction of each of the following compounds with periodic acid.



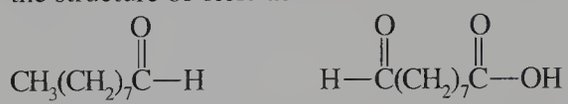
16.44 Which compound of each of the following pairs of isomers should react at the faster rate with HIO_4?

(a)  or 

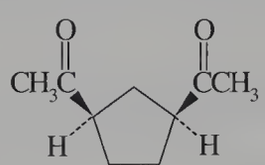
(b)  or 

(c)  or 

16.45 The reaction of oleic acid ($C_{18}H_{34}O_2$) with osmium tetraoxide followed by reaction with periodate yields the following two compounds. Draw the structure of oleic acid.



16.46 A hydrocarbon of molecular formula C_9H_{14} is found in sandalwood oil. Reaction of the compound with osmium tetraoxide followed by reaction with periodate yields the following compound. Draw the structure of the hydrocarbon.



Synthesis of Alcohols from Alkyl Halides

16.47 Which compound of each of the following pairs will react with ethanoate ion at the faster rate?
(a) 1-iodohexane or 1-bromohexane
(b) 1-bromo-1-phenylethane or 1-bromo-2-phenylethane
(c) 1-bromo-2,2-dimethylpropane or 1-bromopentane

16.48 Would DMF or ethanol be the better solvent for the displacement of halide ions from alkyl halides by ethanoate ion?

16.49 Attempted synthesis of bicyclo[2.2.2]octan-1-ol by reaction of ethanoate with 1-bromobicyclo[2.2.2]octane fails. Why?

1-bromobicyclo[2.2.2]octane

16.50 Predict the stereochemistry of the alcohol obtained by the reaction of *cis* 1-bromo-4-*tert*-butylcyclohexane with ethanoate followed by hydrolysis under basic conditions.

Hydration of Alkenes

16.51 Which of the isomeric $C_4H_{10}O$ alcohols can be produced by an acid-catalyzed hydration reaction of an alkene?

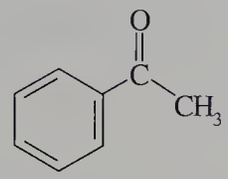
16.52 2-Propanol is produced industrially by a hydration reaction of propene, but 1-propanol is produced by other methods. Why?

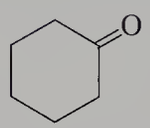
16.53 The acid-catalyzed hydration of 3,3-dimethyl-1-pentene gives a mixture of two tertiary alcohols. Draw the structures and write a mechanism for their formation.

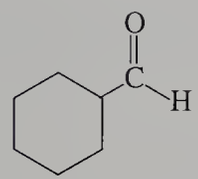
16.54 The acid-catalyzed hydration of 4-*tert*-butylcyclohexene gives a mixture of four secondary alcohols. Draw the structures and write a mechanism for their formation.

Reduction of Carbonyl Compounds

16.55 What is the product when each of the following reacts with lithium aluminum hydride?

(a) 

(b) 

(c) 

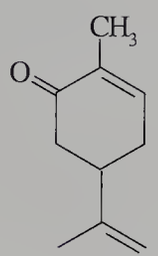
16.56 What is the product when each of the following reacts with sodium borohydride?

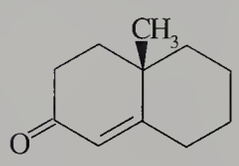
(a) $CH_3CH(CH_3)CHO$

(b) $CH_3C(CH_3)(CH_3)CH_2CHO$

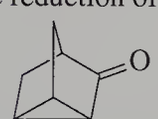
(c) $CH_3C(=O)C(CH_3)(CH_3)CH_3$

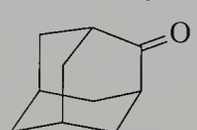
16.57 The reduction of each of the following compounds by lithium aluminum hydride yields two products. Explain why.

(a) 

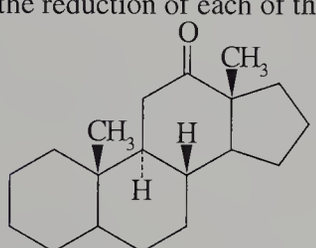
(b) 

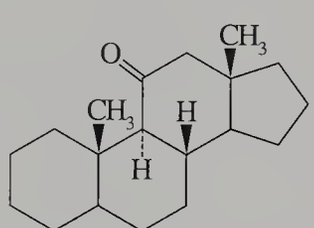
16.58 The reduction of each of the following compounds by sodium borohydride yields only one product. Explain why.

(a) 

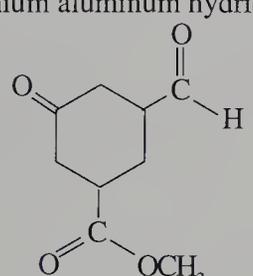
(b) 

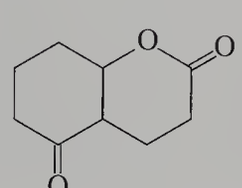
16.59 Assuming that steric factors control the reduction by sodium borohydride, what stereoisomer should predominate for the reduction of each of the following compounds?

(a) 

(b) 

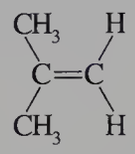
16.60 What is the product of the reaction of each of the following compounds with sodium borohydride and also with lithium aluminum hydride?

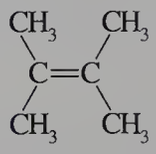
(a) 

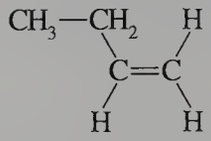
(b) 

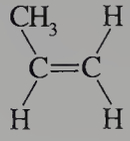
Oxymercuration–Demercuration

16.61 Name the final product of oxymercuration–demercuration of each of the following compounds.

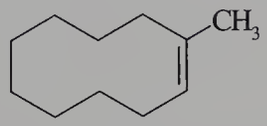
(a) 

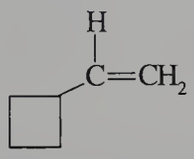
(b) 

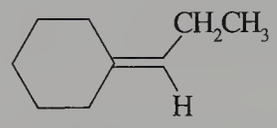
(c) 

(d) 

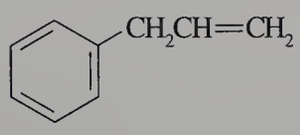
16.62 Draw the structure of the oxymercuration–demercuration product of each of the following compounds.

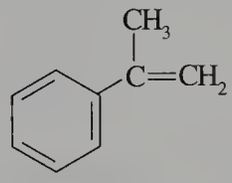
(a) 

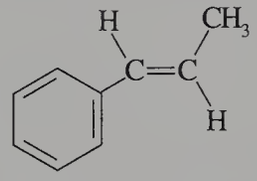
(b) 

(c) 

16.63 Draw the structure of the oxymercuration–demercuration product of each of the following compounds.

(a) 

(b) 

(c) 

16.64 How many products should be formed in the oxymercuration–demercuration of 4-*tert*-butylcyclohexene?

Hydroboration–Oxidation

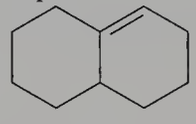
16.65 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 16.61.

16.66 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 16.62.

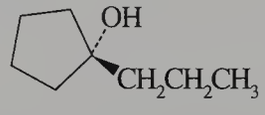
16.67 Draw the final product of hydroboration–oxidation of each of the compounds in Exercise 16.63.

16.68 Draw the structure of the hydroboration–oxidation product of the following bicyclic hydrocarbon.

16.69 Draw the structure of the hydroboration–oxidation product of the following bicyclic hydrocarbon.

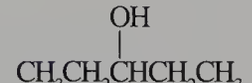


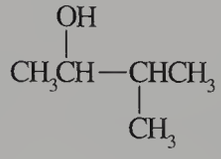
16.70 Can the following alcohol be synthesized by the hydroboration–oxidation method starting from 1-propylcyclopentene?

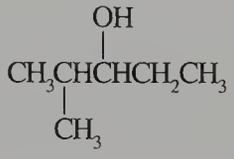


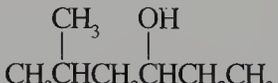
Grignard Reactions

16.71 What carbonyl compound and Grignard reagent are required to produce each of the following compounds?

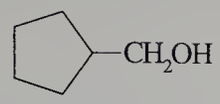
(a) 

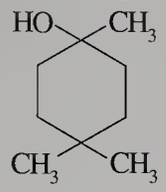
(b) 

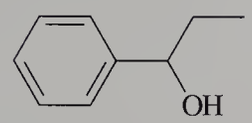
(c) 

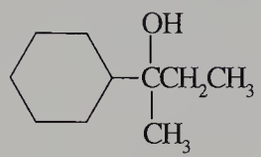
(d) 

16.72 What carbonyl compound and Grignard reagent are required to produce each of the following compounds?

(a) 

(b) 

(c) 

(d) 

16.73 Outline how each of the following alcohols could be made from the indicated starting material and other necessary compounds using the Grignard synthesis.

(a) 2-cyclopentyl-2-propanol starting from bromocyclopentane

(b) 1-cyclopentyl-1-ethanol starting from ethanal (CH_3CHO)

(c) 1-nonanol starting from 1-bromooctane.

(d) 3-heptanol starting from pentanal ($CH_3(CH_2)_3CHO$)

16.74 Using bromobenzene, outline how each of the following alcohols could be made using the Grignard synthesis.

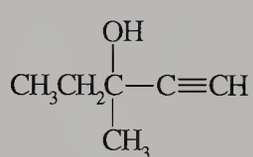
(a) 1-phenylcyclopentanol

(b) 3-phenyl-3-hexanol

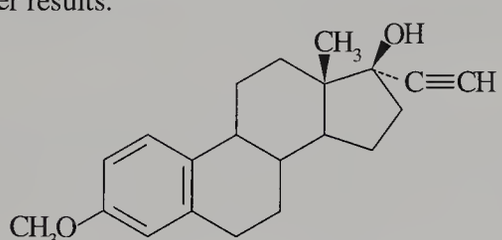
(c) 1-phenyl-1-octanol

(d) benzyl alcohol

16.75 Outline all possible reaction sequences required to prepare Meparfynol, a mild sleep-inducing agent, using the Grignard synthesis.

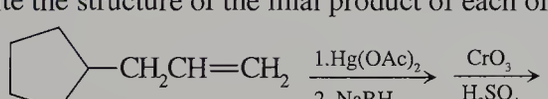


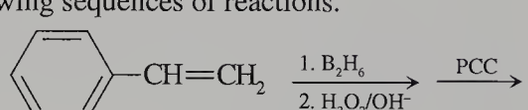
16.76 Mestranol, a component of oral contraceptive drugs, is produced by reaction of an acetylide with a ketone. Explain why the indicated stereoisomer results.

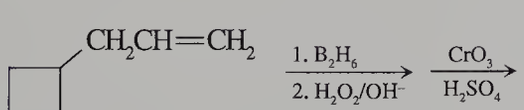


Synthesis Sequences

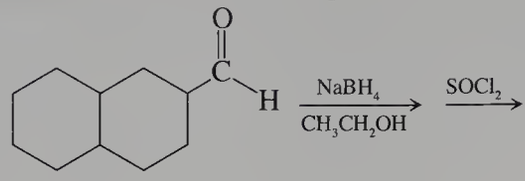
16.77 Write the structure of the final product of each of the following sequences of reactions.

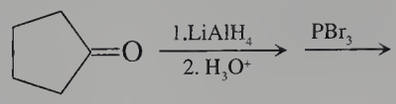
(a) 

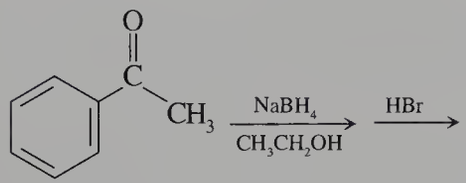
(b) 

(c) 

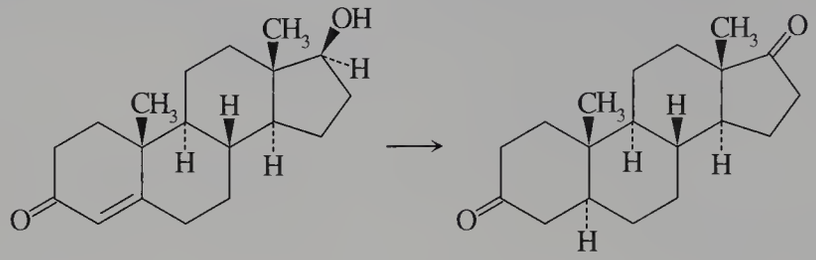
16.78 Write the structure of the final product of each of the following sequences of reactions.

(a) 

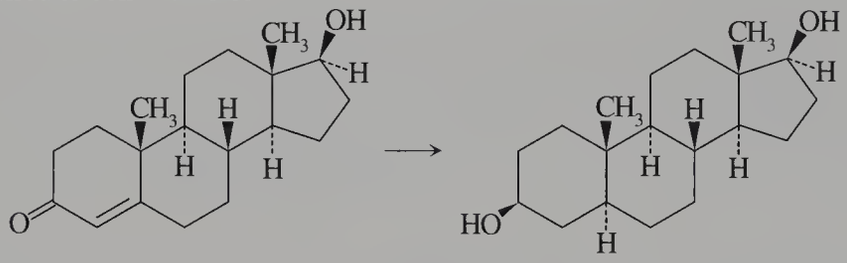
(b) 

(c) 

16.79 Outline the steps required to convert testosterone into the indicated steroid structure.

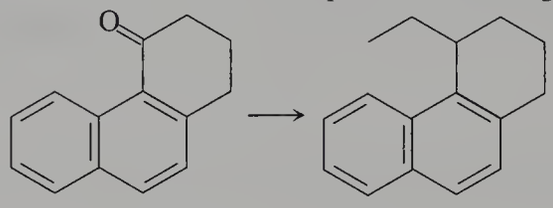


16.80 Outline the steps required to convert testosterone into the indicated steroid structure.



16.81 Propose a sequence of reactions that could be used to convert cyclohexanone into 1-methylcyclohexene.

16.82 Propose a sequence of reactions that could be used to accomplish the following conversion.



Sulfur Compounds

16.83 There are four isomeric compounds $C_4H_{10}S$ with an —SH group. Draw the structures of the compounds.

16.84 There are three isomeric compounds C_3H_8S. Draw their structures.

16.85 Draw the structure of each of the following compounds.
(a) 1-propanethiol
(b) 2-methyl-3-pentanethiol
(c) cyclopentanethiol

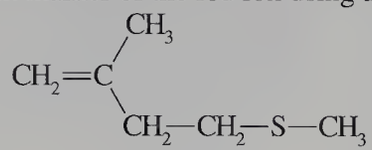
16.86 Draw the structure of each of the following compounds.
(a) 2-propanethiol
(b) 2-methyl-1-propanethiol
(c) cyclobutanethiol

16.87 Addition of sodium hydroxide to an aqueous solution of $CH_3CH_2CH_2SH$ eliminates the odor. Explain why.

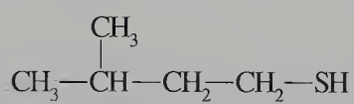
16.88 The boiling points of ethanethiol and dimethyl sulfide are 35 and 37 °C, respectively. Why are the boiling points similar? What types of intermolecular forces are responsible for this similarity?

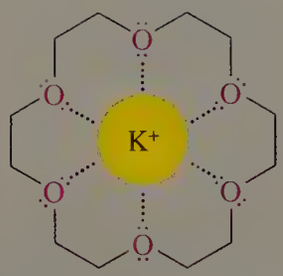
ethanethiol dimethyl sulfide

16.89 Indicate two methods to produce the scent marker of the red fox using a thiol as one of the reactants.



16.90 Outline a series of reactions to produce the compound used for defense by the skunk starting with 3-methyl-1-butene.





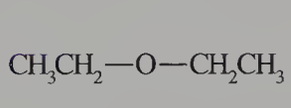
potassium ion solvated by 18-crown-6

17

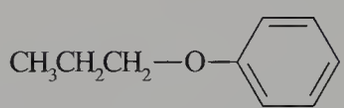
Ethers and Epoxides

17.1 Structure of Ethers

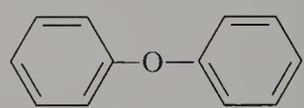
Ethers contain two alkyl or aryl groups bonded to an oxygen atom. The two alkyl or aryl groups are identical in a **symmetrical ether** and different in an **unsymmetrical ether**.



diethyl ether
(symmetrical ether)

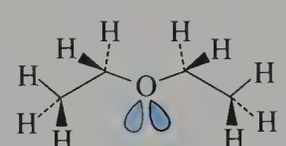


phenyl propyl ether
(unsymmetrical ether)



diphenyl ether
(symmetrical ether)

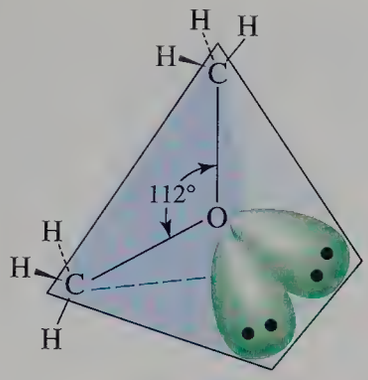
The oxygen atom of an ether is sp^3 hybridized. The C—O—C bond angle of dimethyl ether is 112°, approximately the tetrahedral bond angle (Figure 17.1). Using VSEPR theory, we show the two lone pairs of electrons of the oxygen atom directed to two corners of a tetrahedron. The geometry of the two C—O bonds of ethers allows us to make predictions about their most stable conformations. We can imagine creating an ether by replacing a CH_2 group of an alkane with an oxygen atom. For example, replacing the C-3 methylene group of pentane with an oxygen atom gives diethyl ether. Diethyl ether has an anti arrangement of all atoms in its most stable conformation.

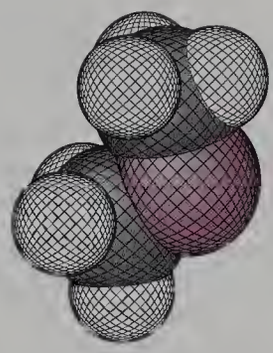


ethoxyethane (diethyl ether)

A similar situation prevails when we compare conformations of cyclic ethers with those of the corresponding cycloalkanes. For example, tetrahydropyran, the ether analog of cyclohexane, exists in a chair conformation. Following predictions of VSEPR theory, the two oxygen lone pair electrons are shown in positions corresponding to

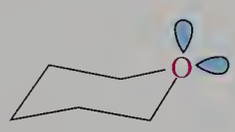
FIGURE 17.1 Structure of Dimethyl Ether
The oxygen atom of ethers is sp^3 hybridized. The C—O—C bond angle is close to the tetrahedral angle. The two sets of lone pair electrons are in sp^3 hybrid orbitals that are directed to two of the corners of a tetrahedron.



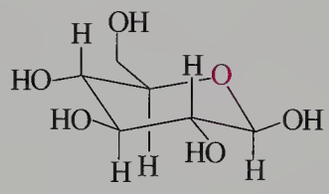


Space-filling model

the axial and equatorial C—H bonds of cyclohexane. The conformation of tetrahydropyran is particularly important because many carbohydrates, such as glucose, exist as six-membered tetrahydropyran rings (Section 20.5).



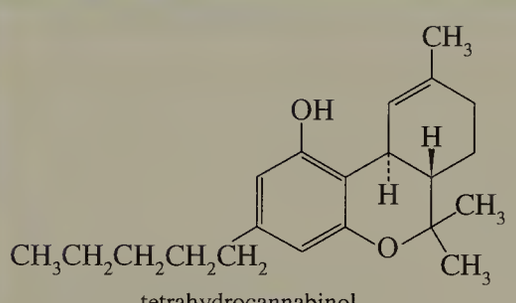
tetrahydropyran



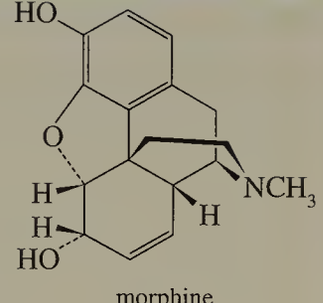
glucose

Figure 17.2 shows examples of naturally occurring, physiologically active cyclic ethers. Tetrahydrocannabinol (THC), the principal active ingredient in marijuana, includes a six-membered ring ether. Morphine contains a five-membered ring ether. Three-membered cyclic ethers (epoxides) are rare in nature. The juvenile hormone of some insects contains a cis-substituted epoxide. This hormone slows and controls the rate of maturation of insects.

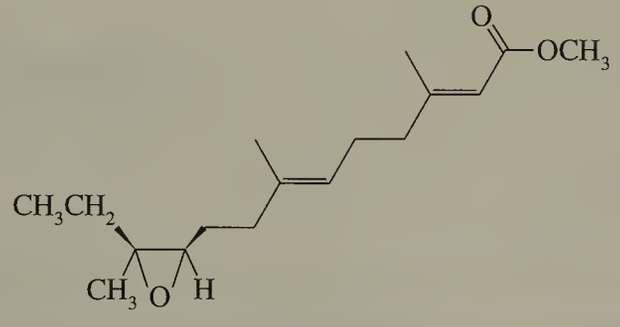
FIGURE 17.2 Naturally Occurring Ethers



tetrahydrocannabinol



morphine

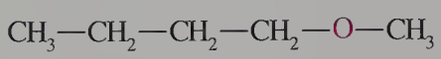


insect juvenile growth hormone

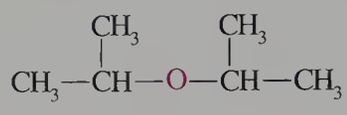
17.2 Nomenclature of Ethers

Common Names

Simple ethers are commonly called *alkyl alkyl ethers*. The name consists of a list of the alkyl (or aryl) groups in alphabetical order followed by the name *ether*. For example, an unsymmetrical ether with a butyl group and a methyl group is named butyl methyl ether. Symmetrical ethers are named by using the prefix di- in conjunction with the name of the alkyl group. For example, an ether with two isopropyl groups is called diisopropyl ether.



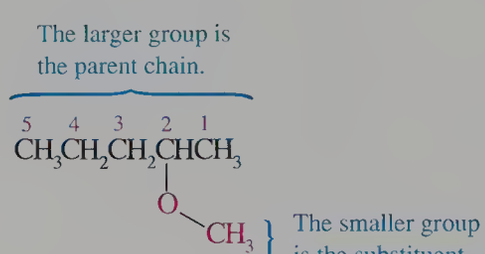
butyl methyl ether



diisopropyl ether

IUPAC Names

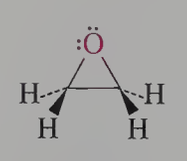
According to IUPAC nomenclature, ethers are named *alkoxyalkanes*, where the smaller alkyl group and the oxygen atom constitute an **alkoxy group**. An alkoxy group is treated as a substituent on the larger parent alkane chain. For example, a five-carbon chain (pentane) with an $—OCH_3$ group at the C-2 atom is named 2-methoxypentane. Figure 17.3 shows other examples of ether nomenclature.



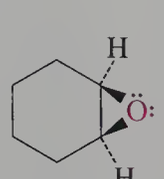
2-methoxypentane

Cyclic Ethers

Three- through six-membered cyclic ethers have common names. Cyclic ethers with three ring atoms are called **epoxides**. As these compounds can be made by the oxidation of an alkene, the common name of an epoxide adds *oxide* to the name of the alkene.



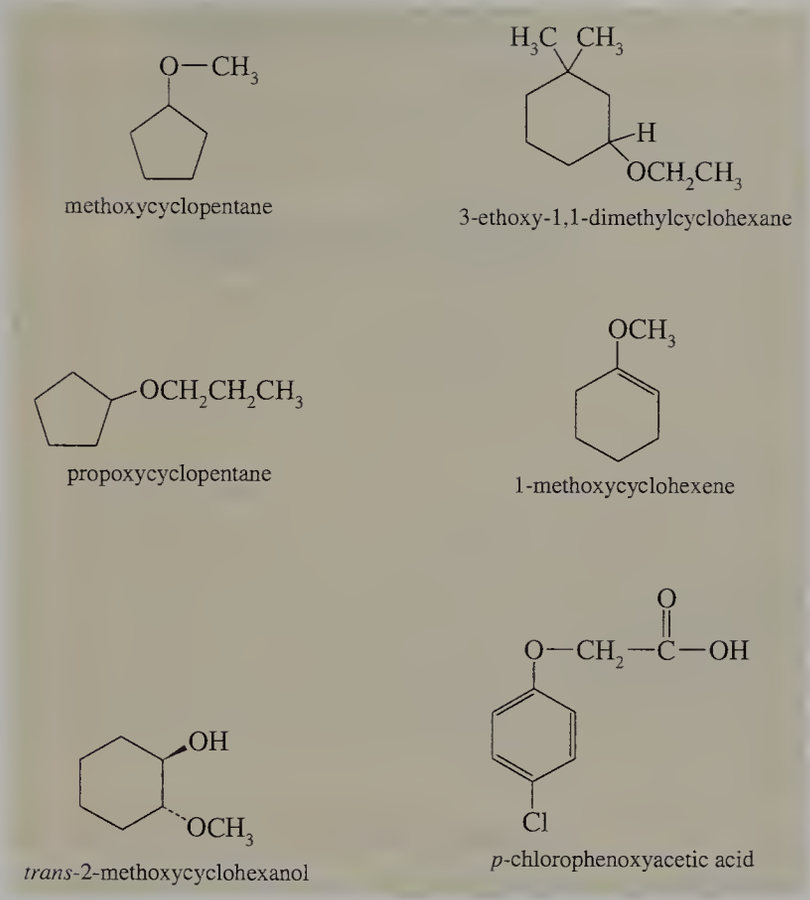
ethylene oxide



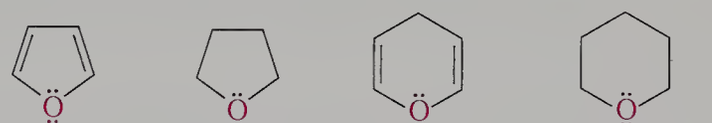
cyclohexene oxide

The four-membered ring ethers, called trimethylene oxides, are not common. The five-membered ring ether is called tetrahydrofuran (THF) because of its relationship

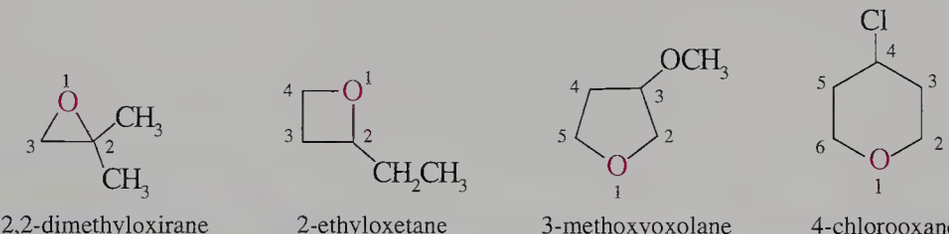
FIGURE 17.3
Nomenclature of Ethers



to the aromatic compound furan. Similarly, tetrahydropyran (THP), a six-membered ring ether, is related to pyran, an unsaturated ether.

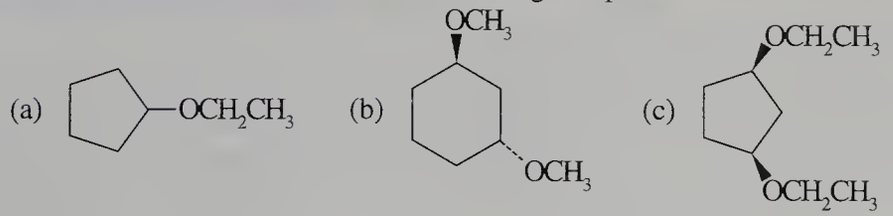


In the IUPAC nomenclature system, the names for cyclic ethers with three-, four-, five-, and six-membered rings are oxirane, oxetane, oxolane, and oxane, respectively. The oxygen atom in each of these rings receives the number 1 in both common names and IUPAC nomenclature. The ring is numbered in the direction that gives the lowest number to the first substituent.



Problem 17.1

What are the IUPAC names of the following compounds?



Problem 17.2

Which of the following compounds can exists as pairs of enantiomers?
(a) 2-methoxytetrahydropyran (b) 4-methyltetrahydropyran
(c) 2-ethoxytetrahydrofuran (d) 3-methyltetrahydrofuran

Problem 17.3

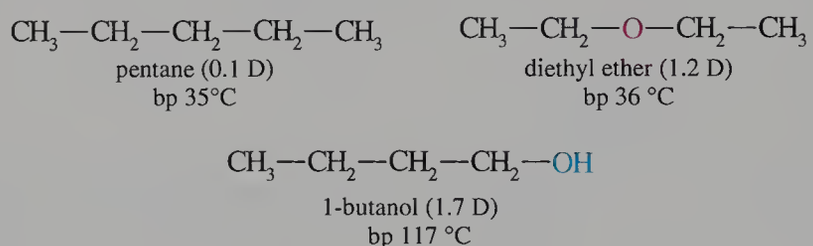
Draw the structure of each of the following compounds.
(a) (2*S*,3*R*)-dimethyloxirane (b) (*Z*)-1-methoxy-1-butene
(d) 2-ethoxyoxane (c) *trans*-1,4-dimethoxycyclohexane

17.3 Physical Properties of Ethers

Diethyl ether—often called ethyl ether or just ether—was used as a general anesthetic as early as 1842. Administered as a vapor, it acts as a depressant on the central nervous system, causing unconsciousness. However, its high flammability and volatility present hazards in the operating room. Ethers such as ethyl vinyl ether, divinyl ether, and methyl propyl ether have also seen use as anesthetics. All the low molecular weight ethers are potentially explosive when mixed with oxygen.

Dipole Moments and Boiling Points

Ethers have two polar C—O bonds and are more polar than alkanes, but less polar than alcohols. Ethers do not have an O—H bond, so they cannot serve as hydrogen bond donors. Therefore, ether molecules do not hydrogen bond to each other, and their boiling points are very close to those of alkanes of similar molecular weight.



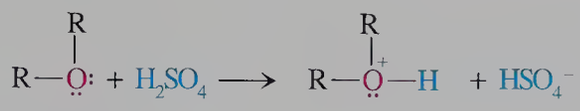
Solubility in Water

Because ethers are polar, they are more soluble in water than alkanes of similar molecular weight. The slight solubility of ethers in water results from hydrogen bonds between the hydrogen atoms of water molecules and the lone pair electrons of the oxygen atom of ether molecules. For example, tetrahydrofuran is miscible in water, and the solubility of diethyl ether is about 10 g per 100 mL of water. The difference in the solubility of cyclic and acyclic ethers reflects the effect of restricted conformational motion in cyclic ethers compared to acyclic ethers. In diethyl ether, the flexible chain of atoms sweeps out a volume that prevents hydrogen bonding between the ether oxygen atom and the hydrogen atoms of water. In tetrahydrofuran, however, the carbon atoms are "tied back", and the lone pair electrons of the oxygen atom are available to form hydrogen bonds with water.

The solubility of diethyl ether in water is much higher than that of pentane, but the solubilities of ethers and alkanes approach one another as their molecular weights

increase. The ether functional group contributes less to the overall properties of high molecular weight molecules, which resemble alkanes in solubility.

Ethers are very soluble in concentrated aqueous solutions of inorganic acids such as sulfuric acid. The increased solubility in acid compared to water results from protonation of the ether oxygen by the acid to form an oxonium ion.

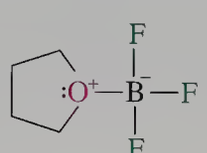


(an oxonium ion)

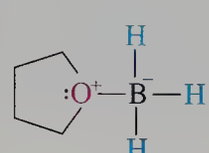
Ethers as Solvents

Ethers such as diethyl ether dissolve a range of nonpolar and polar compounds. Nonpolar compounds are generally more soluble in diethyl ether than in alcohols such as ethanol because ethers do not have a hydrogen-bonding network that must be broken up to dissolve the solute. Because diethyl ether has a moderate dipole moment, polar substances readily dissolve in it. Polar compounds that can serve as hydrogen bond donors dissolve in diethyl ether because they can form hydrogen bonds to the oxygen lone pair electrons of the ether.

Ethers are aprotic. For this reason, basic substances, such as Grignard reagents, can be prepared in ether solvents such as diethyl ether and tetrahydrofuran. These ethers solvate the magnesium atom, which is coordinated to the lone pair electrons of the oxygen atoms (Figure 17.4). The lone pair electrons also stabilize electron-deficient species such as BF_3 and borane (BH_3). For example, the borane–THF complex is used in the hydroboration of alkenes (Section 16.8).

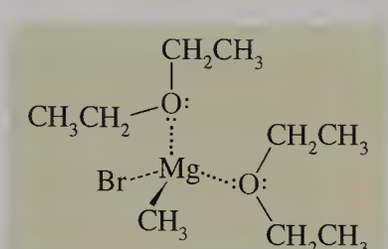


BF_3–THF complex



BH_3–THF complex

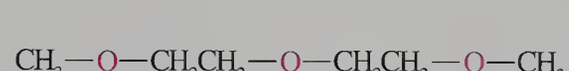
FIGURE 17.4 Solvation of a Grignard Reagent



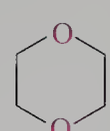
Polyethers

Substances with more than one ether linkage readily dissolve polar compounds or hydrogen bond donors. Examples of such solvents include 1,2-dimethoxyethane (glyme), diglyme, and the cyclic ether 1,4-dioxane.

glyme



diglyme



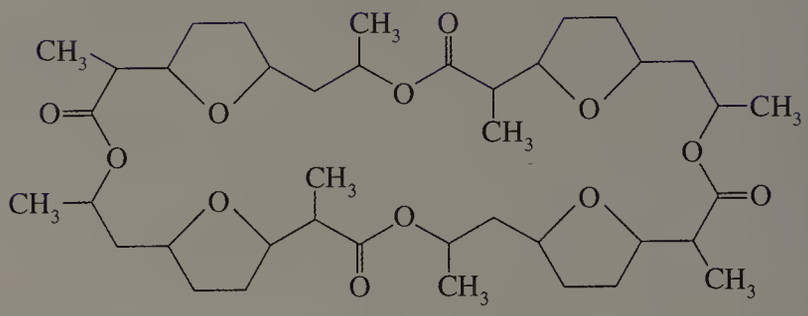
1,4-dioxane

Polyether Antibiotics

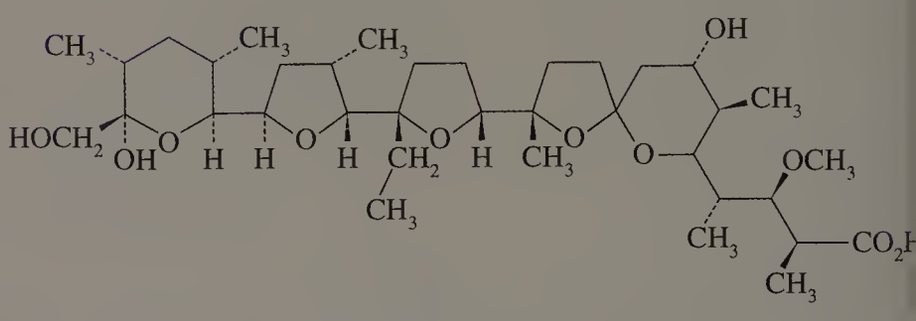
Several cyclic and acyclic polyethers act as antibiotics by transporting ions across biological membranes. These ethers are called **ionophores** (ion carriers). They function by disrupting the electrolyte balance between the interior and exterior of cells that is necessary for normal maintenance of the cell.

The cyclic ether antibiotic nonactin (see the figure) selectively transports potassium out of bacterial cells. This compound, which contains four five-membered ring ethers linked by ester units, binds potassium about 10 times better than it binds sodium. Because cells must maintain a higher internal concentration of potassium ions than of sodium ions, the selective removal of potassium ions kills bacteria.

Monensin (see the figure) is a conformationally flexible acyclic polyether that can form complexes with sodium ions. The complex transports sodium ions into cells. The increase in the concentration of sodium ions within the cell's structure increases the osmotic pressure. Water follows the sodium and the consequent cell membrane rupture kills the cell. Farmers add monensin to poultry feed to kill intestinal parasites.



nonactin



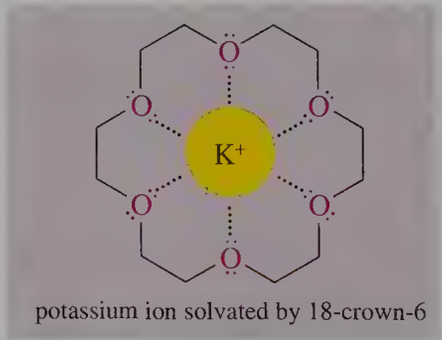
monensin

Antibiotic Polyethers

The cyclic polyethers can coordinate with ions such as alkali metal ions. The selectivity of the ether for one metal ion over another depends on the geometry of the polyether and the location of the ether oxygen atoms.

You may recall from your general chemistry course that cations represented as M^{n+} are solvated by several water molecules in aqueous solution. In 1967, Charles J. Pederson of the Du Pont Company prepared cyclic polyethers that can similarly solvate cations and increase the solubility of ionic compounds in nonpolar organic solvents. These compounds, called **crown ethers**, are named *x*-crown-*y* where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. The 18-crown-6 ether chelates the potassium ion in a cavity within the ring (Figure 17.5).

FIGURE 17.5 Solvation of a Cation by a Crown Ether



potassium ion solvated by 18-crown-6

The chelating characteristics of crown ethers depend on the match between the size of the cavity and the ionic radius of the ion. The internal cavity of 18-crown-6 spans between 260 and 310 pm, close to the ionic radius of the potassium ion, about 270 pm. Thus, not only does the potassium ion fit within the cavity, but all the oxygen atoms of the crown ether lie close enough to the potassium ion to effectively complex it. Because of this chelation, the solubilities of inorganic salts such as KCN or $KMnO_4$ are increased. The separation of the cation from the anion leaves the anion "naked" and greatly increases its nucleophilicity (Section 10.3).

Problem 17.4

Both glyme and 1,4-dioxane are miscible with water. Explain why.

Problem 17.5

15-Crown-5 efficiently complexes a sodium ion. Compare the expected size of the cavity of this crown ether with 18-crown-6. Explain why this cavity can solvate the sodium ion.

Sample Solution

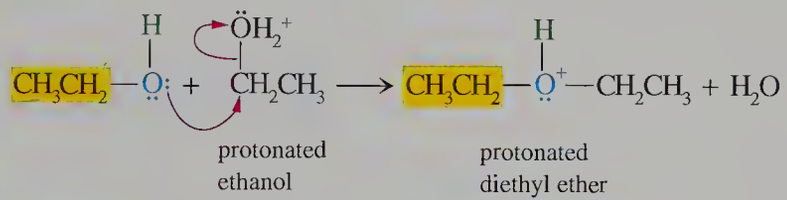
The smaller ring of the 15-crown-5 has a smaller cavity than the 18-crown-6. Sodium has a smaller ionic radius than potassium. We know that potassium ion fits in the cavity of 18-crown-6. Thus the smaller ring of 15-crown-5 and the smaller sodium ion should fit together to form a complex.

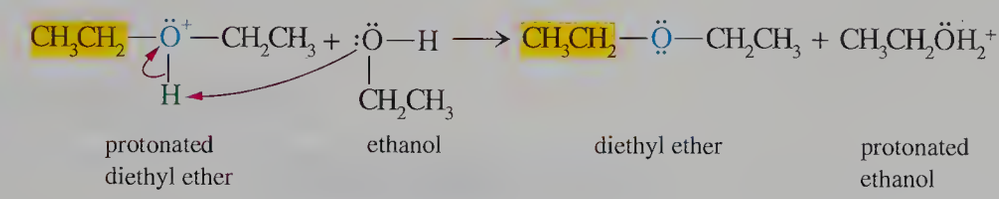
17.4 Industrial Synthesis of Ethers

Some dialkyl ethers are made commercially by the acid-catalyzed condensation of alcohols. This method is used to prepare millions of gallons of diethyl ether from ethanol each year. The method is largely limited to the synthesis of symmetrical ethers in which the alkyl groups are primary. This method requires acid, and secondary and tertiary alcohols tend to dehydrate under comparable reaction conditions.

$$2\,CH_3CH_2{-}OH \xrightarrow[125\ ^\circ C]{H_2SO_4} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O$$

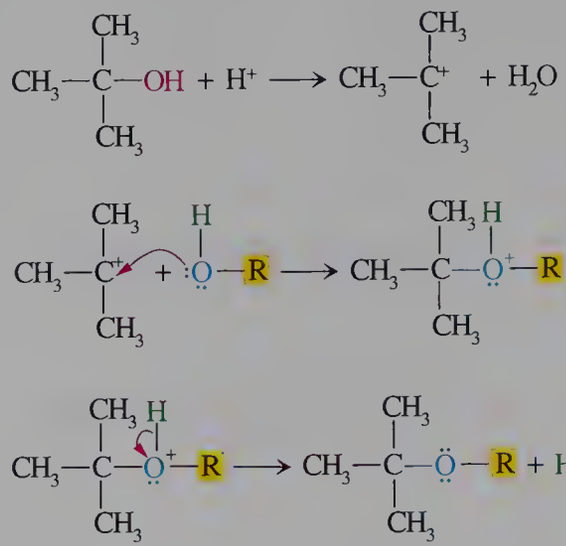
Diethyl ether is formed by the displacement of water from a protonated ethanol molecule by another ethanol molecule. The initial product is the conjugate acid of the ether, which subsequently loses a proton to give the ether. The mechanism is shown below for the formation of diethyl ether.



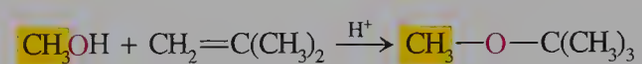


Mixed ethers containing one tertiary group and one primary group can be prepared using dilute acid. The tertiary alcohol is converted into a carbocation, which

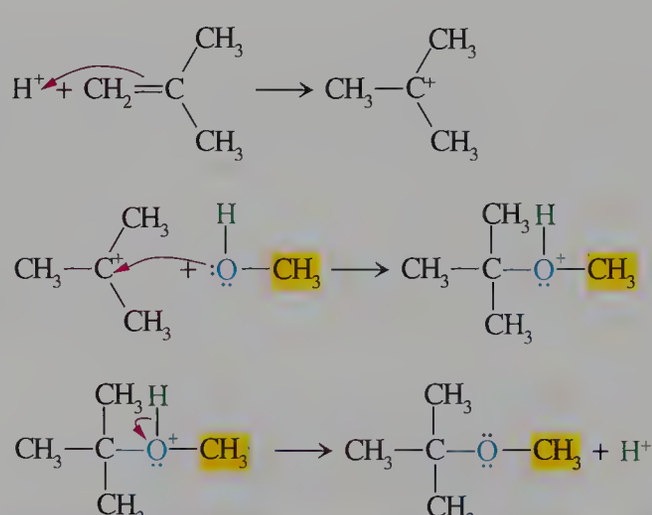
then preferentially combines with the sterically accessible oxygen atom of the primary alcohol rather than the oxygen atom of the tertiary alcohol.



Some unsymmetrical ethers are synthesized in industry by the acid-catalyzed addition of alcohols to alkenes. For example, approximately 2×10^9 lb of *tert*-butyl methyl ether is prepared annually by the addition of methanol to 2-methylpropene. Gasoline manufacturers add the compound to promote cleaner combustion and reduce tailpipe emissions. It is commercially referred to as MTBE, an abbreviation for the incorrect name methyl *tert*-butyl ether. This is incorrect because the alkyl groups are not arranged in alphabetical order in the name.



The addition of an alcohol to an alkene occurs by a mechanism similar to the mechanism for the addition of water to alkenes (Section 7.5). Addition of a proton to the alkene yields a carbocation, which then reacts with the nucleophilic oxygen atom of the alcohol. Thus two steps of the reaction are identical to those described for the reaction of a tertiary alcohol with a primary alcohol in the synthesis of a mixed ether.



Problem 17.6

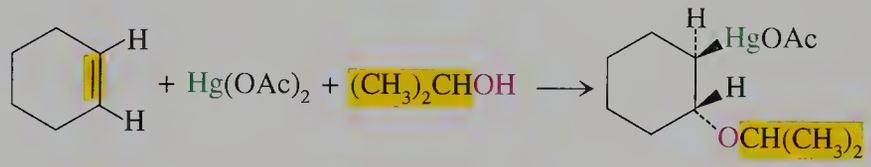
The acid-catalyzed condensation of a mixture of 1-propanol and 1-butanol is not a satisfactory method to produce butyl propyl ether. Why?

Problem 17.7

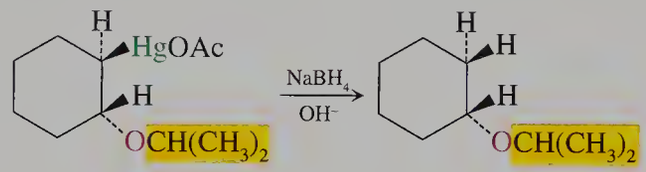
2-Methyl-2,5-hexanediol is converted into a substituted tetrahydrofuran of formula $C_7H_{14}O$ when treated with phosphoric acid. What is the structure of the product? Write a mechanism for its formation. Which of the two oxygen atoms of the diol remains in the product according to your mechanism?

17.5 Alkoxymercuration–Demercuration of Alkenes

In the laboratory, we can add an alcohol to an alkene on a small scale using a method analogous to the oxymercuration–demercuration of alkenes used to prepare alcohols in aqueous solvents (Chapter 16). The oxymercuration–demercuration of an alkene in an alcohol as the solvent produces an ether. In this reaction, the alcohol, rather than water, acts as the nucleophile. This process, called **alkoxymercuration**, occurs by a mechanism analogous to oxymercuration, electrophilic addition of ^+HgOAc to the carbon–carbon double bond. This step forms a mercurinium ion intermediate, which is subsequently attacked by the nucleophilic oxygen atom of the alcohol. Consider the reaction of cyclohexene with mercuric acetate in 2-propanol.



The alkoxymercurated adduct is then demercurated using sodium borohydride in slightly basic solution.



As in oxymercuration, the intermediates do not rearrange. The regiospecificity of the addition follows Markovnikov's rule.

Problem 17.8

Write the structure of the product of a reaction of 3,3-dimethyl-1-butene with mercuric acetate in ethanol as solvent.

Problem 17.9

Select the reagents required to prepare each of the following compounds using the alkoxymercuration–demercuration method.

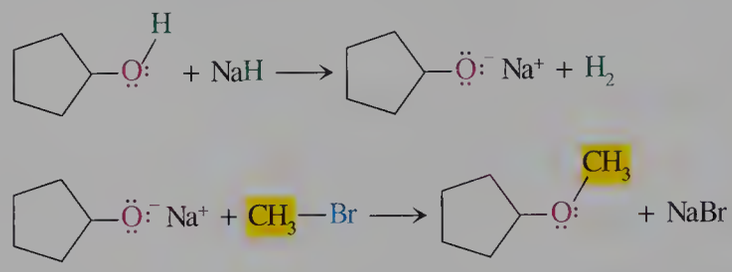
(a) ethoxycyclohexane (b) 1-propoxybutane (c) dicyclohexyl ether

Problem 17.10

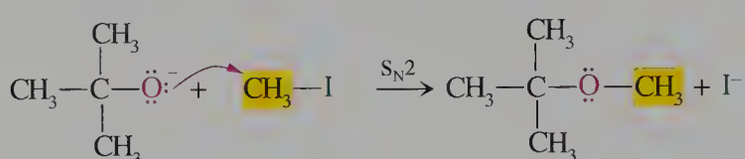
Reaction of 5-hexen-1-ol with mercuric acetate followed by demercuration gives an ether that is isomeric with the unsaturated alcohol. The compound is formed by an intramolecular alkoxymercuration reaction. Draw the structure of the product.

17.6 The Williamson Ether Synthesis

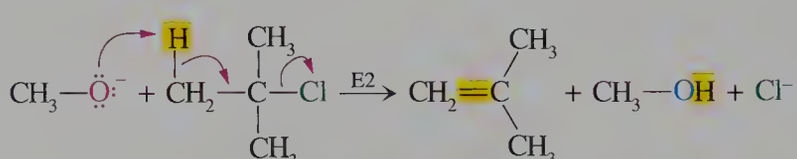
The **Williamson ether synthesis** is the most widely used method to produce ethers. It occurs by an S_N2 reaction in which a metal alkoxide displaces a halide ion from an alkyl halide. The alkoxide ion is prepared by the reaction of an alcohol with a strong base such as sodium hydride.



The Williamson synthesis gives the best yields with methyl or primary halides because the reaction occurs by an S_N2 displacement in which a halide ion is the leaving group. The yield is lower for secondary alkyl halides because they also react with the alkoxide ion in a competing elimination reaction. The Williamson synthesis cannot be used with tertiary alkyl halides because they undergo elimination reactions instead of participating in S_N2 reactions. Thus, to make an unsymmetrical ether with a primary and a tertiary alkyl group, a primary alkyl halide and a tertiary alkoxide ion are the best reagents. For example, *tert*-butyl methyl ether can be prepared by the reaction of sodium *tert*-butoxide with methyl iodide, but not by the reaction of sodium methoxide with 2-chloro-2-methylpropane.



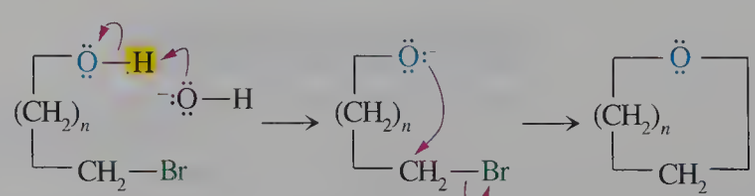
primary halide



tertiary halide

Cyclization Reactions

Cyclic ethers can be prepared by the intramolecular S_N2 reaction of a halogen-substituted alcohol such as a bromo alcohol. Proton transfer to a base such as sodium hydroxide gives a bromo alkoxide. If the solution is dilute, the alkoxide acts as a nucleophile and intramolecularly displaces a bromide ion.



In more concentrated solutions, an intermolecular Williamson reaction occurs to give a bromo alkoxy ether. Continued reactions of this type yield long-chain ethers.

$$Br{-}CH_2{-}(CH_2)_n{-}O^- + Br{-}CH_2{-}(CH_2)_n{-}O^- \longrightarrow Br{-}CH_2{-}(CH_2)_n{-}O{-}CH_2{-}(CH_2)_n{-}O^-$$

The intramolecular reaction is favored in dilute solution because it is first order. The competing intermolecular reaction is second order, and the rate of the reaction falls off with the square of the concentration. Thus, in dilute solution, the rate of the intermolecular reaction decreases more rapidly than the rate of the intramolecular reaction.

Rates of Cyclization Reactions

The rates of cyclization of bromo alkoxides as a function of the number of atoms forming the ring (including the oxygen atom) stand in an order that at first glance may appear illogical.

Rates of cyclization: $3 > 5 > 6 > 4 > 7 > 8$

For all these reactions, the same number and types of bonds are being formed and broken. However, the ΔH°_{rxn} will not be the same for all compounds. We recall that because of angle strain, three- and four-membered rings are less stable than the larger five-, six-, seven-, and eight-membered rings (Section 4.7). The same angle strain should affect the energy barrier for the formation of the small ether rings. Because the energy barrier is higher, the rate of reaction is expected to be smaller. The total strain energies of cyclopropane and cyclobutane are approximately equal. In contrast, the strain energies of the five-, six-, seven-, and eight-membered rings are quite small. To the extent that ring strain similarly affects the rate of cyclization, we expect the rates to approximately stand in the following order.

Predicted rates based on strain energy: $3 = 4 > 5 = 6 = 7 = 8$

However, this order does not consider an entropy factor. What is the probability that the two reacting centers will approach each other as the length of the chain increases? The degree of freedom and number of conformations of the chain increase with the number of atoms in the chain. To form a conformation suitable for an intramolecular reaction, the flexibility of the chain must be restricted. With a small number of atoms, the two reacting centers lie close to each other, and we say that the reaction is entropically favored. With an increased number of atoms, the probability of a cyclization reaction decreases. The order of the rates of reaction based only on the probability of cyclization is

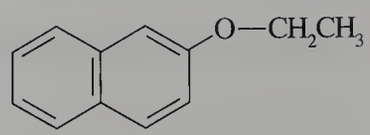
Predicted rates based on probability: $3 > 4 > 5 > 6 > 7 > 8$

Now we can interpret the observed order of reactivity. Three-membered rings form rapidly because the contribution of entropy to reaching the transition state is sufficiently favorable to overcome the unfavorable enthalpy of activation associated with ring strain. However, the rate of formation of a four-membered ring is considerably slower because the ring strain is similar to that of a three-membered ring but the probability of the reacting sites being in a conformation suitable for reaction is smaller. Thus, the rate of formation of four-membered rings falls below that of the essentially strain-free five- and six-membered rings.

The five-membered ring, somewhat more strained than the six-membered ring, forms at the faster rate as a result of the probability factor. For larger rings, which have relatively small ring strain, the rate of cyclization is controlled by the entropy factor and falls off with increasing number of atoms in the ring formed.

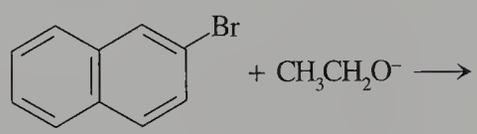
Problem 17.11

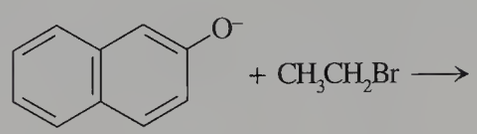
2-Ethoxynaphthalene, known by its tradename Nerolin II, is used in perfumery for its odor of orange blossoms. Propose a synthesis of this compound using the Williamson method.



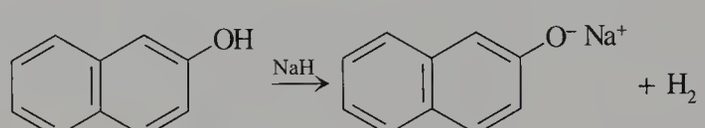
Sample Solution

Consider the following two combinations of reagents.





The first combination will not give the ether product because S_N2 reactions cannot occur by back-side displacement of halogen atoms at sp^2-hybridized carbon atoms. However, the reaction of the conjugate base of the hydroxyl group at the 2 position of naphthalene with bromoethane occurs readily because bromoethane is an unhindered primary alkyl halide. The nucleophilic oxygen atom of the naphthalene compound is generated by reaction with sodium hydride.



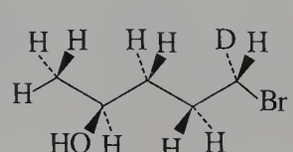
Problem 17.12

Propose a synthesis of each of the following compounds using the Williamson ether synthesis.

(a) phenyl propyl ether (b) benzyl *tert*-butyl ether (c) 1,4-dimethoxybutane

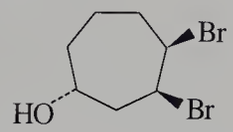
Problem 17.13

Assign the configuration of the following bromo alcohol. Draw the structure of the tetrahydrofuran formed by an intramolecular Williamson ether synthesis and assign its configuration.



Problem 17.14

Draw the structures of two possible bicyclic ethers that could result from the intramolecular displacement of bromide by the alkoxide derived from the following dibromo alcohol. Which compound should predominate?

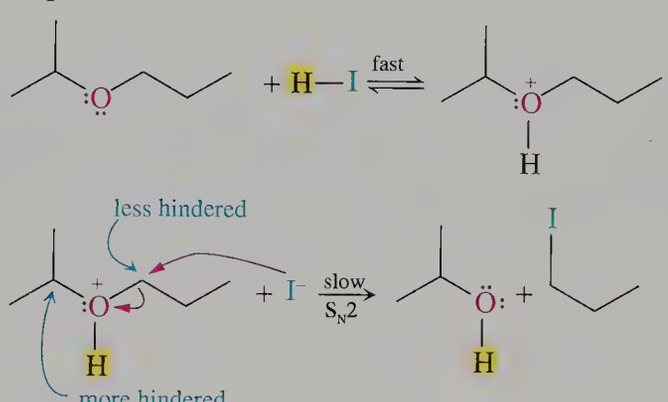


17.7 Reactions of Ethers

Ethers are very stable compounds that react with few common reagents. They do not react with bases, but do react with strong acids whose conjugate bases are good nucleophiles. For example, ethers react with HI (or with HBr) with cleavage of the carbon – oxygen bond to produce alkyl iodides (or bromides).

$$R{-}O{-}R' \xrightarrow{HX} R{-}X + R'{-}OH \xrightarrow{HX} R{-}X + R'{-}X$$

The cleavage reaction does not occur with a halide salt: A proton from the halogen acid must protonate the oxygen atom, providing an alcohol as the leaving group. We recall a similar reaction in which alcohols are converted to alkyl halides by way of an S_N2 reaction in which halide ions displace water from a protonated alcohol (Section 8.14). In general, the less substituted alkyl halide forms in this S_N2 reaction. The halide ion attacks the less hindered carbon atom, and the oxygen atom of the displaced alkoxy group remains bonded to the more substituted carbon atom.

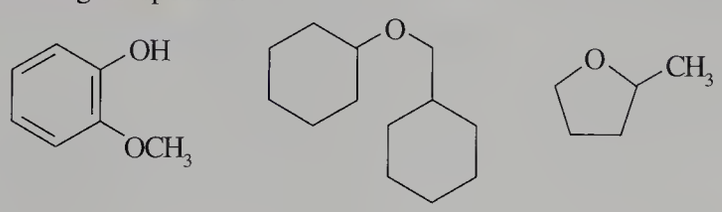


If excess HI is used, a subsequent reaction of the alcohol gives a second mole of an alkyl halide. Both alkyl groups of the ether are eventually converted into alkyl halides.

The cleavage of ethers to produce alkyl halides and alcohols can be used to break complex molecules into simpler units to determine their structures. Considering the identity of the cleavage products, one can picture the original ether by joining the two alkyl groups of the products to an oxygen atom. Note that a cyclic ether would yield a single dihalogen compound.

Problem 17.15

Based on the mechanism of ether cleavage, write the products of the reaction of HI with each of the following compounds.



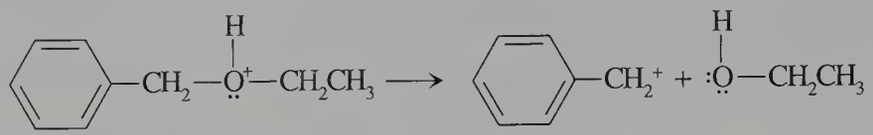
I II III

Problem 17.16

Allylic and benzylic ethers are not cleaved by an S_N2 process. Suggest an alternate mechanism for the acid-catalyzed cleavage of benzyl ethyl ether.

Sample Solution

A benzyl carbon–oxygen bond of the conjugate acid of benzyl ethyl ether can cleave heterolytically in an S_N1 reaction. The leaving group is ethanol, and the resulting benzyl carbocation is resonance stabilized.

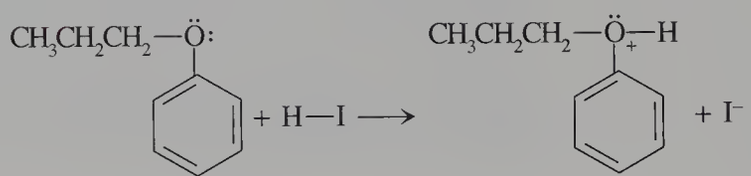


Problem 17.17

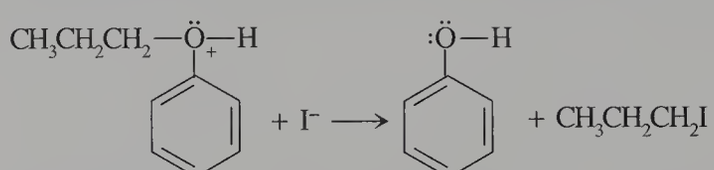
Based on the mechanism of ether cleavage, write the products of the reaction of HI with phenyl propyl ether.

Sample Solution

First, the strong acid protonates the ether oxygen atom to give an oxonium ion.



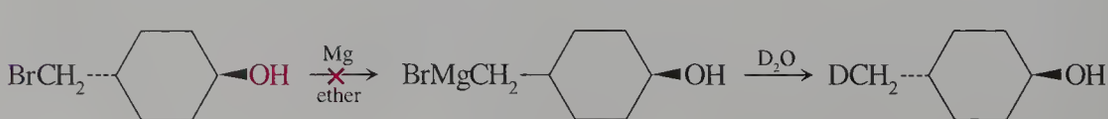
Subsequent nucleophilic attack by the iodide ion can occur only at the methylene carbon atom of the propyl group bearing the oxygen atom. An S_N2 reaction at the carbon atom of the benzene ring that bears the oxygen atom is not possible. The phenol produced also will not react further with HI for the same reason.



17.8 Ethers as Protecting Groups

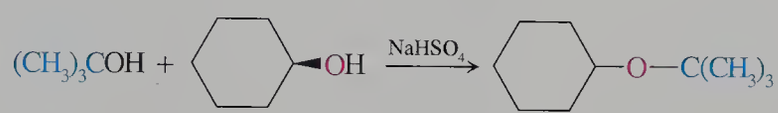
Synthetic transformations at one functional group in a molecule that contains two or more functional groups are often complicated by competing reactions at the other reactive sites. However, a functional group can often be converted into an unreactive form called a protecting group. The protected functional group can subsequently be converted back to the original functional group after other synthetic goals are achieved. A protecting group is selected that is both easy to form and easy to remove at the end of the synthesis. Both reactions should occur in high yield.

Consider the possibility of forming a Grignard reagent of *trans*-4-(bromomethyl)cyclohexanol followed by reaction with deuterium oxide to produce a deuterated methyl compound.

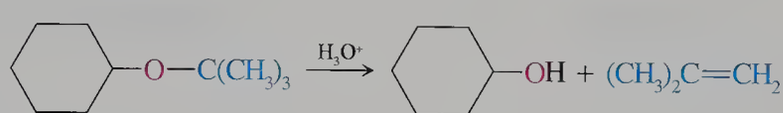


The synthesis would fail because the hydroxyl group would react immediately with the Grignard reagent. To get around this problem, we first convert the hydroxyl group to an ether. Then, after the formation of the Grignard and subsequent deuteration, the ether could be cleaved to reform the alcohol.

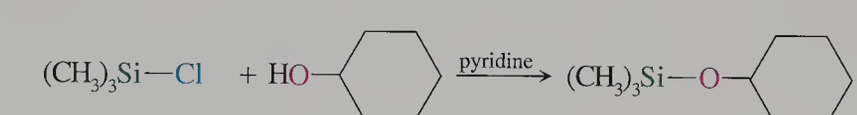
Independent of any specific synthesis, let's consider the general method of using ethers as protecting groups for alcohols. The formation of mixed ethers directly from two alcohols usually gives a mixture of three products. However, it is possible to form mixed ethers in which one alkyl group is tertiary and the other is primary or secondary (Section 17.4). We carry out this acid-catalyzed reaction, converting the tertiary alcohol to a tertiary carbocation, which then reacts with the other alcohol. Consider the protection of the hydroxyl group of cyclohexanol with a *tert*-butyl group.



The protecting group is removed by treating the ether with dilute aqueous acid. The acid protonates the ether to give an oxonium ion that dissociates by an S_N1 reaction to give a *tert*-butyl carbocation and cyclohexanol. Cyclohexanol is the leaving group in this S_N1 reaction. The *tert*-butyl carbocation then gives 2-methylpropene by an E1 process. Because 2-methylpropene is a gas, it escapes from the solution, pulling the reaction to completion. The desired alcohol remains in the solvent.



Other alternatives to protecting hydroxyl groups are available that avoid the acidic conditions that could interfere with other functional groups in a molecule. Hydroxyl groups react with trialkylchlorosilanes to give **silyl ethers** in a reaction analogous to the Williamson ether synthesis. The reaction is carried out with one equivalent of pyridine, which reacts with the HCl by-product to give pyridinium hydrochloride.

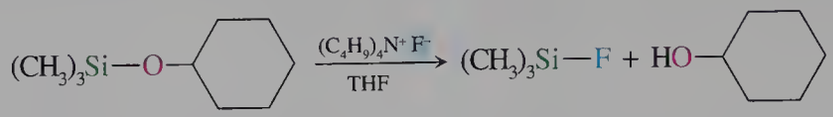


The Si—Cl bond is so reactive that chloride ion is displaced by the alcohol directly. That is, in contrast to the Williamson synthesis, the alcohol need not be converted to an alkoxide.

The silyl ether forms by an S_N2 reaction at a tertiary center. This reaction can occur at a tertiary silicon center because the C—Si bond length is 195 pm, compared to the 154 pm of a C—C bond length. The alkyl groups bonded to the tertiary silicon atom are farther away from each other than alkyl groups bonded to a tertiary carbon atom. Therefore, they do not present as much steric interference to the approach of a nucleophile as do the alkyl groups in the analogous carbon compound, *tert*-butyl chloride.

Silyl ethers are less reactive than ethers to both acid and base and therefore are stable under most reaction conditions. In practice, *tert*-butyldimethylsilyl (TBDMS) ethers are prepared rather than trimethylsilyl (TMS) ethers because they are somewhat more stable. However, either trialkylsilyl group is easily removed by reaction with fluoride ion, provided in the form of the salt tetrabutylammonium fluoride. This

cleavage reaction is highly regioselective because the fluoride ion has no effect on most other functional groups.

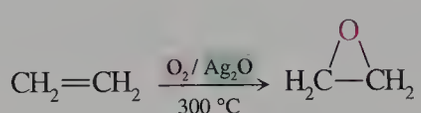


(a trimethylsilyl ether)

The fluoride ion preferentially attacks at silicon because the bond dissociation energy of the Si—F bond is 535 kJ mole^{-1} (128 kcal mole^{-1}). The bond dissociation energy of the Si—O bond broken is 372 kJ mole^{-1} (89 kcal mole^{-1}), so the formation of an Si—F bond is thermodynamically favorable. Furthermore, the Si—F bond is stronger than a C—F bond, which has a bond dissociation energy of 426 kJ mole^{-1} (102 kcal mole^{-1}). Therefore, cleavage of the C—O bond of the silyl ether is thermodynamically less favorable than cleavage of the Si—O bond.

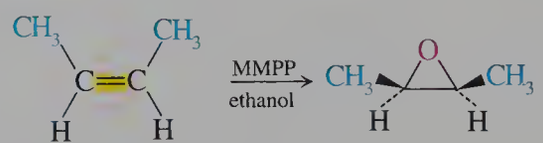
17.9 Synthesis of Epoxides

About 3 million tons of ethylene oxide are produced annually from ethylene by direct air oxidation over a silver oxide catalyst. The major use of ethylene oxide is conversion to ethylene glycol, which is used for automobile antifreeze and in the formation of polyesters.

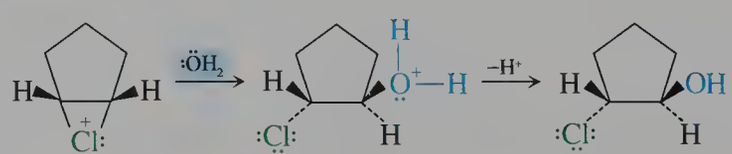


Direct air oxidation cannot be used with many alkenes, and it is not a useful method for the synthesis of complex compounds with multiple functional groups. Two general methods for epoxide synthesis are the oxidation of alkenes and the cyclization of halohydrins.

We recall that epoxides can be synthesized by oxidizing an alkene (Section 7.8). The possible oxidizing agents are peroxyacetic acid (CH_3CO_3H), *m*-chloroperoxybenzoic acid (MCPBA), and magnesium monoperoxyphthalate (MMPP). The epoxidation of alkenes with peroxy acids is stereospecific. The stereochemistry of the groups in the alkene remains: cis groups in the alkene remain cis in the epoxide, and trans groups in the alkene remain trans in the epoxide.

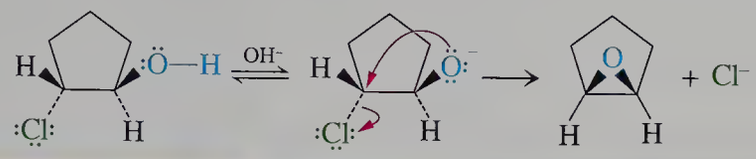


A second method of synthesizing epoxides is an *intramolecular* variation of the Williamson ether synthesis. First, a halohydrin forms in the reaction of an alkene with an aqueous solution of a halogen. For example, chlorine gives a cyclic chloronium ion, which then reacts with water as the nucleophile to give the chlorohydrin.



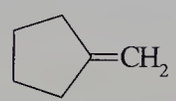
(a chlorohydrin)

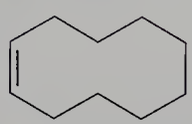
The chlorohydrin is treated with a base, producing an alkoxide ion that displaces a chloride ion from the adjacent carbon atom to form the epoxide ring.

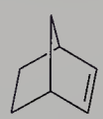


Problem 17.18

Draw the structure of the epoxide formed in the reaction of each of the following compounds with MMPP in ethanol.

(a) 

(b) 

(c) 

Problem 17.19

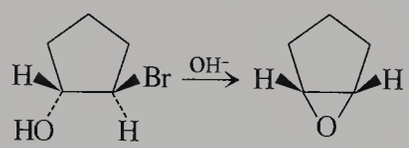
Write the halohydrin product of the electrophilic addition of bromine in water to *cis*-2-butene. Considering the expected stereochemistry of the product, predict the stereochemistry of the epoxide formed from this bromohydrin.

Problem 17.20

(1*R*,2*R*)-2-Bromocyclopentanol reacts with sodium hydroxide to form an optically inactive product with the molecular formula C_5H_8O. However, the isomeric 1*S*,2*R* compound is significantly less reactive and forms elimination and substitution products. Explain why.

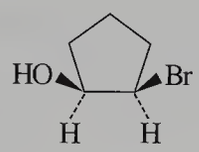
Sample Solution

In the 1*R*,2*R* isomer the nucleophilic alkoxide ion, derived from loss of a proton from the hydroxyl group, and the bromine atom, which can leave as a bromide ion, are trans to each other. An intramolecular Williamson reaction gives an epoxide.



1*R*,2*R*

The 1*S*,2*R* compound cannot react to form an epoxide because the alkoxide ion and the bromine are cis to each other. Only E2 and S_N2 reactions typical of a secondary halide can occur.



1*S*,2*R*

17.10 Reactions of Epoxides

Epoxides undergo ring-opening reactions and are more reactive than acyclic and larger cyclic ethers because the three-membered ring has considerable ring strain. When epoxides undergo ring-opening reactions by cleavage of a C—O bond, the products have normal tetrahedral bond angles, so they are not strained. As a result the energy barrier for cleavage of a C—O bond of an epoxide is smaller than for other ethers, and the rate of cleavage of epoxides is more rapid.

Ring Opening by Nucleophiles

Ethers do not generally react with nucleophiles to displace an alkoxide ion. However, epoxides are so strained that the C—O bond of the ring is cleaved even by nucleophiles such as OH^-, SH^-, or NH_3 or the related organic species RO^-, RS^-, and RNH_2. For example, hydroxide ion displaces an alkoxide of an epoxide. The alkoxide is not released, as are typical leaving groups of S_N2 reactions, because the ether is cyclic.

$$HO^- + CH_3CH_2{-}O{-}CH_2CH_3 \not\longrightarrow CH_3CH_2{-}OH + {}^-O{-}CH_2CH_3$$

$$HO^- + \underset{\diagdown O \diagup}{CH_2{-}CH_2} \longrightarrow HO{-}CH_2{-}CH_2{-}O^- \xrightarrow{H^+} HO{-}CH_2{-}CH_2{-}OH$$

A mechanistically related reaction occurs when epoxides react with Grignard reagents to produce alcohols. The carbon skeleton contains two more carbon atoms than the starting alkyl halide. The sequence of reactions is

$$R{-}MgBr + \underset{\diagdown O \diagup}{CH_2{-}CH_2} \longrightarrow R{-}CH_2{-}CH_2{-}O{-}MgBr$$

$$R{-}CH_2{-}CH_2{-}O{-}MgBr + H_2O \longrightarrow R{-}CH_2{-}CH_2{-}O{-}H + HOMgBr$$

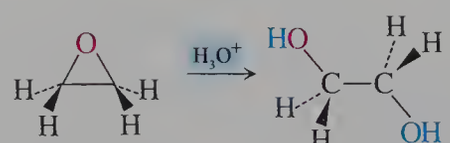
Ethylene oxide is an important material for the production of several commercial products. For example, the reaction of ethylene oxide with ammonia gives 2-aminoethanol, a compound used commercially as a corrosion inhibitor.

$$\underset{\diagdown O \diagup}{CH_2{-}CH_2} + :NH_3 \longrightarrow NH_2{-}CH_2{-}CH_2{-}OH$$

A similar reaction occurs in the sterilization of temperature-sensitive equipment by exposing the equipment to ethylene oxide gas. The epoxide ring reacts with a variety of nucleophilic functional groups in bacterial macromolecules, killing the bacteria.

Acid-Catalyzed Ring Opening

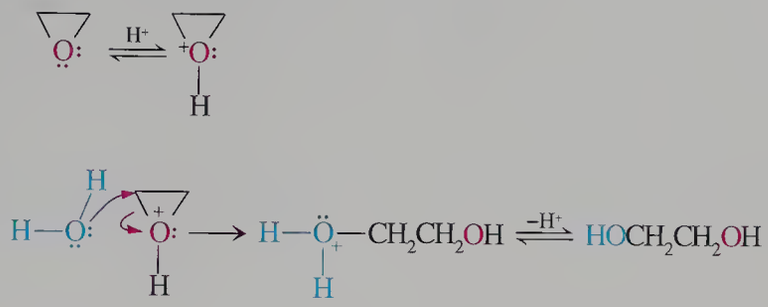
Epoxides react very readily with nucleophiles in acid-catalyzed reactions. Consider the reaction of dilute aqueous HCl with ethylene oxide to form ethylene glycol.



oxirane (ethylene oxide) → 1,2-ethanediol (ethylene glycol)

In this acid-catalyzed ring opening of epoxides, water functions as the nucleophile and the protonated oxygen atom of the epoxide as the "leaving group". In general,

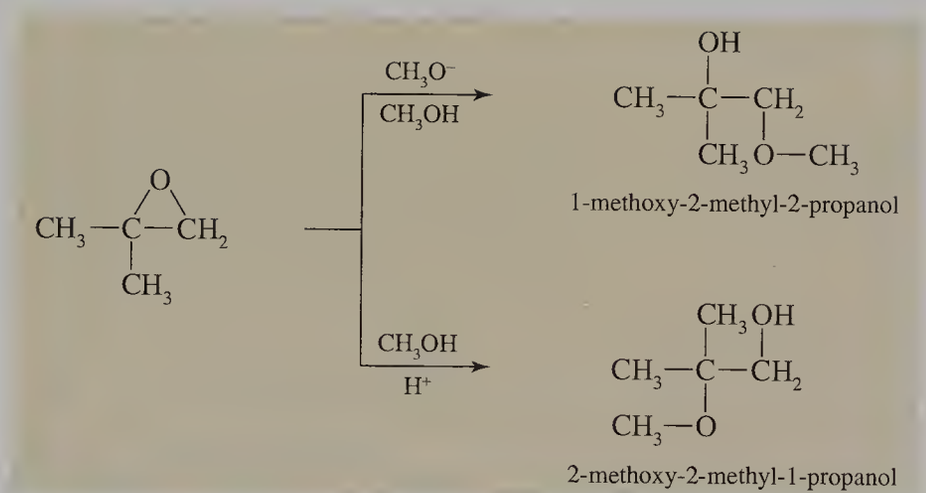
acid catalysis allows the use of a weak nucleophile in epoxide ring cleavages because a better leaving group is generated at the carbon undergoing nucleophilic attack.



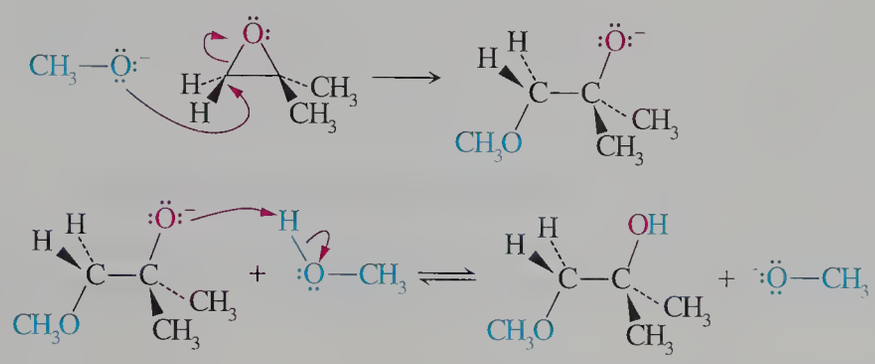
Direction of Ring Opening

Ring-opening reactions of symmetrical epoxides yield the same products under acidic and basic conditions. However, ring-opening reactions of unsymmetrical epoxides could yield two isomeric products. Under basic conditions, the reaction is regioselective and the major product results from attack of the nucleophile at the less substituted carbon atom. In the acid-catalyzed reaction, the regioselectivity is different. The major product results from attack of the nucleophile at the more substituted carbon atom. These generalizations are illustrated by comparing the reaction of 2,2-dimethyloxirane with methoxide ion to the acid-catalyzed reaction with methanol (Figure 17.6).

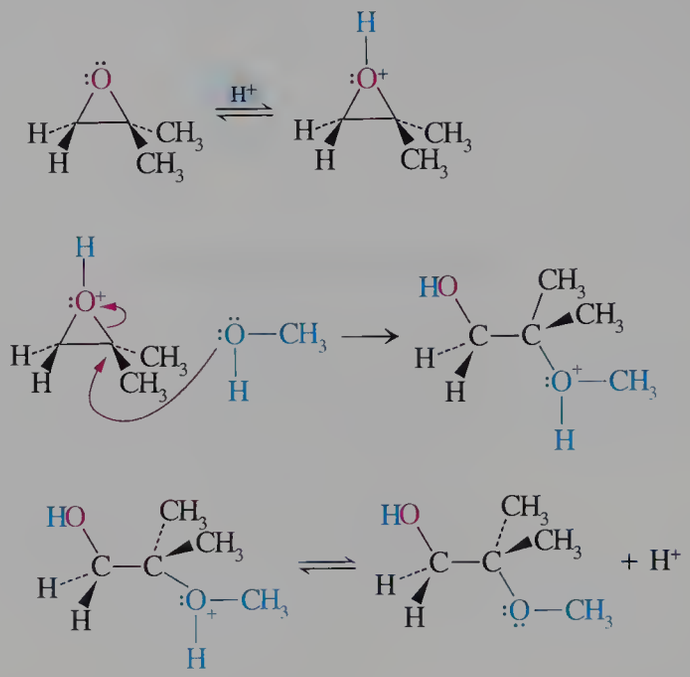
FIGURE 17.6
Regioselectivity of Epoxide Cleavage



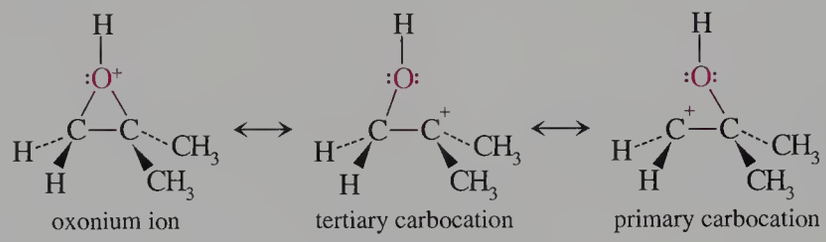
Let's consider the proposed mechanism to account for the regioselectivity of the ring opening by CH_3O^- in methanol when epoxides are cleaved under basic conditions. The reaction is controlled by the same features as the S_N2 displacement reactions we considered in Chapter 10. The nucleophilic methoxide anion regioselectively attacks the least hindered carbon atom. That is, it attacks the primary rather than the tertiary carbon atom of 2,2-dimethyloxirane in the rate-determining step. This intermediate alkoxide then abstracts a proton from the solvent in a rapid second step, regenerating the methoxide base.



Why is the regioselectivity different for the reaction of the same epoxide with methanol in acid? The first step is a rapid reversible protonation of the epoxide. The epoxide then reacts with the nucleophile methanol in the rate-determining step. Subsequently the protonated product reversibly transfers a proton to the solvent.



The mechanism for the acid-catalyzed reaction in many ways resembles the mechanism for the reaction under basic conditions. However, there is an important difference that explains why the nucleophile now attacks the more hindered carbon atom. That difference is attributed to the structure of the substrate that reacts with the nucleophile in the rate-determining step. Consider the following resonance forms of the conjugate acid of the epoxide, formed before the rate-determining step.

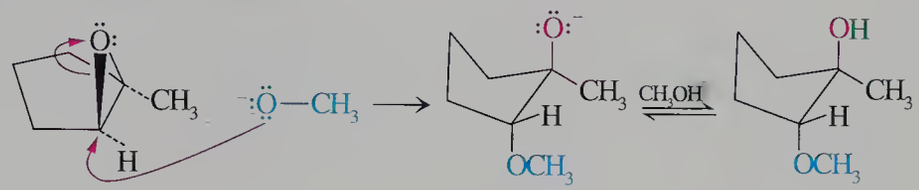


Because a positive charge is more stable on the tertiary carbon atom than on the primary carbon atom, the tertiary carbocation resonance form is a more important contributor to the resonance hybrid than the primary carbocation. This uneven charge distribution accounts for the difference in the energy barriers for the formation of the two possible isomeric products. Nucleophilic attack at the carbon atom with the greater positive charge is favored. That is, it has the lower energy barrier. This stabilization of charge is apparently sufficient to override the effect of steric hindrance, which disfavors attack at the tertiary center.

Stereochemistry of Ring Opening

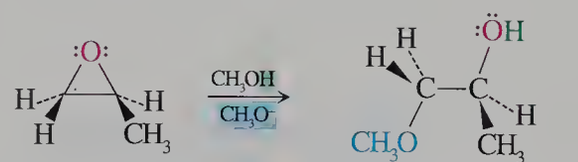
Now we turn to the question of the stereochemistry of the ring-opening reactions of epoxides. There are two centers to consider, the center at which the nucleophile

attacks and the center that retains the carbon–oxygen bond. The stereochemistry of the reaction under basic conditions or acid-catalyzed conditions can be determined by using geometric or optical isomers. For example, the ring opening of 1-methylcyclopentene epoxide with methoxide ion in methanol produces the trans isomer, indicating that the nucleophilic methoxide ion attacks from the back of the epoxide ring and the ring oxygen atom leaves from the opposite side. Thus, inversion occurs at the site of nucleophilic attack. The configuration of the other carbon atom of the epoxide is unaffected because it does not participate in the reaction. Its bond to oxygen remains intact.



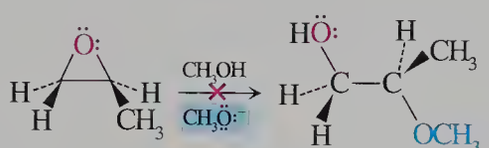
Considerably more information is provided by the reaction of optically active substrates such as (*S*)-2-methyloxirane. The reaction of this substrate could be less regioselective than the reaction of 2,2-dimethyloxirane because there is a smaller difference between the steric environments of the two possible sites for reaction. The sites are primary and secondary in 2-methyloxirane, compared to primary and tertiary in 2,2-dimethyloxirane. However, as we shall shortly see, the reaction is still stereospecific in spite of a decrease in its regioselectivity.

Let's first consider the reaction of (*S*)-2-methyloxirane with methoxide ion. Nucleophilic attack still occurs at the less substituted site and gives (*S*)-1-methoxy-2-propanol. The reaction is highly regioselective.



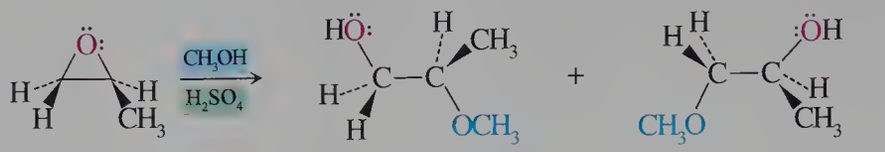
(*S*)-2-methyloxirane (*S*)-1-methoxy-2-propanol

This regioselectivity is the result of the substantial difference in the rates of S_N2 reactions of primary and secondary substrates (Section 10.3). The reaction is stereospecific and the configuration of the stereogenic center remains because the secondary carbon atom does not participate in the reaction. Its carbon–oxygen bond remains intact in the process. Note that if the regioisomer had formed, the mechanism predicts that the product would be (*R*)-2-methoxy-1-propanol, the result of the typical inversion of configuration of an S_N2 reaction.



The reaction of (*S*)-2-methyloxirane with methanol in the acid-catalyzed reaction is somewhat less regioselective. However, both products result from stereo-

specific reactions. The major product is (*R*)-2-methoxy-1-propanol. The minor product, 1-methoxy-2-propanol, has the *S* configuration.



(*R*)-2-methoxy-1-propanol (major product)

(*S*)-1-methoxy-2-propanol (minor product)

The decreased regioselectivity of the reaction of (*S*)-2-methyloxirane compared to 2,2-dimethyloxirane results from the opposing effects of charge stabilization and steric hindrance. There is a smaller difference in the charge stabilization of a secondary and a primary carbocation compared to the difference between a tertiary and primary carbocation. As a result, the role of steric hindrance becomes more important in (*S*)-2-methyloxirane, and some product results from attack at the primary center.

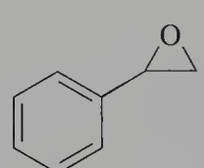
As established in the reaction of methoxide ion at the primary center, the reaction of methanol at the primary center occurs to give a product with retention of configuration at the secondary center. The C—O bond at C-2 is unaffected in the reaction. More important, this acid-catalyzed reaction provides information about the stereochemistry of the nucleophile's site of attack. Inversion of configuration occurs, as is usually observed for S_N2 reactions.

Problem 17.21

Predict the product of each of the following reactions.
(a) sodium cyanide and ethylene oxide
(b) (*R*)-2-methyloxirane and the ethyl Grignard reagent
(c) propynyl sodium in liquid NH_3 and 2,2-dimethyloxirane

Problem 17.22

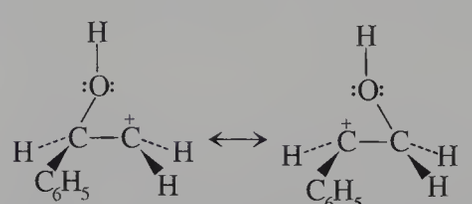
Predict the product of the reaction of styrene oxide in an acid-catalyzed reaction with methanol.



styrene oxide

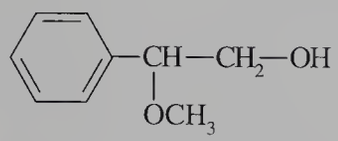
Sample Solution

Consider the following resonance forms for the protonated styrene oxide that forms in acid solution.



primary carbocation benzylic carbocation

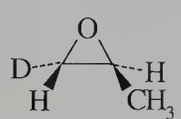
The benzyl carbocation form contributes more to the structure than does the primary carbocation form. The attack of the nucleophilic methanol should occur at the benzylic center to give 2-methoxy-2-phenyl-1-ethanol.



2-methoxy-2-phenylethanol

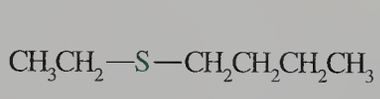
Problem 17.23

Assign the configuration of both stereogenic centers of the following epoxide. Draw two possible products that could form in the reaction of the epoxide with methanol in an acid-catalyzed reaction. Assign the configuration at any stereogenic centers in both products.

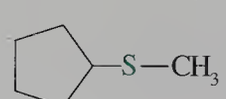


17.11 Sulfides

The sulfur analogs of ethers are sulfides, R—S—R′. The common names are derived in the same way as ethers. That is, they are called alkyl alkyl sulfides. Sulfides are named according to IUPAC nomenclature as *alkylthioalkanes*, where the smaller alkyl group and the sulfur atom constitute an **alkylthio group**. An alkylthio group is treated as a substituent on the larger parent alkane chain. For example, a five-carbon chain (pentane) with an $-SCH_3$ group at the C-2 atom is named 2-(methylthio)pentane.



1-(ethylthio)butane
(butyl ethyl sulfide)

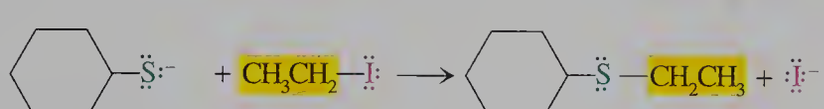


methylthiocyclopentane
(cyclopentyl methyl sulfide)

The cyclic sulfide analogs of ethers are named using *thi* in place of *ox*. Thus, the three-, four-, five-, and six-membered sulfides are thiirane, thietane, thiolane, and thiane, respectively.

Synthesis of Sulfides

Sulfides may be prepared by a method analogous to the Williamson ether synthesis. The nucleophile is a thiolate anion rather than an alkoxide. Thiolate ions, RS^-, are better nucleophiles than alkoxides because sulfur is more polarizable than oxygen. Thus, thiolate ions displace halide ions from alkyl halides by an S_N2 reaction to give good yields of sulfides.

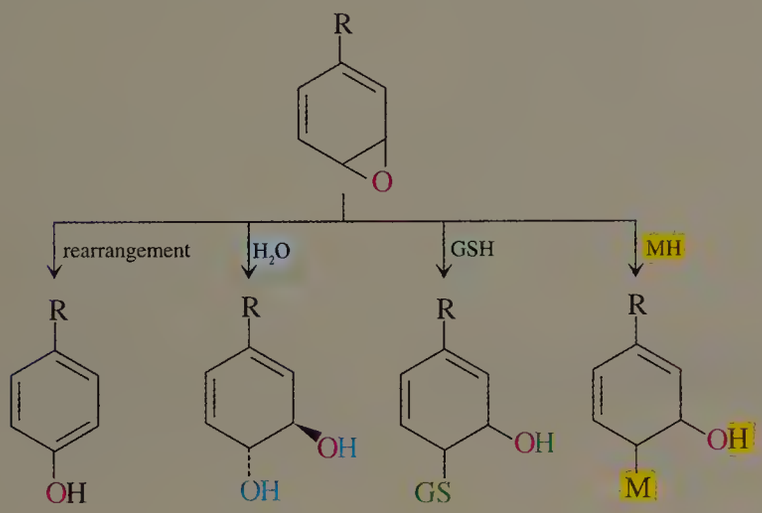


cyclohexylthiolate

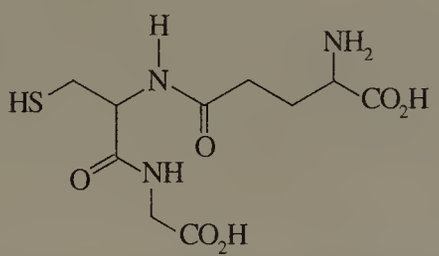
cyclohexyl ethyl sulfide

Biological Epoxides

In earlier chapters we saw that epoxides are produced biologically as oxidation products of alkenes and aromatic compounds. These epoxides are formed in the liver by cytochrome P-450, and they undergo ring-opening reactions with different substances. If the epoxide reacts with a biological macromolecule, the result is potentially devastating. When epoxides are made from aromatic compounds, the products are called arene oxides. These molecules can undergo four kinds of reactions, as shown.

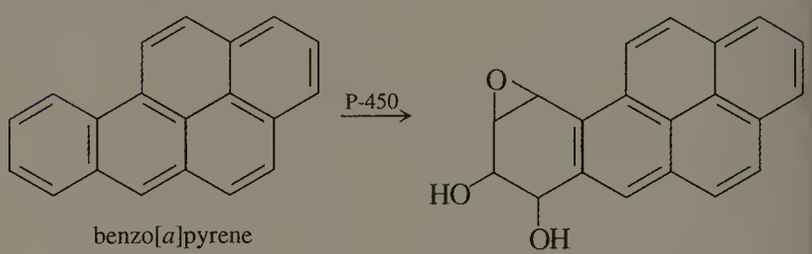


The rearrangement of an arene oxide gives a water-soluble phenol that is easily eliminated from the body. Hence, this pathway does not lead to the accumulation of toxic by-products. Ring opening of the arene oxide by water gives a trans diol by an S_N2 process. The diol is water soluble and is also easily eliminated from the body. We saw in Section 10.1 that glutathione contains a nucleophilic sulfhydryl group that reacts with toxic metabolites. Glutathione (GSH) reacts with arene oxides in a ring-opening reaction. Because the product contains many polar functional groups, it is water soluble and can be excreted.



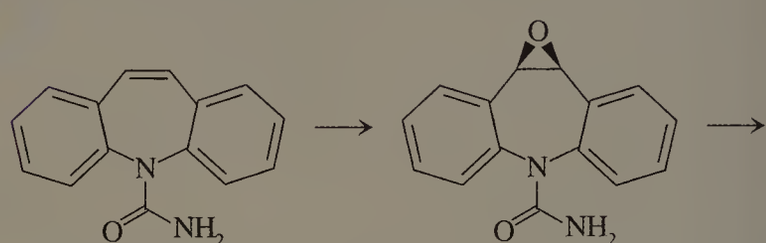
glutathione

Arene oxides react with nucleophilic functional groups present in most macromolecules (represented by MH in the equation) including enzymes, RNA, and DNA. These reactions can cause significant alterations in biological functions. A particularly dangerous arene oxide is the epoxide of benzo[*a*]pyrene, which reacts with amino groups in DNA. Benzo[*a*]pyrene is a combustion product found in tobacco smoke.

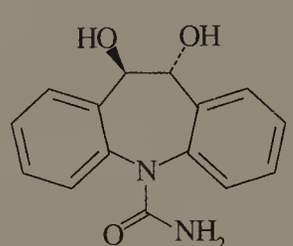


benzo[*a*]pyrene

The epoxide metabolites of alkenes tend to be more stable than arene oxides. They undergo ring opening with water to give diols. One example of this type of reaction is the ring opening of the epoxide of the anticonvulsant drug carbamazepine.



carbamazepine

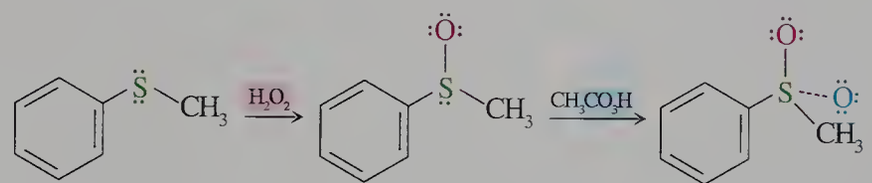


It is not easy to predict whether an epoxide will react with water or glutathione and be nontoxic or whether it will react harmfully with macromolecules. However, it appears that relatively stable epoxides tend to undergo ring opening by water or glutathione. Unfortunately, epoxides that have sterically hindered oxirane rings, benzo[*a*]pyrene, for example, tend to react with nucleophilic groups of macromolecules.

There are two important differences between reactions to form ethers and those that form sulfides. First, because thiolates are better nucleophiles and weaker bases than alkoxides, elimination reactions do not compete much with substitution reactions. Even secondary alkyl halides can be used to form sulfides. Second, because thiols are more acidic ($pK_a = 8$) than alcohols ($pK_a = 16$), they are quantitatively converted to thiolates by sodium hydroxide. Therefore, it is not necessary to prepare the thiolate in a separate reaction with a strong base, as is required in the reaction of alcohols with sodium hydride. Sulfides are usually prepared by adding the alkyl halide to a basic alcoholic solution of the thiol.

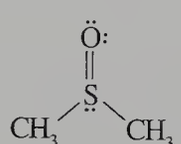
Oxidation of Sulfides

Sulfides are easily oxidized by hydrogen peroxide at room temperature to form **sulfoxides**. Continued oxidation to form **sulfones** occurs with excess reagent, but usually requires peroxy acids such as peroxyacetic acid. Sodium periodate ($NaIO_4$) oxidizes sulfides to sulfoxides, but not to sulfones.



(a sulfoxide) (a sulfone)

Dimethyl sulfoxide (DMSO) has a high dielectric constant and is an excellent aprotic solvent for nucleophilic substitution reactions. DMSO readily penetrates the skin, and any compound dissolved in DMSO is carried with it across the skin. Hence, great caution is required when this compound is used as a solvent.



dimethyl sulfoxide

Problem 17.24

Write the product of the base-catalyzed reaction of CH_3CH_2SH and ethyloxirane. Explain why only a catalytic amount of base is required.

17.12 Spectroscopy of Compounds with C—O and C—S Bonds

Infrared Spectroscopy

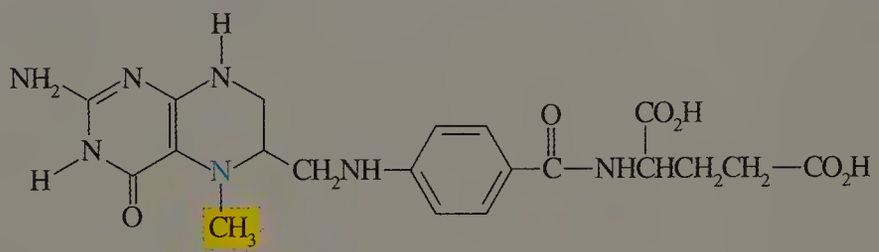
The O—H stretching vibration of an alcohol occurs at 3600 cm^{-1} if the sample is observed at low pressures in the gas phase. However, in the liquid phase or even a relatively dilute solution, there is extensive hydrogen bonding and the absorption occurs in the 3200–3400 cm^{-1} region. The band is very broad because of the variety of hydrogen-bonded species present, but it is characteristic and is a positive identification of an O—H bond.

The S—H stretching vibration of a thiol occurs in the 2550–2600 cm^{-1} region. This lower wavenumber position compared to the O—H stretching vibration is the result of the weaker S—H bond. The absorption of the S—H bond is much less in-

Methyl Transfer Reactions in Biochemical Reactions

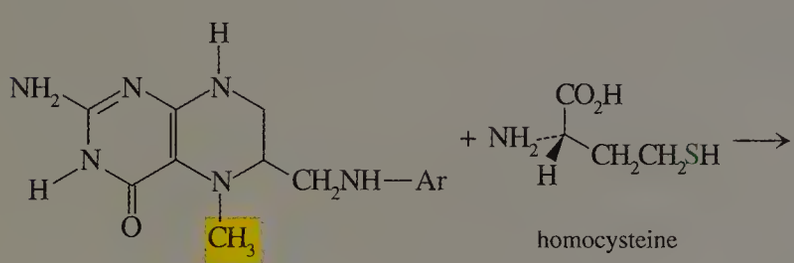
The methylation of numerous nucleophilic sites in biological molecules occurs via sulfur-containing molecules. Although these molecules may look formidable, we simply have to keep our eye on the important site of the functional group and apply the chemical principles that we have learned in order to understand the biochemistry.

The methyl group bonded to the nitrogen atom of 5-methyltetrahydrofolic acid can be transferred to an other molecule by an S_N2 reaction in which the remaining major portion of the molecule is the leaving group.

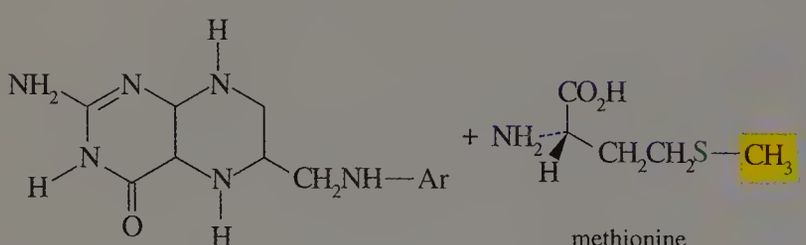


However, based on our study of the leaving group characteristics of oxygen-containing molecules, we suspect that negatively charged nitrogen species represented as R_2N^- should not be a good leaving group. However, protonation of oxygen allows the oxygen atom to leave as a neutral alcohol (or water) molecule rather than an alkoxide ion (or hydroxide ion). Similarly, the protonation of the nitrogen atom bearing the methyl group in 5-methyltetrahydrofolic acid allows the leaving group to depart as R_2NH.

Transfer of a methyl group by 5-methyltetrahydrofolic acid to the sulfur atom of homocysteine gives methionine, an important amino acid. The nucleophilic sulfur atom, which is present as a sulfhydryl group, is converted into a sulfide. Only a partial structure for 5-methyltetrahydrofolic acid is shown in the following equation. The symbol Ar represents the aromatic ring and its substituents to the right of the structure.

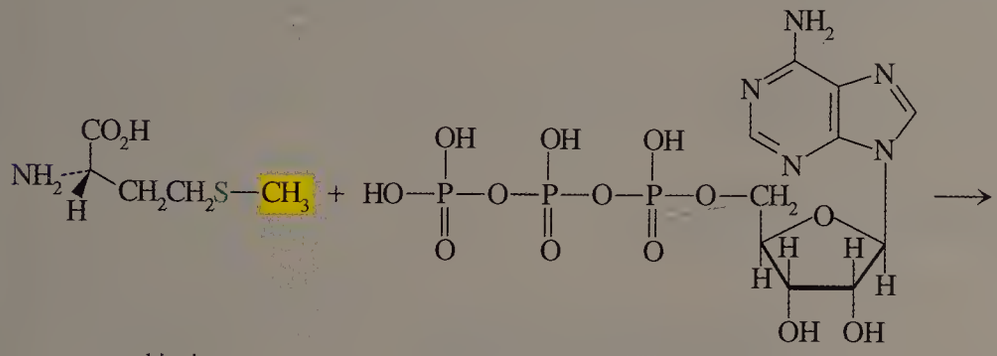


homocysteine

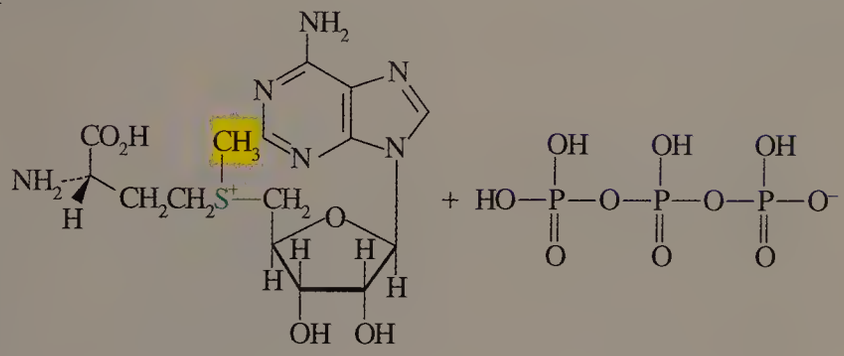


methionine

Methionine can also transfer a methyl group. Reaction of methionine with ATP gives *S*-adenosylmethionine. The nucleophilic sulfur atom of the sulfide is converted into a sulfonium ion by the displacement of triphosphate, an excellent leaving group.

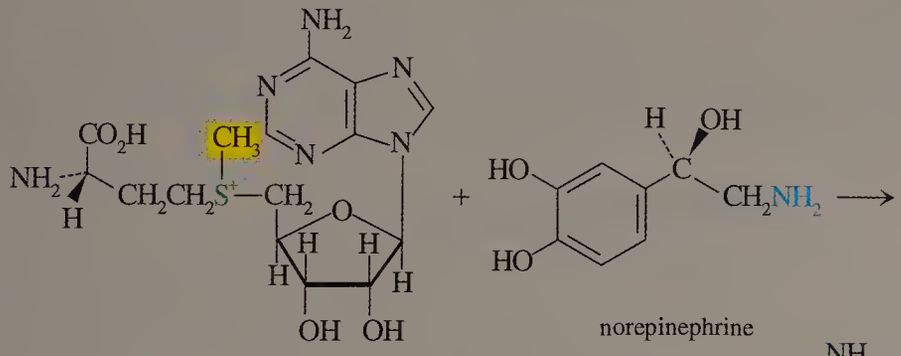


methionine ATP

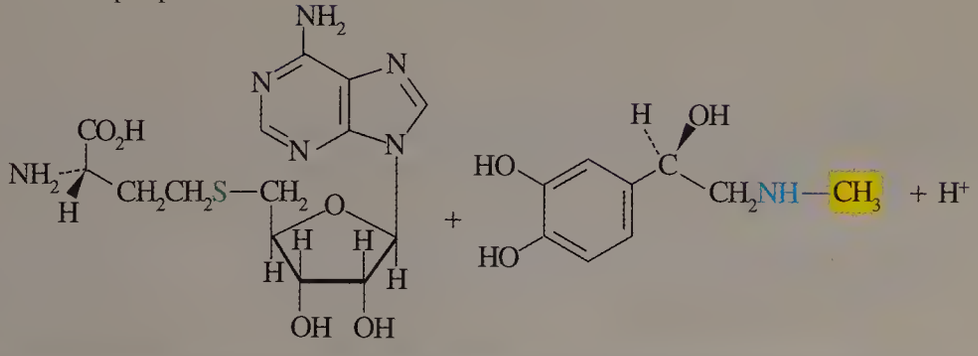


S-adenosylmethionine triphosphate

The chemistry of the sulfonium ion was presented in Section 8.11. *S*-Adenosylmethionine (SAM) can transfer a methyl group to nucleophilic centers such as in norepinephrine to give epinephrine.



norepinephrine



epinephrine

tense than that of the O—H bond because the S—H bond is less polar. In addition, the S—H absorption is not broad because S—H does not form hydrogen bonds.

The intense C—O stretching vibration of alcohols occurs in the 1050–1200 cm^{-1} region. However, because so many other absorptions occur in this region, a strong peak in this region does not necessarily imply that the unknown compound contains a C—O bond. On the other hand, the absence of a strong absorption in the region indicates the absence of a C—O bond. The stretching vibration of the weaker C—S bond appears in the 590–700 cm^{-1} region. This absorption is very weak because the C—S bond is essentially nonpolar. As a consequence, the identification of a thiol by the C—S bond is quite tenuous. For the reasons just stated for alcohols and thiols, it is not possible to identify either an ether by the C—O stretching vibration or a thioether by the C—S vibration.

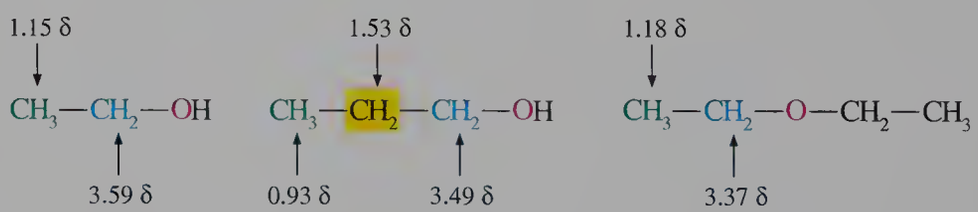
Hydrogen NMR Spectroscopy

The chemical shift of the hydrogen atom of the hydroxyl group varies depending on its concentration and the solvent used to obtain the spectrum. In pure ethanol the O—H resonance occurs at 5.3 δ. In a dilute solution of ethanol in CCl_4, in which there is decreased hydrogen bonding, the resonance occurs in the 2–3 δ region. Regardless of the concentration, the resonance is usually unsplit because the hydrogen atoms exchange too rapidly to be observed as discrete atoms coupled to specific atoms.

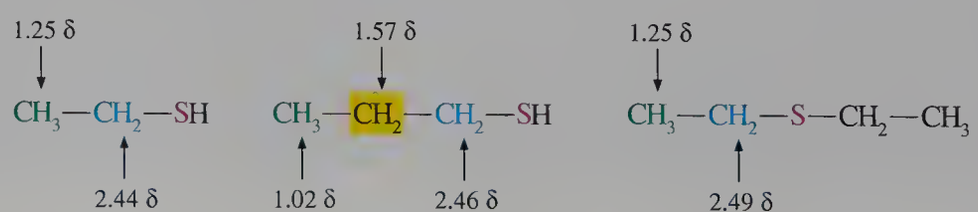
The O—H resonance can be confirmed by an exchange reaction using D_2O. A drop of D_2O is added to the sample of the alcohol in a solvent such as CCl_4, and the mixture is shaken. The O—H group of the alcohol is converted to an O—D group. The other product, HOD, floats to the top of the solvent. A subsequent NMR spectrum obtained from the CCl_4 solution no longer has the resonance of the O—H group of the alcohol, but the remainder of the spectrum is unchanged.

The chemical shift of the hydrogen atom of the S—H group varies slightly with concentration and the solvent used to obtain the spectrum. However, the effect is less pronounced than that of the O—H group. The range is 1–2 δ. The S—H resonance can be confirmed by an exchange reaction using D_2O. After adding a drop of D_2O the S—H group of the thiol is converted to an S—D group, which is not observed in the hydrogen NMR spectrum. The remainder of the spectrum is unchanged.

Hydrogen atoms on the α-carbon atoms of primary and secondary alcohols as well as the related ethers have chemical shifts in the 3.0–4.1 δ region. The deshielding effect of the electronegative oxygen atom falls off with distance, as shown by the following examples.

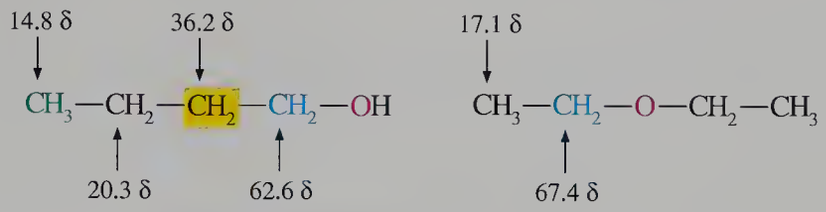


Hydrogen atoms on the α-carbon atoms of primary and secondary thiols as well as the related thioethers have chemical shifts in the 2.5 δ region. The deshielding effect of the sulfur atom falls off with distance, as shown by the following examples.

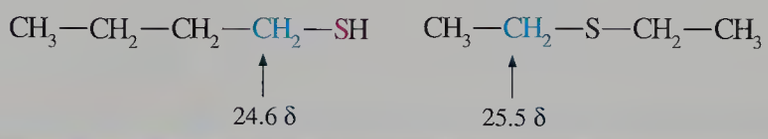


Carbon NMR Spectroscopy

The α carbon atoms of alcohols and ethers are deshielded by the oxygen atom. The effect on the chemical shift of β carbons is small, as shown by the following examples.

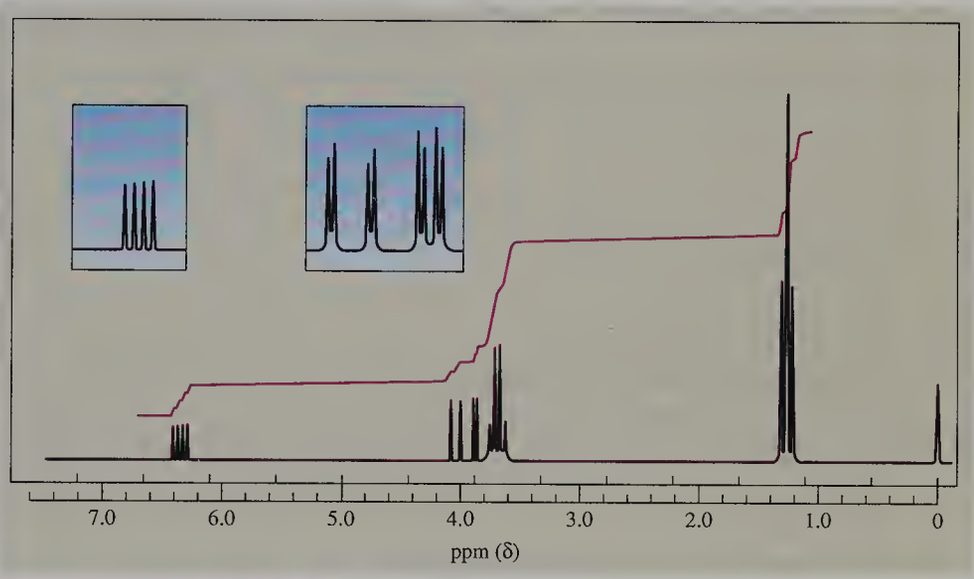


The α carbon atoms of thiols and thioethers are only slightly deshielded by the sulfur atom.



Problem 17.25

Deduce the structure of a compound with molecular formula C_4H_8O having the following hydrogen NMR spectrum.



Problem 17.26

Deduce the structure of isomeric compounds having the molecular formula $C_4H_{10}O$ based on the following carbon NMR spectra. The multiplicities are given in parentheses.

(a) 10.0 ppm (quartet), 27.7 ppm (quartet), 37.0 ppm (triplet), 69.2 ppm (doublet)
(b) 18.9 ppm (quartet), 30.8 ppm (doublet), 69.4 ppm (triplet)
(c) 31.7 ppm (quartet), 68.9 ppm (singlet)

EXERCISES

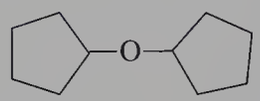
Ether Isomers

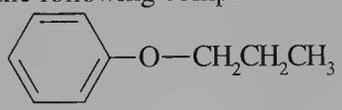
17.1 Draw the structures of the isomeric ethers with the following characteristics.
(a) molecular formula $C_4H_{10}O$
(b) methyl ethers with molecular formula $C_5H_{12}O$
(c) saturated ethers with the molecular formula C_3H_6O

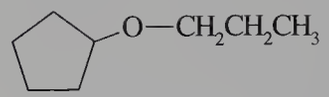
17.2 Draw the structures of the isomeric ethers with the following characteristics.
(**a**) cyclic ethers with molecular formula $C_5H_{10}O$
(**b**) unsaturated ethers with the molecular formula C_4H_8O
(**c**) dimethyl-substituted oxetanes

Nomenclature of Ethers

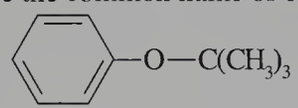
17.3 Give the common name of each of the following compounds.

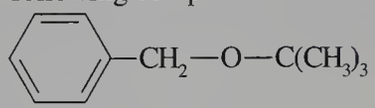
(**a**) 

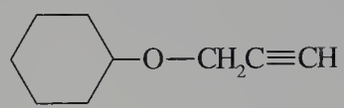
(**b**) 

(**c**) 

17.4 Give the common name of each of the following compounds.

(**a**) 

(**b**) 

(**c**) 

17.5 Assign the IUPAC name of each of the following compounds.

(**a**) $CH_3CH_2CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_3$ (**b**) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_3$ (**c**) $CH_3CH_2CH_2\underset{\displaystyle OCH_2CH_3}{\underset{|}{C}}HCH_2CH_3$

17.6 Assign the IUPAC name of each of the following compounds.

(**a**) $CH_3CH_2CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2OCH_3$ (**b**) $CH_3\underset{\displaystyle CH_3O}{\underset{|}{C}}HCH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_3$ (**c**) $CH_3CH_2\underset{\displaystyle CH_3CH_2O}{\underset{|}{C}}HCH_2\underset{\displaystyle OCH_2CH_3}{\underset{|}{C}}HCH_3$

17.7 Draw the structure of each of the following general anesthetics.
(**a**) 1,1,1,3,3,3-hexafluoroisopropyl methyl ether (isoindoklon)
(**b**) 2-chloro-1,1,2-trifluoro-1-(difluoromethoxy)ethane (enflurane)

17.8 What is the common name of each of the following anesthetics?
(**a**) $CH_2{=}CH{-}O{-}CH{=}CH_2$
(**b**) $CF_3CHCl{-}O{-}CHF_2$

17.9 Draw the structure of each of the following compounds.
(**a**) *trans*-4-methoxycyclohexanol
(**b**) 3-ethoxy-1,1-dimethylcyclohexane
(**c**) *cis*-2,3-dimethyloxetane
(**d**) 12-crown-4

17.10 Draw the structure of each of the following compounds.
(**a**) 3-methoxyoxolane
(**b**) *trans*-2-chloro-1-methoxycyclobutane
(**c**) *cis*-2-ethoxy-3-methyloxirane
(**d**) 15-crown-5

Properties of Ethers

17.11 1,4-Dioxane is miscible in water. Why?

17.12 *p*-Ethylphenol is more soluble in water than the isomeric ethoxybenzene. Explain why.

17.13 The boiling points of dipropyl ether and diisopropyl ether are 91 and 68 °C, respectively. Explain why the boiling points of these isomeric ethers differ.

17.14 The boiling points of 1-ethoxypropane and 1,2-dimethoxyethane are 64 and 83 °C, respectively. Explain why.

17.15 Explain why dipropyl ether is soluble in concentrated sulfuric acid whereas heptane is insoluble.

17.16 Aluminum trichloride dissolves in tetrahydropyran, releasing heat. Explain why.

17.17 Some potassium compounds dissolve in 18-crown-6, but the related rubidium compounds do not. Why?

17.18 Some sodium compounds dissolve in 15-crown-5. Would the related lithium compounds be more or less likely to be soluble in 18-crown-6 or 12-crown-4?

17.19 Draw the stable conformation of 1,4-dioxane.

17.20 The most stable chair conformation of 1,3-dioxan-5-ol has an axial hydroxyl group, but the most stable chair conformation of 5-methoxy-1,3-dioxane has an equatorial methoxy group. Explain why.

Synthesis of Ethers

17.21 Write a mechanism for the formation of 1,4-dioxane from ethylene glycol catalyzed by sulfuric acid.

17.22 Write a mechanism for the formation of 2,2-dimethyloxolane from 4-methyl-1,4-pentanediol and sulfuric acid. Which of the two oxygen atoms remains in the ether?

17.23 Reaction of 1-hexene with mercuric acetate in methanol as solvent followed by reduction of the intermediate product with sodium borohydride yields 2-methoxyhexane. What is the structure of the intermediate product? How is it formed?

17.24 Reaction of 4-penten-1-ol with mercuric acetate followed by reduction with sodium borohydride yields 2-methyloxolane. Write the structure of the intermediate and explain the formation of this ether.

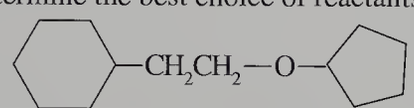
17.25 Reaction of 5-chloro-2-pentanol with sodium hydride yields 2-methyloxolane. Write the structure of the intermediate and explain the formation of this ether.

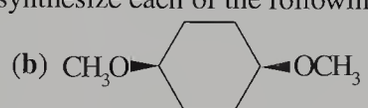
17.26 Treatment of 3,4-dibromo-1-butanol with sodium hydroxide yields a cyclic ether. What is the structure of the ether? What alternate ether could form and why doesn't it?

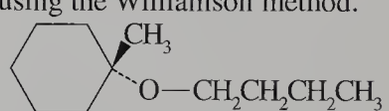
17.27 Which of the following compounds can be synthesized in good yield using the Williamson method? Explain why the method would fail for the remaining compounds.

(a) ethyl cyclopentyl ether **(b)** 1-methyl-1-methoxycyclohexane **(c)** *tert*-butyl cyclohexyl ether
(d) di-*sec*-butyl ether **(e)** 2-methyl-3-phenoxyhexane

17.28 Determine the best choice of reactants to synthesize each of the following ethers using the Williamson method.

(a) 

(b) 

(c) 

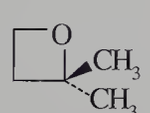
17.29 2-Octanol with $[\alpha] = -9.9$ reacts with sodium hydride followed by treatment with iodoethane to give 2-ethoxyoctane with $[\alpha] = -17.5$. Based on the mechanism of this reaction, assign the configuration of the product relative to the reactant.

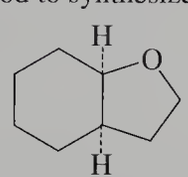
17.30 2-Octanol with $[\alpha] = -9.9$ reacts with toluenesulfonyl chloride to give a tosylate with $[\alpha] = -6.8$. Subsequent reaction of the tosylate in ethanol gives 2-ethoxyoctane with $[\alpha] = +17.5$. Based on the mechanism of these reactions, assign the configuration of the tosylate and the ether relative to the reactant. Why does the sign of rotation of the ether formed in this reaction differ from the sign of rotation of the product of Exercise 17.29?

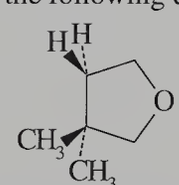
17.31 The following compound reacts with sodium hydroxide to produce 1,4-dioxane. Write the sequence of reactions leading to this product.

$$Cl—CH_2CH_2—O—CH_2CH_2—Cl$$

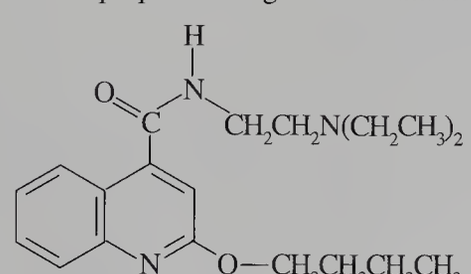
17.32 Determine the best method to synthesize each of the following ethers using the Williamson method.

(a) 

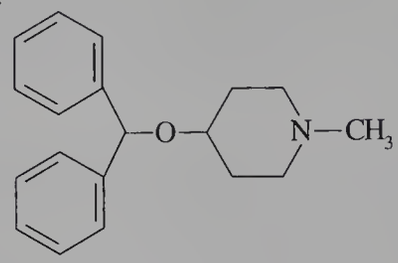
(b) 

(c) 

17.33 How could the local anesthetic dibucaine be prepared using the Williamson synthesis?

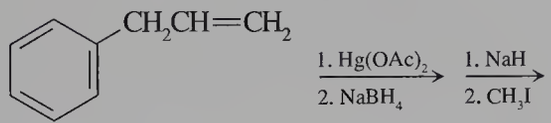


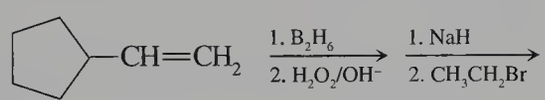
17.34 What reactants might be used to produce the antihistamine diphenylpyraline using the Williamson synthesis. What difficulties might be encountered?

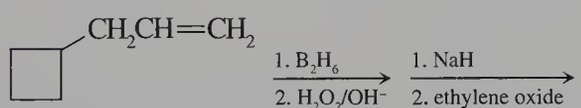


Synthetic Sequences

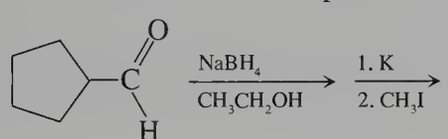
17.35 Draw the structure of the final product of each of the following sequences of reactions.

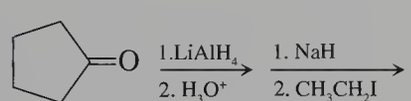
(a) 

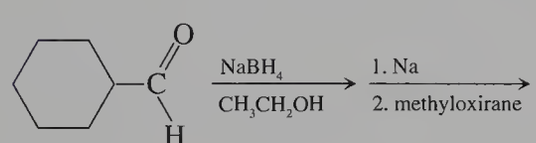
(b) 

(c) 

17.36 Draw the structure of the final product of each of the following sequences of reactions.

(a) 

(b) 

(c) 

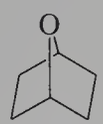
Reactions of Ethers

17.37 Write the structure of a compound with the given molecular formula that reacts with HI to yield the indicated iodo compound(s).

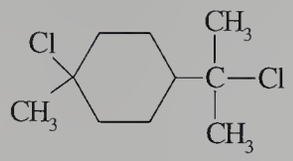
(a) $C_5H_{12}O_2$ yields a mixture of iodomethane, iodoethane, and 1,2-diiodoethane
(b) $C_5H_{12}O_2$ yields a mixture of iodomethane and 1,3-diiodopropane
(c) $C_5H_{10}O$ yields only 1,5-diiodopentane
(d) $C_4H_8O_2$ yields only 1,2-diiodoethane

17.38 Anisole can be cleaved by LiI in dimethylformamide to give iodomethane and phenoxide ion. What is the mechanism of the reaction? Explain why the reaction can occur without a source of acid.

17.39 Write the product of the reaction of the following bicyclic ether with HBr.

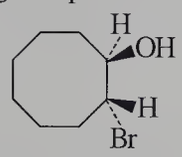


17.40 A compound with the molecular formula $C_{10}H_{18}O$ reacts with HCl to yield the following product. What is the structure of the compound?



Synthesis of Epoxides

17.41 Draw the product of the reaction of the following compound with sodium hydroxide.

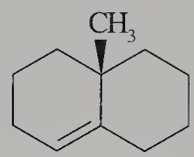


17.42 Reaction of *trans*-2-chlorocyclohexanol with sodium hydroxide yields an epoxide, but the cis isomer does not. Explain this difference.

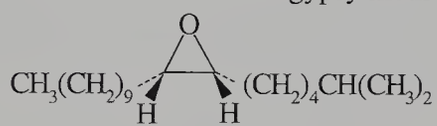
17.43 Write the structure of the bromohydrin formed by adding aqueous bromine to (*E*)-2-butene. What is the stereochemistry of the epoxide formed from this bromohydrin?

17.44 Write the structure of (2*S*,3*S*)-3-bromo-2-butanol. What is the stereochemistry of the epoxide formed from this bromohydrin?

17.45 Two products can result from the epoxidation of the following bicycloalkene with MCPBA. Draw their structures.

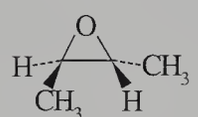


17.46 What alkene is required to synthesize the sex attractant of the gypsy moth using MCPBA?

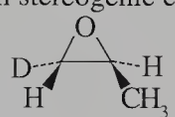


disparlure

17.47 Draw the structure of a bromo alcohol that could yield the following epoxide. Assign the configuration of each stereogenic center of this bromo alcohol.



17.48 Draw the structure of two possible bromo alcohols that could yield the following epoxide. Which one should give the higher yield? Assign the configuration of each stereogenic center of this bromo alcohol



Reactions of Epoxides

17.49 Each of the following compounds is a commercial product that is made from ethylene oxide. Using other necessary reactants, propose a synthesis of each compound.
(**a**) ethyl cellosolve, $CH_3CH_2—O—CH_2CH_2—OH$
(**b**) ethyl carbitol, $CH_3CH_2—O—CH_2CH_2—O—CH_2CH_2—OH$
(**c**) diethanolamine, $HO—CH_2CH_2—NH—CH_2CH_2—OH$

17.50 Divinyl ether is prepared by an elimination reaction of the following compound. Propose a synthesis of divinyl ether starting from ethylene oxide.

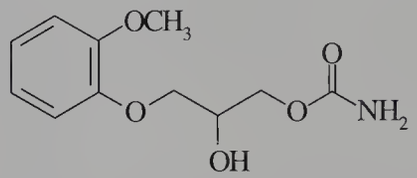
$$Cl—CH_2CH_2—O—CH_2CH_2—Cl$$

17.51 Write the product of reaction of cyclopentene oxide with aqueous base.

17.52 The reaction of methyllithium with an epoxide followed by neutralization gives an alcohol. Write the product of the reaction of cyclohexene oxide with methyllithium, showing the structure in its most stable conformation.

17.53 Write the structure of the amino alcohol formed in the reaction of (2*S*,3*R*)-2,3-dimethyloxirane with aqueous ammonia. Explain why this compound forms in preference to a diol. Assign the stereochemistry of each chiral center in the product.

17.54 Epoxide rings can be cleaved by phenoxides. Propose a synthesis of the muscle relaxant methocarbamol using this fact.



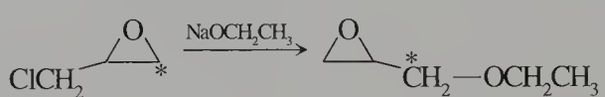
17.55 A mixture of 2,2-dimethyloxirane and ethanethiol is treated with sodium hydroxide. Write the structure of the expected product.

17.56 Epoxide rings can be cleaved by metal hydrides, which serve as a source of hydride ion. Write the product of the reaction of 1-methylcyclohexene oxide and $LiAlD_4$.

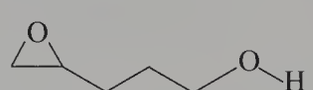
17.57 The reaction of (2*S*,3*R*)-2,3-dimethyloxirane with aqueous acid gives a mixture of enantiomers. Explain why a mixture is obtained. What are the configurations of all stereogenic centers of both isomers?

17.58 The reaction of (2*R*,3*R*)-2,3-dimethyloxirane with aqueous acid gives a single optically inactive product. Explain the origin of this product. What are the configurations of all stereogenic centers of the product?

17.59 Sodium ethoxide in ethanol reacts with 1-(chloromethyl)oxirane containing a ^{14}C label at the position shown by the asterisk. Write a two-step mechanism that explains why the label is at the indicated position in the product.

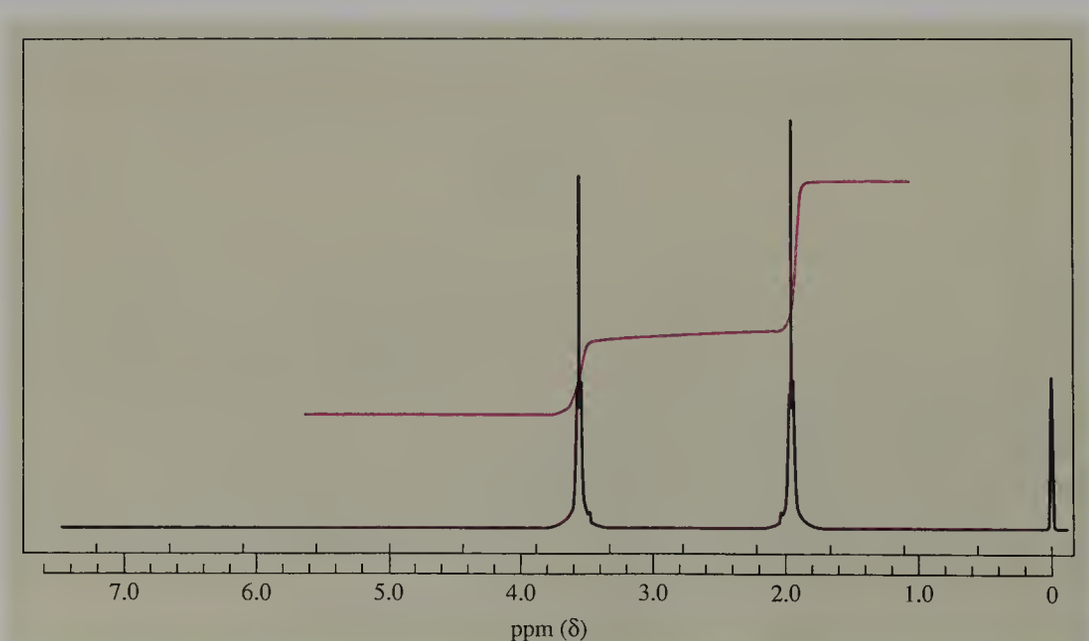


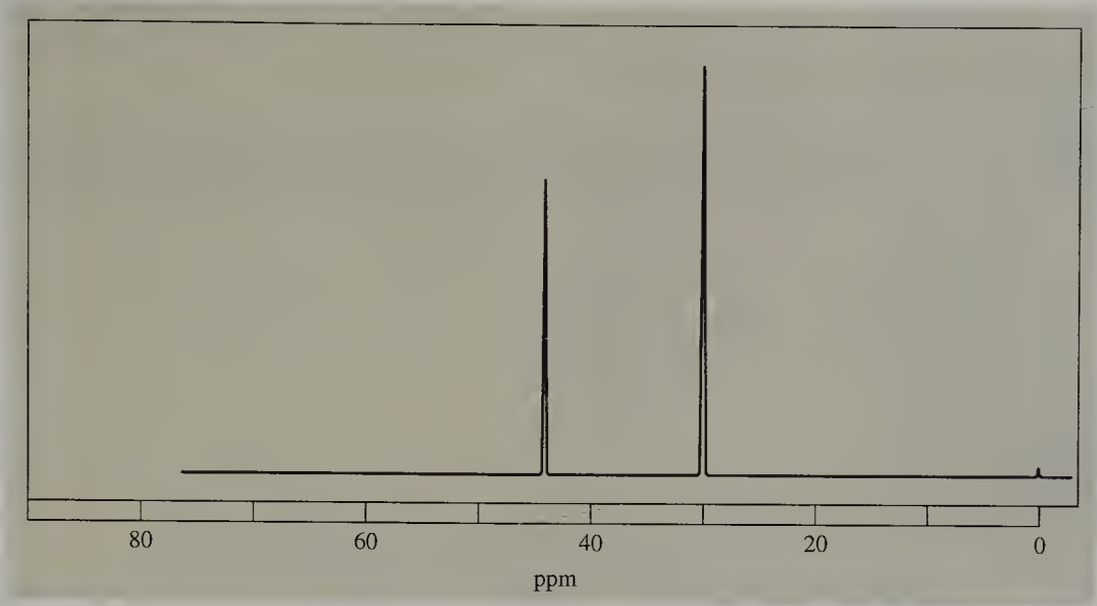
17.60 The following epoxide is isomerized by aqueous hydroxide to give a tetrahydropyran. What is the structure of the compound? Write a mechanism for its formation.



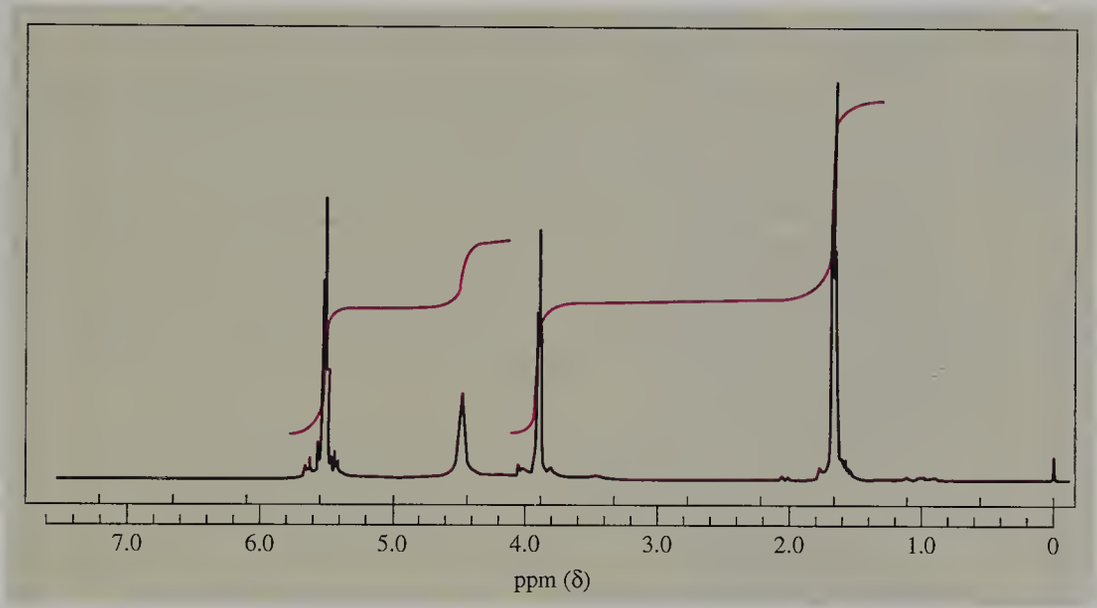
Spectroscopy of Alcohols and Ethers

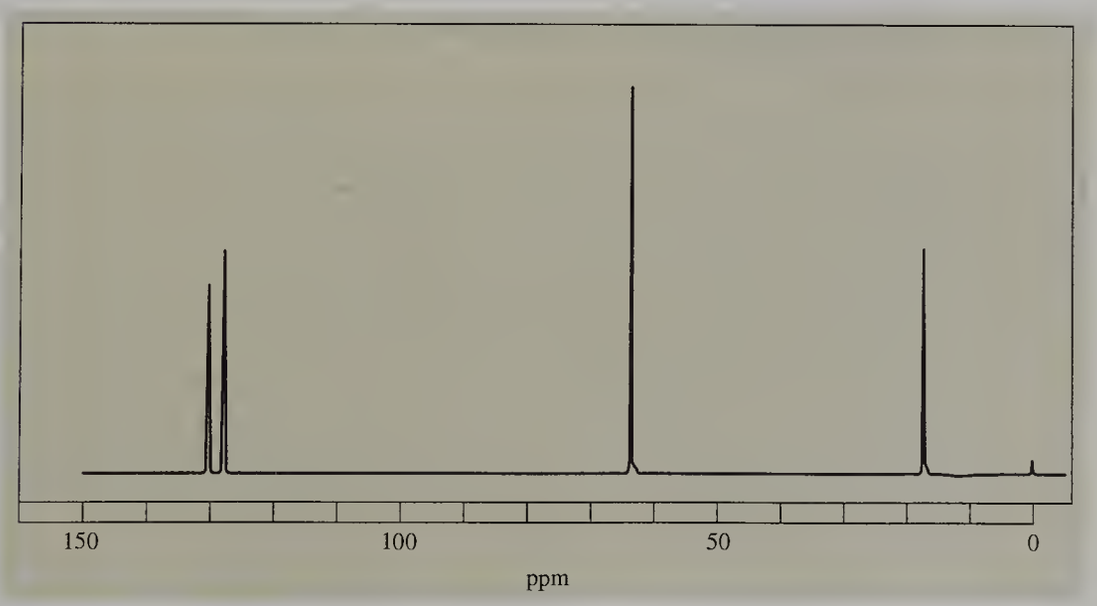
17.61 Deduce the structure of a compound with the molecular formula C_4H_8O based on the following hydrogen and carbon NMR spectra.

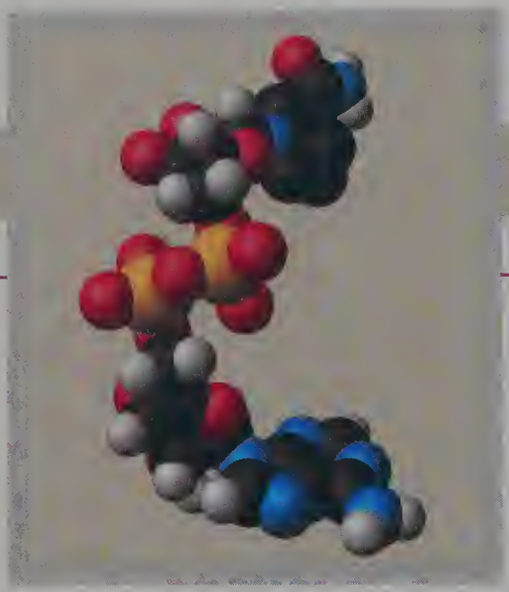




17.62 Deduce the structure of a compound with the molecular formula C_4H_8O based on the following hydrogen and carbon NMR spectra.





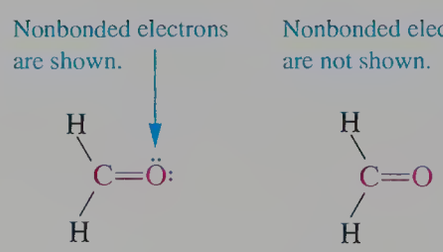


18

Aldehydes and Ketones

18.1 The Carbonyl Group

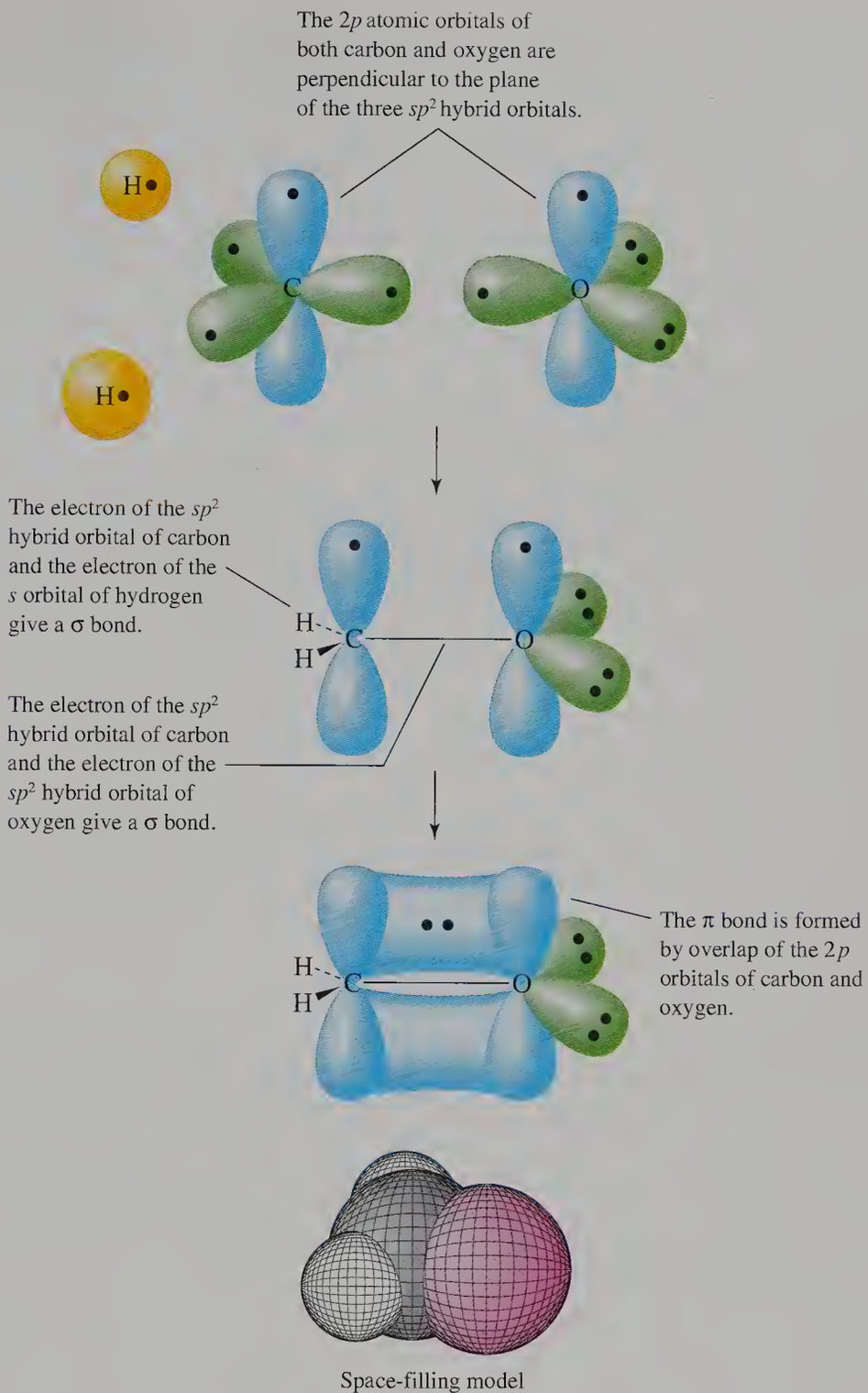
A **carbonyl group** consists of a double bond linking a **carbonyl carbon atom** and a **carbonyl oxygen atom**. The carbonyl oxygen atom shares two of its six valence electrons with the carbonyl carbon atom. Its remaining four valence electrons remain as two sets of electron lone pairs. The carbonyl carbon atom shares two of its four valence electrons with the carbonyl oxygen atom, and its remaining two electrons form two single bonds to other atoms. Formaldehyde (CH_2O) is the simplest compound with a carbonyl group. Note that the lone pairs on the oxygen atom of the carbonyl group are not always shown in drawings of molecular structures.



representations of formaldehyde

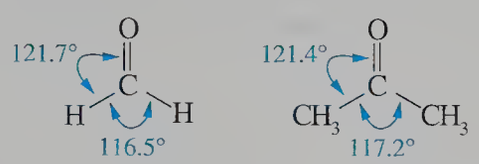
The carbonyl carbon atom, which is sp^2 hybridized, contributes one electron to each of the three hybrid orbitals, forming three σ bonds. Formaldehyde has two σ bonds to hydrogen atoms and one σ bond to the carbonyl oxygen atom. These coplanar bonds lie at approximately 120° to each other. The fourth electron of the carbonyl carbon atom occupies a $2p$ orbital perpendicular to the plane of the three sp^2 hybrid orbitals. The carbonyl oxygen atom, also sp^2 hybridized, contributes one of its six valence electrons to the sp^2 hybrid orbital that forms a σ bond with the carbonyl carbon atom. Four valence electrons remain as two sets of nonbonded electron pairs in the other two sp^2 hybrid orbitals. They lie in the same plane approximately 120° to each other and to the carbon–oxygen bond (Figure 18.1). The last valence electron occupies a $2p$ orbital perpendicular to the plane of the sp^2 hybrid orbitals. The $2p$ orbitals of the carbon and oxygen atoms overlap to form a π bond.

FIGURE 18.1 Bonding in the Carbonyl Group



Space-filling model

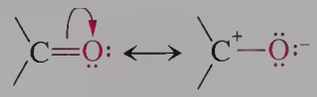
The three atoms or groups of atoms bonded to the carbonyl carbon of an aldehyde or ketone are not equivalent, but the bond angles around the carbonyl carbon atom in aldehydes and ketones come close to the idealized 120° bond angles of an sp^2-hybridized carbon atom, as shown for formaldehyde and acetone.



formaldehyde acetone

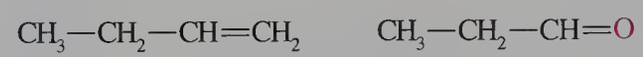
The carbon–oxygen bond length in aldehydes and ketones is approximately 122 pm, smaller than the carbon–oxygen bond length of 141 pm in alcohols. This decrease in bond length is similar to the decrease from a carbon–carbon single bond to a carbon–carbon double bond. It reflects the contribution of the π bond, which brings the bonded atoms closer together.

Because oxygen is more electronegative than carbon, the oxygen atom attracts the electrons in the carbon–oxygen double bond, making the carbonyl bond polar. The carbonyl group is also resonance stabilized, as shown by the charged contributing structure 2.



1 2

Contributing structure 1 is more important because each atom has a Lewis octet and there is no formal charge on either atom. However, the contribution of polar structure 2 significantly affects the physical properties of the carbonyl group. For example, the dipole moment of propanal is significantly larger than that of 1-butene, a compound with a similar structure.

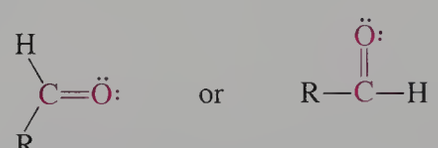


1-butene (0.3 D) propanal (2.5 D)

The polar resonance forms of carbonyl compounds also help us explain the chemical properties of aldehydes and ketones. We shall see that the carbonyl carbon atom is electrophilic and the carbonyl oxygen atom is nucleophilic.

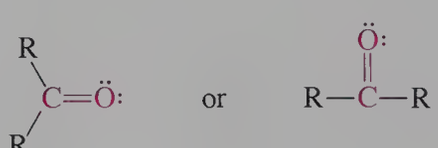
Carbonyl Compounds

When a carbonyl carbon atom is bonded to at least one hydrogen atom, the resulting compound is an **aldehyde**. The aldehyde with the simplest structure is formaldehyde, in which the carbonyl carbon atom is bonded to two hydrogen atoms. The carbonyl group is bonded to one hydrogen atom and either an alkyl group (R) or an aromatic group (Ar) in other aldehydes. Although the bond angles around the carbonyl carbon atom are approximately 120°, structures are often written with a linear arrangement of carbon atoms.



general structural formulas of aldehydes

When a carbonyl carbon atom is bonded to two other carbon atoms, the compound is a **ketone**. The bonded groups may be any combination of alkyl or aromatic groups. As with the carbonyl carbon atom, a ketone has 120° bond angles at the carbonyl carbon atom, but structures are often written with a linear arrangement of carbon atoms.

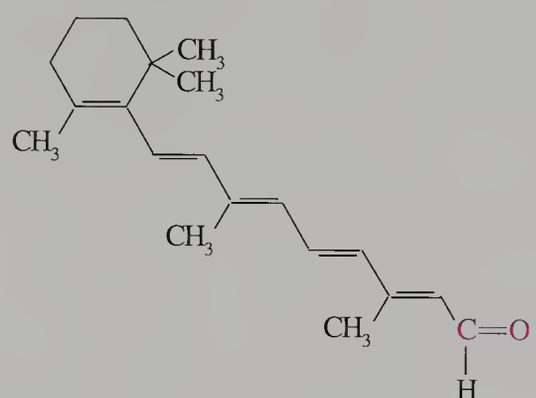


general structural formulas of ketones

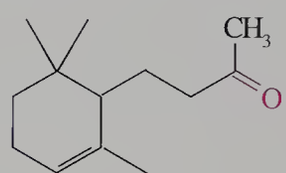
An aldehyde can be written with the condensed formula RCHO or ArCHO, where the symbol CHO indicates that both hydrogen and oxygen atoms are bonded to the carbonyl carbon atom. A ketone has the condensed formula RCOR. In this condensed formula, the symbol CO represents the carbonyl group, and the two R groups flanking the CO group are bonded to the carbonyl carbon atom.

18.2 Occurrence of Aldehydes and Ketones

The carbonyl group is the most common functional group in oxygen-containing organic compounds isolated from biological sources. One of two suffixes in common names may indicate the presence of a carbonyl group in a molecule. If the carbonyl compound is an aldehyde, we find the suffix *-al*. If the carbonyl compound is a ketone, we use the suffix *-one*. For example, retinal is an aldehyde required for vision. The first part of the name indicates that this compound is present in the retina, and the suffix tells us that it is an aldehyde. Another example of a common name is α-ionone, a fragrant ketone responsible for the scent of irises, that is used in perfumes.

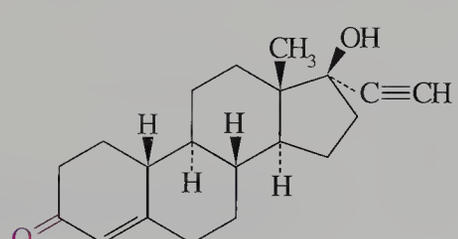


retinal

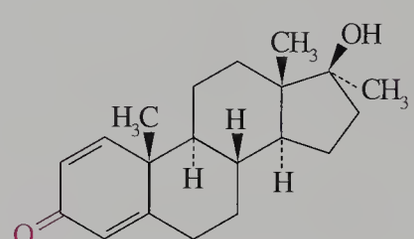


α-ionone

Carbonyl groups are present in some steroids. For example, the synthetic steroids norethindrone, an oral contraceptive, and methandrostenolone, an anabolic steroid, both contain a carbonyl group.



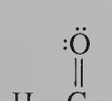
norethindrone



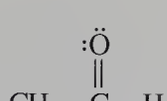
methandrostenolone

18.3 Nomenclature of Aldehydes and Ketones

Aldehydes and ketones with low molecular weights are often referred to by their common names. Chapter 21 discusses the origins of these names, along with the related common names of acids.



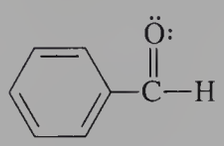
formaldehyde



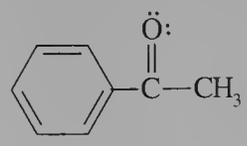
acetaldehyde

acetone

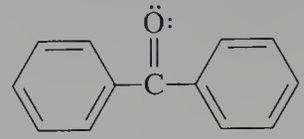
The common names of some aromatic aldehydes and ketones include the following.



benzaldehyde



acetophenone

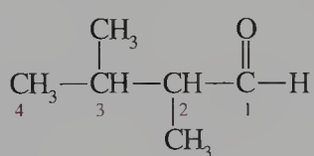


benzophenone

IUPAC Names of Aldehydes

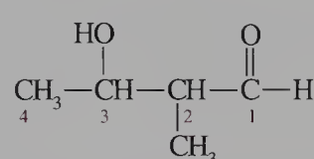
The IUPAC rules for naming aldehydes are similar to those outlined for alcohols.

1. Name the longest continuous carbon chain that contains the carbonyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon by the ending *-al*.
2. Number the parent chain to make the carbonyl carbon atom C-1. The number 1 is unnecessary in the name because the position of the carbonyl carbon atom is understood to be located at the end of the chain. Determine the name of each substituent and the number of the carbon atom to which it is attached. Add this information to the parent name as a prefix.



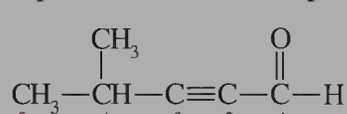
This is 2,3-dimethylbutanal, not 2,3-dimethyl-1-butanal.

3. The aldehyde functional group has a higher priority than alkyl, halogen, hydroxyl, and alkoxy groups. If any of these groups is present, indicate their names and positions as prefixes to the name of the parent aldehyde.



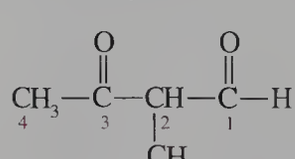
3-hydroxy-2-methylbutanal

4. The aldehyde functional group has a higher priority than double or triple bonds. When the parent chain contains a double or triple bond, replace the final *-e* of the name of the parent alkene or alkyne with the suffix *-al*. Indicate the position of the multiple bond with a prefix.



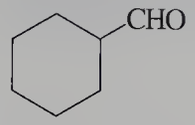
4-methyl-2-pentynal

5. If an aldehyde or ketone contains other groups with a higher priority, such as carboxylic acids, give the carbonyl group the prefix *oxo-*. Use a number to indicate the position of the oxo group. The priority order is carboxylic acid > aldehyde > ketone.

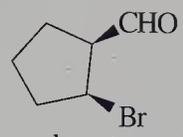


2-methyl-3-oxobutanal

6. If an aldehyde group is attached to a ring, use the suffix *-carbaldehyde*.



cyclohexanecarbaldehyde

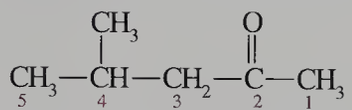


cis-2-bromocyclopentanecarbaldehyde

IUPAC Names of Ketones

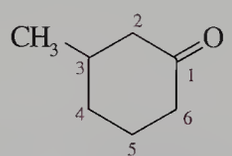
The IUPAC rules for naming ketones are similar to those used for aldehydes. However, because the carbonyl group in a ketone is not on a terminal carbon atom, we use a number to indicate its position.

1. Name the longest continuous carbon chain that contains the carbonyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon with the ending *-one*.
2. Number the carbon chain so that the carbonyl carbon atom has the lower number. Use this number as a prefix to the parent name. Indicate the identity and location of substituents as a prefix to the parent name.

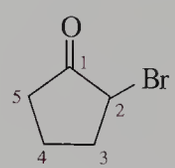


This is 4-methyl-2-pentanone, not 2-methyl-4-pentanone.

3. Name cyclic ketones as cycloalkanones. The carbonyl carbon atom receives the number 1. Number the ring in the direction that gives the lower number to the first substituent encountered.



3-methylcyclohexanone

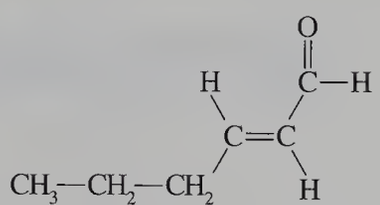


2-bromocyclopentanone

4. Halogen, hydroxyl, alkoxy groups, and multiple bonds have lower priorities than the ketone group. These substituted ketones are named using the same method described for aldehydes.

Problem 18.1

Give the IUPAC name for the following compound, an alarm pheromone in some species of ants.



Sample Solution

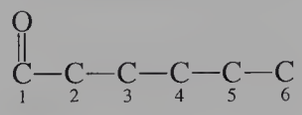
The aldehyde carbon atom on the right of the structure is assigned the number 1. The double bond is therefore located at the C-2 atom, and the name, disregarding stereochemistry, is 2-hexenal. The higher priority groups bonded to the unsaturated carbon atoms—the CHO and propyl groups—are in an *E* arrangement. The IUPAC name is (*E*)-2-hexenal.

Problem 18.2

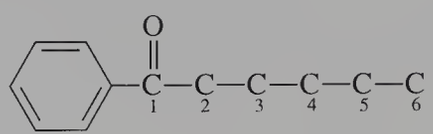
The IUPAC name for capillin, used against skin fungi, is 1-phenyl-2,4-hexadiyn-1-one. Draw its structure.

Sample Solution

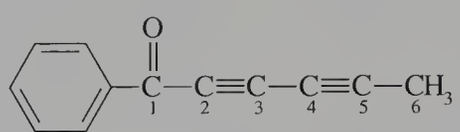
When we dissect the name, we see that it has the suffix -1-one and the stem name hexa, indicating that the parent chain is a ketone containing six carbon atoms. We write the carbon skeleton and number the chain. Place the carbonyl oxygen atom on the C-1 atom.



The name has the prefix 1-phenyl. Therefore, we add a phenyl group at the C-1 atom. Note that the presence of the phenyl group makes the compound a ketone. A carbonyl carbon atom at the end of a chain would otherwise be an aldehyde.



The diyn tells us that there are two triple bonds; they are located at the C-2 and C-4 atoms. Fill in the requisite hydrogen atoms.



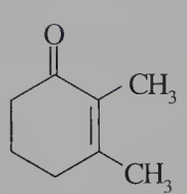
Problem 18.3

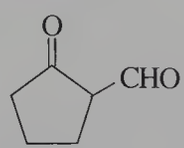
Draw the structure of each of the following compounds.

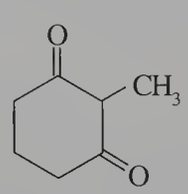
(a) 2-methylcyclohexanecarbaldehyde
(b) 1,3-diphenyl-1,3-propanedione
(c) *cis*-2,3-dibromocyclohexanone
(d) 5-methyl-4-hexenal
(e) 1-hydroxy-3-pentanone
(f) 7-fluoro-7-methyl-4-octen-2-one

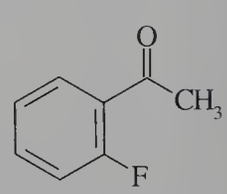
Problem 18.4

Assign the IUPAC name to each of the following structures.

(a) 

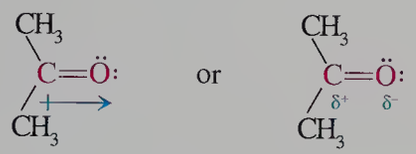
(b) 

(c) 

(d) 

18.4 Physical Properties of Aldehydes and Ketones

Because oxygen is more electronegative than carbon, it pulls the electrons in the carbonyl bond toward it, making the carbonyl group polar. (The contributing charged structure of the resonance hybrid we described earlier predicts this property.) An arrow, in which the arrowhead represents the negative end of the dipole, indicates the polarity of the carbonyl group. We also represent the positive and negative ends of the carbonyl bond by the symbols δ^+ and δ^-, where the lowercase Greek letter delta means "partial charge" (Section 1.5).



2-propanone (2.9D)
(acetone)

The dipole moment for acetone, a typical ketone, is 2.9 D. The dipole moment of 2-methylpropane is 0.1 D. The high polarity of the carbonyl group reflects the contribution of the charged structure to the resonance hybrid. The physical properties of aldehydes and ketones reflect the polarity of the carbonyl group.

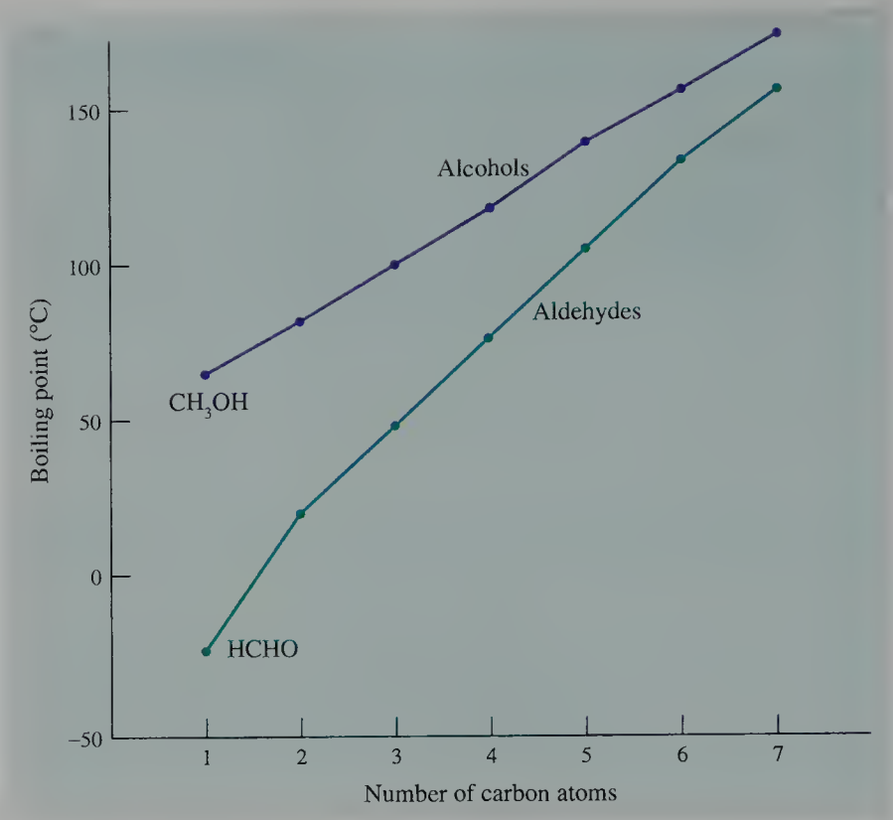
Boiling Points

Aldehydes and ketones have boiling points distinctly different from those of alkanes or alcohols of similar molecular weight (Table 18.1). Aldehydes and ketones have higher boiling points than alkanes because of dipole–dipole intermolecular forces due to the carbonyl group. Alcohols have higher boiling points than aldehydes and ketones of similar molecular weight (Figure 18.2). Thus, the dipole–dipole attractive forces of carbonyl compounds are weaker than hydrogen-bonding interactions between alcohol molecules. As the molecular weights of the carbonyl compounds increase, their dipole–dipole attractive forces become less important compared to London forces of the hydrocarbon skeleton. As a result, the physical properties of aldehydes and ketones become more like those of hydrocarbons as chain length increases. Although the boiling point differences become smaller, the order of boiling points remains alcohol > carbonyl compound > alkane.

Table 18.1
Effect of Functional Groups on Boiling Points

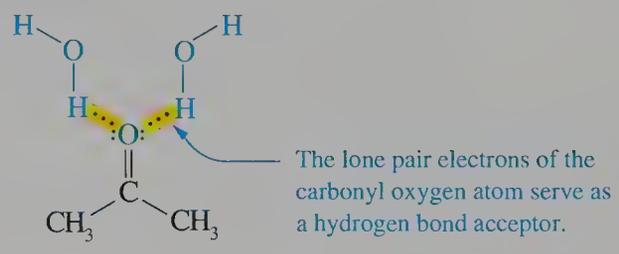
Compound	*Structure*	*Molecular weight (amu)*	*Boiling point (°C)*
ethane	CH_3CH_3	30	−89
methanol	CH_3OH	32	64.6
methanal	HCHO	30	−21
propane	$CH_3CH_2CH_3$	44	−42
ethanol	CH_3CH_2OH	46	78.3
ethanal	CH_3CHO	44	20
butane	$CH_3CH_2CH_2CH_3$	58	−1
1-propanol	$CH_3CH_2CH_2OH$	60	97.1
propanal	CH_3CH_2CHO	58	48.8
methylpropane	$CH_3CH(CH_3)_2$	58	−12
2-propanol	$CH_3CH(OH)CH_3$	60	82.5
propanone	CH_3COCH_3	58	56.1

FIGURE 18.2 Boiling Points of Aldehydes and Alcohols



Solubility in Water

Aldehydes and ketones cannot form hydrogen bonds with one another because they cannot function as hydrogen bond donors. However, because the carbonyl oxygen atom has lone pair electrons that can serve as hydrogen bond acceptors, carbonyl groups can form hydrogen bonds with water. As a result, the lower molecular weight compounds formaldehyde, acetaldehyde, and acetone dissolve in water in all proportions.

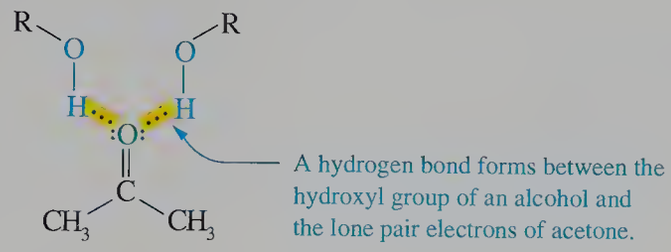


However, the solubility of carbonyl compounds in water decreases as chain length increases, making their solubilities more like those of hydrocarbons.

Solvent Characteristics

Both acetone and 2-butanone (known in industry as methyl ethyl ketone or MEK) are excellent solvents for a variety of organic compounds. These polar solvents dissolve polar solutes because "like dissolves like." Acetone is especially effective in

dissolving protic solutes such as alcohols and carboxylic acids because the carbonyl group acts as a hydrogen bond acceptor for these compounds.



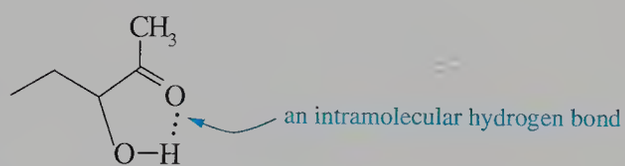
Acetone can function as an aprotic solvent (Section 10.3) because it does not have hydrogen atoms that can form hydrogen bonds to nucleophiles. The electron pairs of the carbonyl oxygen atom can solvate cations but not anions. Consequently, anions have greater nucleophilicity in acetone than in protic solvents such as ethanol.

Problem 18.5

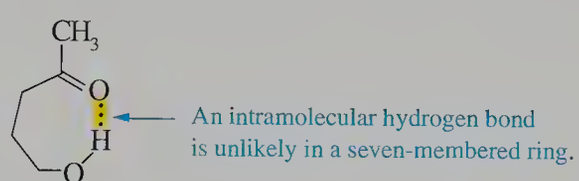
The boiling points of 3-hydroxy-2-pentanone and 5-hydroxy-2-pentanone are 147 and 210 °C, respectively. Suggest a reason for this difference.

Sample Solution

Intermolecular hydrogen bonding decreases the escaping tendency of molecules from the liquid phase and increases the boiling point. In both compounds the hydroxyl group can form intermolecular hydrogen bonds not only to hydroxyl groups but to the carbonyl oxygen atoms as well. In 3-hydroxy-2-pentanone, the proximity of the hydroxyl hydrogen atom to the carbonyl oxygen atom allows formation of an intramolecular hydrogen bond via a five-membered ring.



As a consequence, the extent of intermolecular hydrogen bonding is decreased. Decreased intermolecular hydrogen bonding allows molecules to escape more readily and lowers the boiling point. The probability of an intramolecular hydrogen bond in 5-hydroxy-2-pentanone is far less than in 3-hydroxyl-2-pentanone because a seven-membered ring would be required.

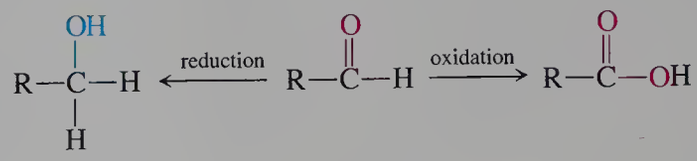


Problem 18.6

Draw two conformations of 2-methylacetophenone that have the carbonyl group conjugated with the aromatic ring. Which is the more stable?

18.5 Redox Reactions of Carbonyl Compounds

The carbonyl group of an aldehyde is in an oxidation state between that of an alcohol and a carboxylic acid. Thus, the carbonyl group of an aldehyde can be reduced to an alcohol or oxidized to a carboxylic acid.



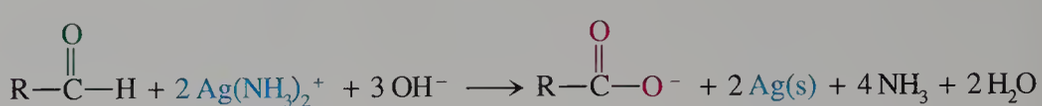
The carbonyl group of a ketone can be reduced to an alcohol, but cannot be easily oxidized.

Oxidation Reactions

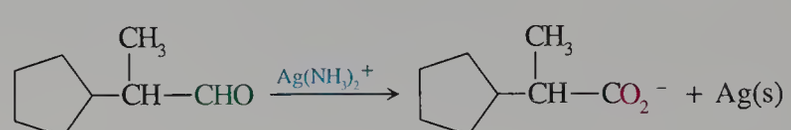
In Chapter 16, we saw that primary alcohols are oxidized to aldehydes, which are then easily oxidized to acids. Under the same conditions, secondary alcohols are oxidized to ketones, but no further. This difference in reactivity distinguishes primary from secondary alcohols.

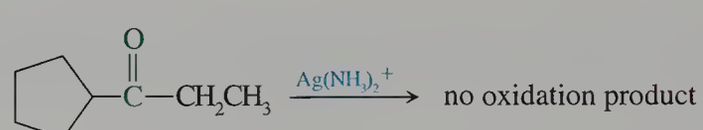
In a similar way, we can use oxidation to distinguish aldehydes from ketones. Aldehydes are easily oxidized. They react with several mild oxidizing reagents, including Tollens's reagent, Benedict's solution, and Fehling's solution. Each of these reagents converts aldehydes to carboxylic acids. None of them oxidize ketones. These reagents therefore provide a qualitative way of distinguishing aldehydes from ketones.

Tollens's reagent is a basic solution of a silver ammonia complex ion. When an aldehyde is added to a test tube containing Tollens's reagent, the aldehyde is oxidized and deposits metallic silver as a mirror on the wall of the test tube.



The addition of Tollens's reagent to each of the following isomeric carbonyl compounds gives a clear result that distinguishes between the two isomers.



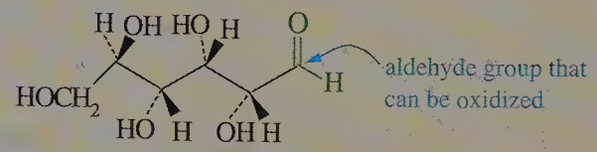


Benedict's solution contains cupric ion (Cu^{2+}) as a complex ion in a basic solution, and it converts aldehydes to carboxylic acids. In this reaction, Cu^{2+} is reduced to Cu^{+}, which forms as a brick-red precipitate, Cu_2O. Benedict's solution has the characteristic blue color of Cu^{2+}, which fades as the red precipitate of Cu_2O forms. Bene-

Benedict's Test and Diabetes

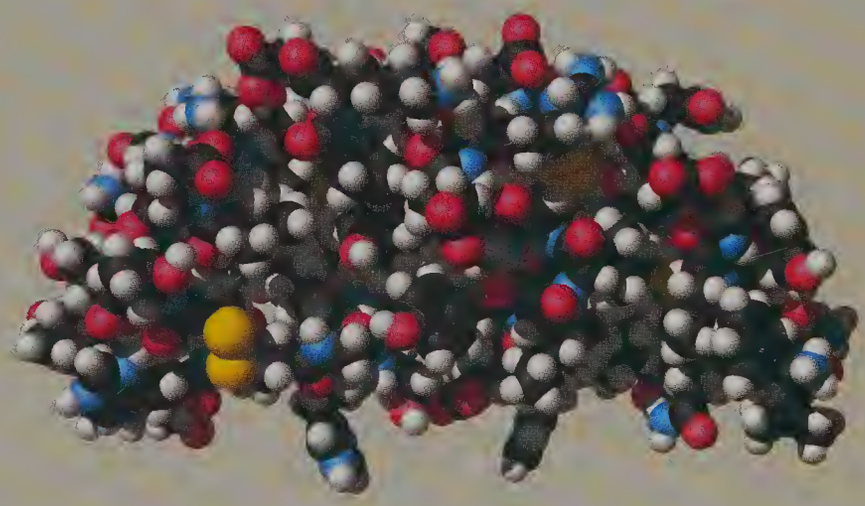
The disease Type I diabetes mellitus results from a lack of insulin, a polypeptide hormone that regulates glucose transport into cells. Loss of insulin-producing cells in the pancreas causes a sudden onset of the disease in childhood. Without enough insulin, body cells cannot take up glucose and the concentration in the blood rises. The kidneys, which normally return glucose to the blood, cannot handle the overload and pass it into the urine. A person who suffers from Type I diabetes can determine the timing of insulin injections required to maintain the proper blood glucose concentration by performing Benedict's test on a urine sample. Recently, an alternative method based on oxidation of glucose in blood directly has been developed.

Glucose has an aldehyde group that reacts with Benedict's solution. Benedict's solution contains blue Cu^{2+}. If the solution turns a greenish yellow color, the sample contains about 0.5% glucose. If the sample solution turns red (the color of Cu_2O), the concentration of glucose in the original sample was greater than 2%.



glucose

A newer more convenient One Touch method uses blood obtained by pricking the finger. Chemicals on a test strip oxidize the glucose in the blood and yield products that react with a dye on a test strip. The color is then read by an electronic device about the size of a hand calculator to give the blood glucose level.



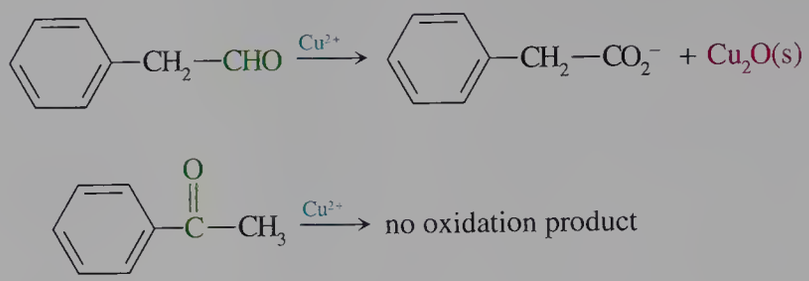
insulin

dict's solution is basic, and in basic solution a carboxylic acid is converted to its conjugate base, that is, a carboxylate anion.

$$\underset{}{\overset{O}{\overset{\|}{R-C-H}}} + \underset{\text{blue solution}}{2\,Cu^{2+}} + 5\,OH^- \longrightarrow \underset{}{\overset{O}{\overset{\|}{R-C-O^-}}} + \underset{\text{red precipitate}}{Cu_2O(s)} + 3\,H_2O$$

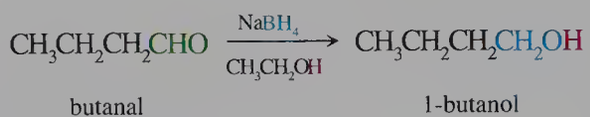
Fehling's solution, which contains Cu^{2+} as a different complex ion in a basic solution, also oxidizes aldehydes but not ketones. Either of the reagents can

be used to distinguish between compounds such as the following isomeric aldehyde and ketone.

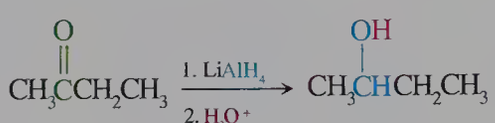


Reduction to Alcohols

In Chapter 6, we learned that hydrogen gas can reduce carbon–carbon double bonds in the presence of a nickel, palladium, or platinum catalyst. In Chapter 16, we learned that hydrogen gas can reduce aldehydes and ketones to alcohols in the presence of Raney nickel. However, this type of reduction requires more severe conditions than those required to reduce alkenes. We also learned that both lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) reduce carbonyl groups, but that neither reagent reduces carbon–carbon double or triple bonds.

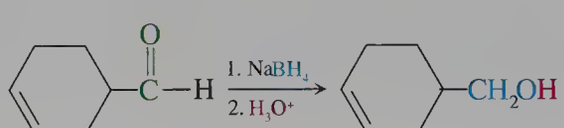


butanal 1-butanol



butanone 2-butanol

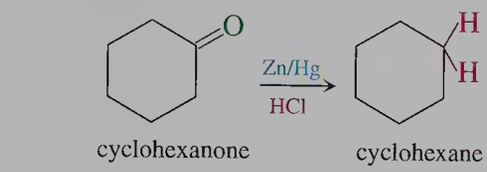
Because neither lithium aluminum hydride nor sodium borohydride reacts with alkenes or alkynes, these reagents selectively reduce a carbonyl group in compounds with carbon–carbon multiple bonds.



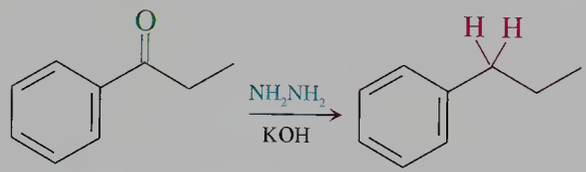
Reduction to a Methylene Group

We first introduced the reduction of a carbonyl group to a methylene group in Section 14.3 as a method of converting the ketone product of a Friedel–Crafts acylation to an alkyl group that could not be produced by direct Friedel–Crafts alkylation. The carbonyl group of either an aldehyde or a ketone can be reduced directly to a methylene group using either the Clemmensen reduction or the Wolff–Kishner reduction. The former uses a zinc amalgam (Zn/Hg) and HCl, and the latter uses hydrazine (NH_2NH_2)

and base in a high-boiling-point solvent such as diethylene glycol, $(HOCH_2CH_2)_2O$. Neither reagent reduces the carbonyl group of carboxylic acids or esters.



cyclohexanone cyclohexane



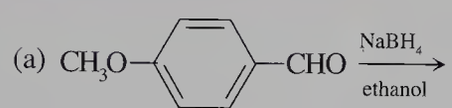
propiophenone propylbenzene

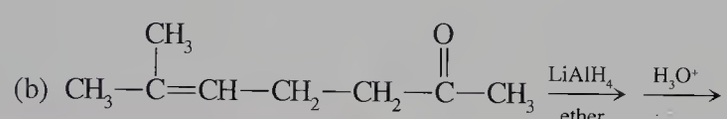
Problem 18.7

Can the isomeric carbonyl-containing compounds of molecular formula C_4H_8O be distinguished from each other by Tollens's reagent?

Problem 18.8

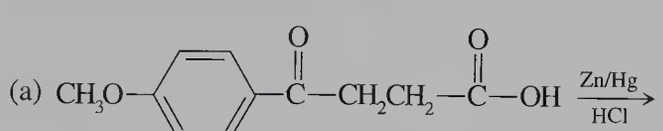
Draw the structure of the product of each of the following reactions.

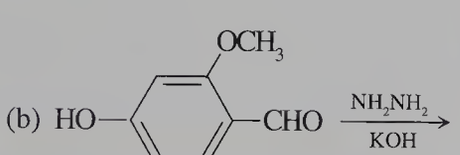
(a) 

(b) 

Problem 18.9

Draw the structure of the product of each of the following reactions.

(a) 

(b) 

Problem 18.10

Devise a synthesis of each of the following compounds starting from the Friedel–Crafts acylation of benzene.

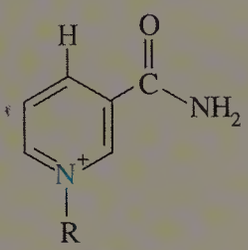
(a) 1-phenyl-1-butanol (b) 1-phenylbutane (c) 2-phenyl-2-pentanol

The oxidation of an alcohol to a carbonyl group is a common metabolic reaction. The reverse reaction, reduction of a carbonyl compound to an alcohol, is also common. In fact, the two related reactions often occur by the same mechanism, with the direction of the reaction controlled by needs of the cell. The two reactions transfer a hydride ion either to or from carbon atoms bonded to the oxygen atom in the substrate to a carbon atom of a coenzyme.

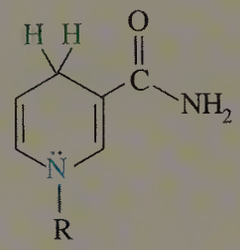
We recall that the oxidation of ethanol in a human liver cell to yield ethanal (acetaldehyde) is catalyzed by alcohol dehydrogenase, involving the reduction of the coenzyme nicotinamide adenine dinucleotide, NAD^+ (Section 16.4).

$$CH_3CH_2OH + NAD^+ \xrightarrow{ADH} CH_3CHO + NADH + H^+$$

The oxidized and reduced forms of the coenzyme are drawn using a shorthand in which the R group attached to the heterocyclic ring represents a part of the molecule not directly involved in its reactions. The oxidation or reduction of the coenzyme occurs within the six-membered pyridine ring. However, as we will see, the R group contains several chiral centers and is responsible for the stereospecificity of the coenzyme.



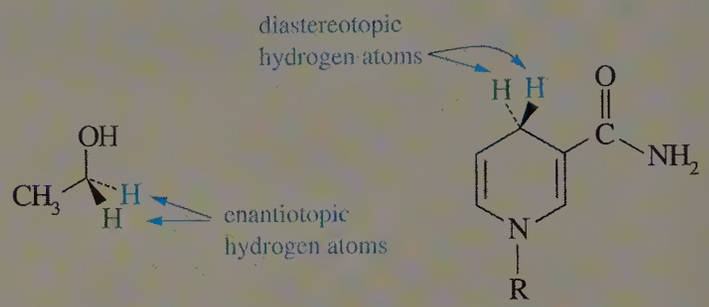
NAD^+
(oxidized form)



NADH
(reduced form)

When ethanol is oxidized by NAD^+, a hydride ion is transferred from the C-1 atom of ethanol to the C-4 atom of the heterocyclic ring. In the reverse reaction, acetaldehyde is reduced by transfer of a hydride ion from the C-4 atom of NADH to the carbonyl carbon atom.

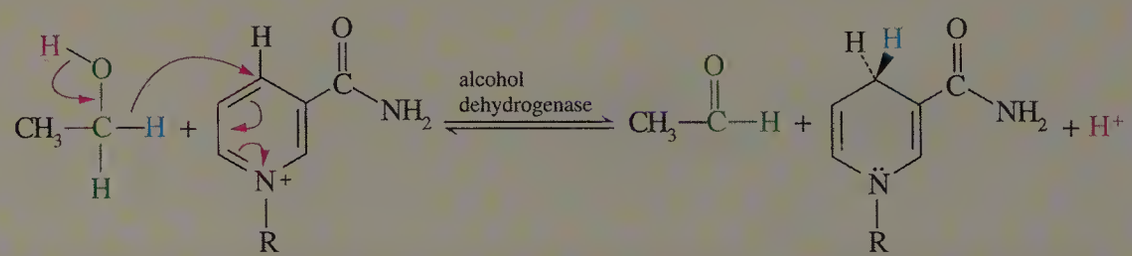
Note that the hydrogen atoms at C-1 of ethanol are prochiral. Thus, chiral reagents can distinguish these enantiotopic hydrogen atoms. Now let's examine the relationship between the two hydrogen atoms of NADH. They are not equivalent because replacing one of them with deuterium yields two different stereoisomers. However, the relationship in this case is one of diastereotopic hydrogen atoms because the R group has several stereogenic centers.



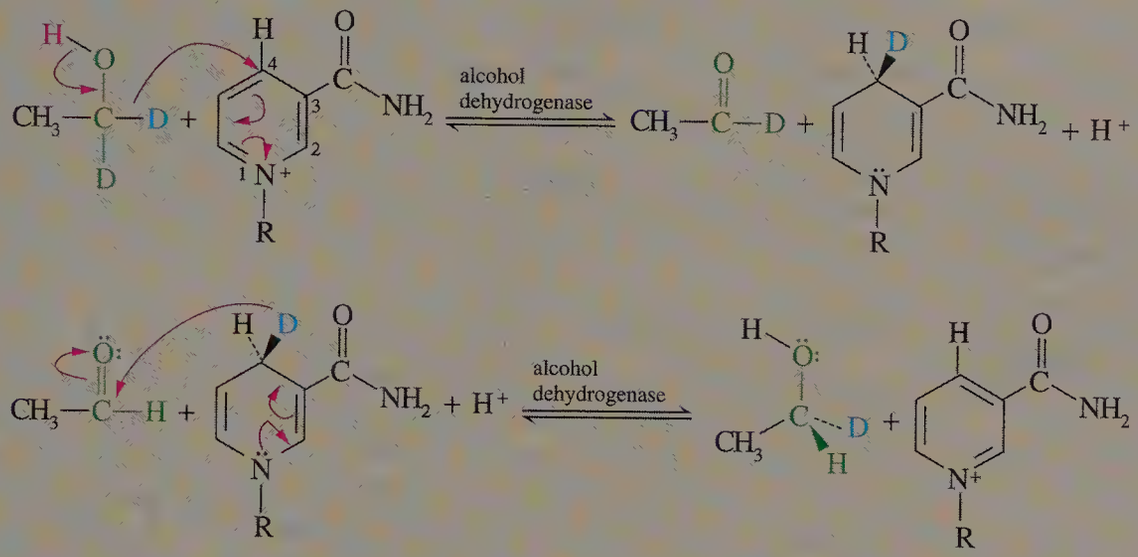
The stereochemistry of the oxidation of ethanol and the reduction of acetaldehyde have been determined using deuterium-labeled reactants. Reaction of ethanol-*1,1*-d_2 with NAD^+ occurs to give NADH-*4*-*d* with the *R* configuration at the C-4 atom. Using conventions outlined in Section 9.12, we conclude that the hydride ion was transferred to the *re* face.

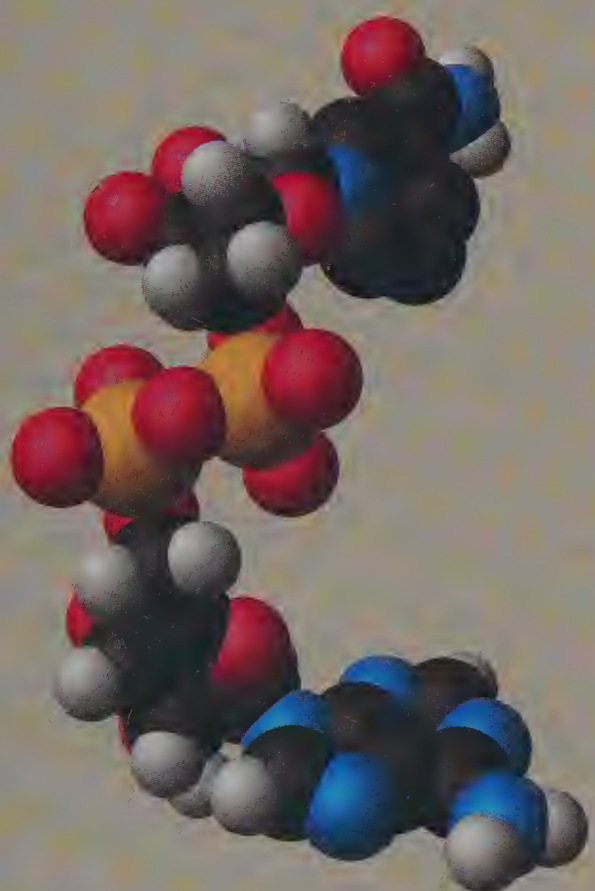
Now let's consider the reverse reaction, the reduction of acetaldehyde by (*R*)-NADH-*4*-*d*. Only the deuterium is transferred yielding (*R*)-ethanol-*1*-*d*—even though cleaving a C—D bond requires more energy than cleaving a C—H bond.

We conclude that the arrangement of the reac-

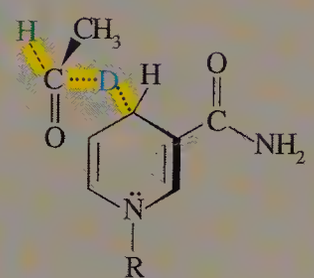


tants within the reactive site of the enzyme places the deuterium in a position to be transferred to the carbonyl carbon atom. The plane of NAD^+ and the plane of acetaldehyde are arranged so that the two *re* faces are next to each other. As a consequence, the deuterium is stereospecifically transferred.





nicotinamide adenine dinucleotide (NAD)



transition state

Sample Solution

The additional four carbon atoms required to synthesize 1-phenyl-1-butanol and 1-phenylbutane can be provided by a Friedel–Crafts reaction of benzene and a four-carbon acid chloride. This product, 1-phenyl-1-butanone, has a carbonyl group that can be reduced to provide products (a) and (b). Reduction of 1-phenyl-1-butanone with a metal hydride such as $NaBH_4$ gives 1-phenyl-1-butanol. Reduction of 1-phenyl-1-butanone using either Clemmensen or Wolff–Kishner conditions gives 1-phenylbutane.

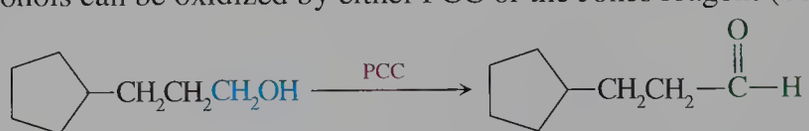
The third compound is a tertiary alcohol that can be prepared by the addition of a Grignard reagent to a ketone. There are three possible combinations of ketones and Grignard reagents that could be used. One is 1-phenyl-1-butanone and methylmagnesium bromide.

18.6 Synthesis of Carbonyl Compounds—A Review

Aldehydes and ketones can be made in many ways. In this section we will review reactions introduced in earlier chapters. A preview of synthetic methods to prepare aldehydes and ketones, based on the chemistry of functional groups to be discussed in later chapters, is given in Section 18.7.

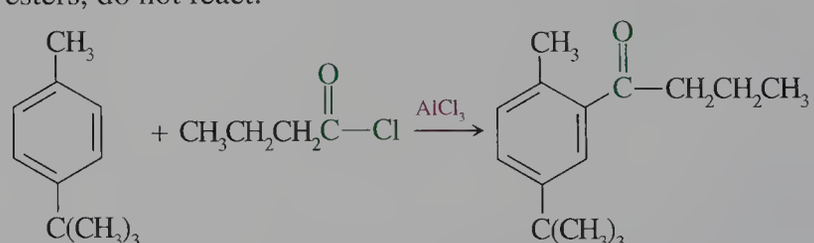
Oxidation of Alcohols

Alcohols provide the most common starting materials for the synthesis of carbonyl compounds. Because alcohols can be prepared by a variety of synthetic methods, they are very important synthetic intermediates. Oxidation of alcohols yields carbonyl compounds. Primary alcohols yield aldehydes; secondary alcohols yield ketones. However, we recall that the oxidation of primary alcohols is complicated because aldehydes are easily oxidized to carboxylic acids. Thus, PCC, which does not oxidize aldehydes is the reagent of choice for the oxidation of primary alcohols. Secondary alcohols can be oxidized by either PCC or the Jones reagent (Section 16.4).

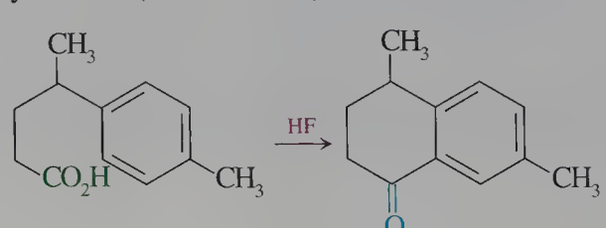


Friedel–Crafts Acylation

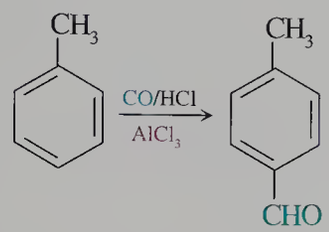
Both alkyl aryl ketones and diaryl ketones can be synthesized using the Friedel–Crafts reaction. However, the method is limited. Aromatic compounds that have strongly deactivating groups, such as NO_2, or carbonyl groups, such as aldehydes, ketones, acids, and esters, do not react.



The intramolecular acylation of an aromatic compound can be accomplished using a carboxylic acid rather than the acid halide. The reaction requires HF to produce the intermediate acyl cation (Section 14.2).

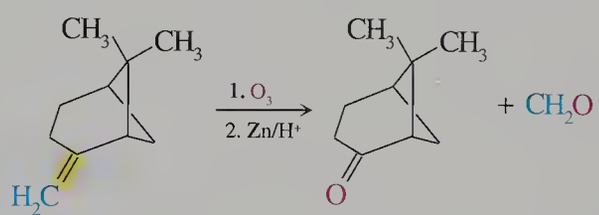


Aldehydes cannot be synthesized by the Friedel–Crafts reaction using methanoyl chloride (formyl chloride) because it is an unstable compound. However, a gaseous mixture of carbon monoxide and hydrogen chloride reacts like formyl chloride. The formylation of an aromatic compound using this gaseous mixture and aluminum trichloride is called the **Gatterman–Koch** synthesis. Like the Friedel–Crafts reaction, this method is limited to activated aromatic compounds.



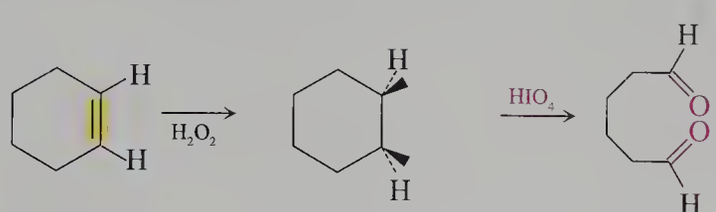
Ozonolysis of Alkenes

Ozonolysis followed by reductive workup gives a mixture of aldehydes and ketones whose structures depend on the groups bonded to the sp^2-hybridized carbon atoms. Thus, as a synthetic method, the process is limited by the requirement of having the appropriate alkene. This reaction also "wastes" part of the starting material because usually only one of the cleavage products is desired and the two carbonyl compounds must be separated. Nevertheless, the method proves useful in specific cases, such as the oxidative cleavage of α-pinene. In this case, the methanal by-product is a gas that does not contaminate the bicyclic ketone product.



Oxidative Cleavage of Vicinal Diols

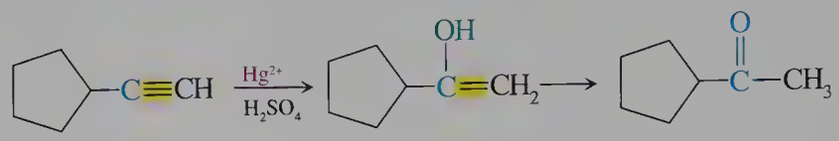
For the same reasons as described for the ozonolysis of alkenes, the oxidative cleavage of vicinal diols by periodate is limited as a synthetic method. The vicinal diol is seldom directly available, and it must be prepared from an alkene. Finally, we recall that the hydroxyl groups must be located in a cis configuration or the molecule must have sufficient conformational freedom to bring the two hydroxyl groups into a gauche conformation. The vicinal diol is prepared from an alkene by oxidation using osmium tetraoxide.



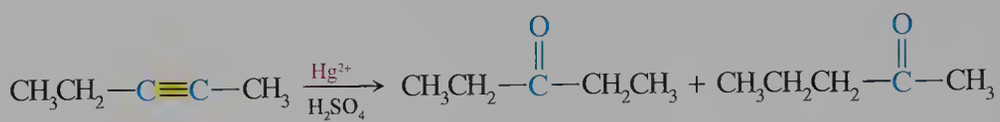
cyclohexene *cis*-1,2-cyclohexanediol 6-oxohexanal

Hydration of Alkynes

The hydration of alkynes to yield ketones is generally useful only for terminal alkynes. For example, ethynylcyclopentane reacts with water in aqueous sulfuric acid and mercuric ion to give an enol, which quickly isomerizes to a methyl ketone.

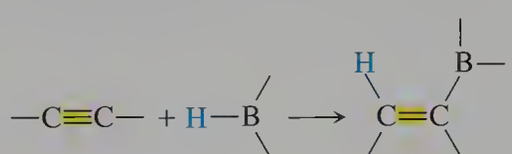


For internal alkynes, regioselectivity seldom occurs. The Markovnikov addition of water to internal alkynes gives a mixture of ketone products that have to be separated.

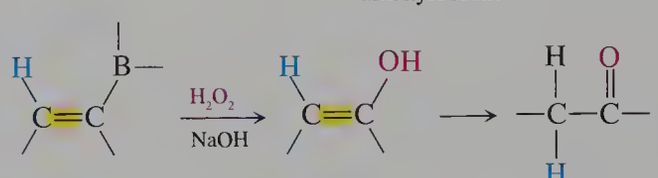


(approximately equal amounts)

We recall that alkenes react regiospecifically with borane to give an alkylborane, the anti-Markovnikov product. Subsequent oxidation of the alkylborane ultimately yields an alcohol that corresponds to anti-Markovnikov addition of water. Borane and substituted boranes also react with alkynes. The resulting alkenylborane is subsequently oxidized to give an enol, which quickly rearranges to give a carbonyl compound. The general equations are

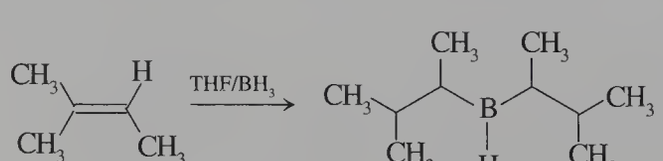


alkenylborane



enol

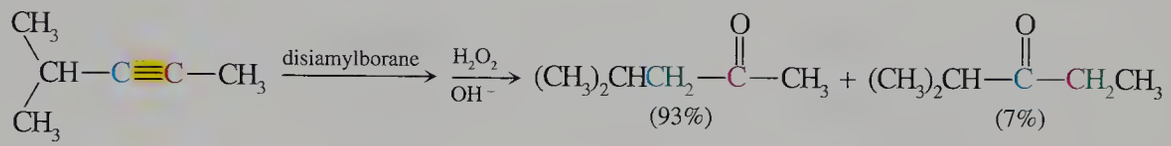
Terminal alkynes undergo regiospecific hydroboration in which boron is bonded to the less hindered carbon atom. Subsequent oxidization and isomerization therefore yield an aldehyde. In contrast, a terminal alkyne reacts with mercury(II) acetate to give a methyl ketone. The hydroboration reaction actually requires a substituted, hindered borane rather than diborane itself. With diborane, the alkenylborane can react with a second equivalent of diborane. Di(1,2-dimethylpropyl)borane—also called di(*sec*-isoamyl)borane and abbreviated disiamylborane—is prepared by adding borane to 2-methyl-2-butene.



disiamylborane

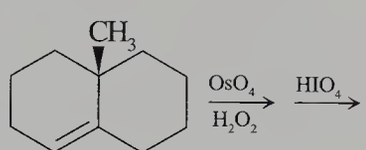
Diborane adds two equivalents of the alkene because the resulting substituted borane is sterically hindered and does not easily add to another equivalent of an alkene. However, disiamylborane is sufficiently reactive to add to an alkyne. The resulting alkenyl borane is too sterically hindered to react with a second equivalent of disiamylborane.

Disiamylborane is very regioselective and adds to terminal alkynes to give aldehydes after the oxidation step. Furthermore, the reagent is quite regioselective in the hydroboration of unsymmetrical internal alkynes. The boron atom of the reagent adds to the less hindered carbon atom of the alkyne. Upon oxidation, a hydroxyl group replaces the boron atom, and after rearrangement of the enol, a carbonyl group forms. Thus, the carbonyl oxygen atom ends up at the position originally occupied by boron.



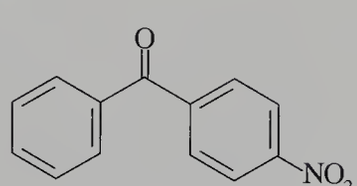
Problem 18.11

Draw the structures of the compounds formed in each step of the following reaction sequence, showing the stereochemistry of each.



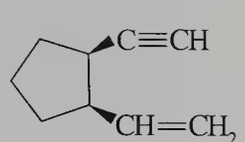
Problem 18.12

Outline a synthesis of the following compound using starting materials that contain no more than seven carbon atoms.



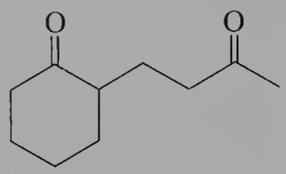
Problem 18.13

Draw the structure of the product formed from reaction of the following compound with disiamylborane followed by oxidation with basic hydrogen peroxide.



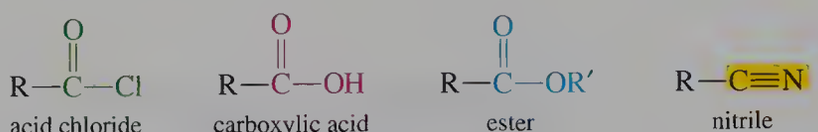
Problem 18.14

A hydrocarbon with the molecular formula $C_{10}H_{16}$ reacts with ozone followed by a reductive workup to give the following compound. What is the structure of the hydrocarbon?



18.7 Synthesis of Carbonyl Compounds—A Preview

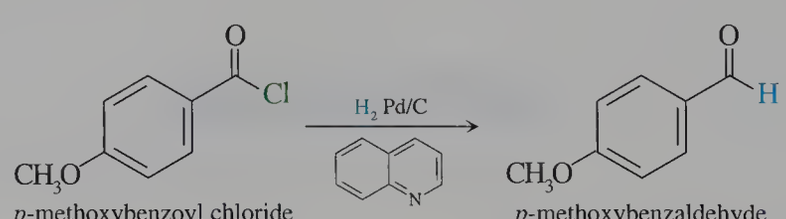
In this section we consider the synthesis of carbonyl compounds using functional groups whose chemistry will be examined in detail only in later chapters. We will preview some of the reactions of acid chlorides, carboxylic acids, esters, and nitriles that yield carbonyl compounds.



Reduction of Acid Chlorides

The extremely reactive acid chlorides are usually prepared for the single purpose of reacting them with another compound. They are prepared by the reaction of a carboxylic acid with thionyl chloride. The stoichiometry is the same as for the conversion of an alcohol to an alkyl halide using thionyl chloride (Section 16.3).

Acid chlorides can be reduced to aldehydes either by catalytic hydrogenation or by reaction with a metal hydride. In both cases, the reagent and the reaction conditions are selected to avoid the further reduction of the aldehyde produced. The conversion of an acid chloride to an aldehyde can be carried out by the Rosenmund reduction, which uses hydrogen gas and a modified palladium catalyst. The palladium catalyst is altered to prevent further reduction of the aldehyde product. To prepare the catalyst, the palladium is treated with quinoline, an aromatic heterocyclic amine, and is heated with sulfur.

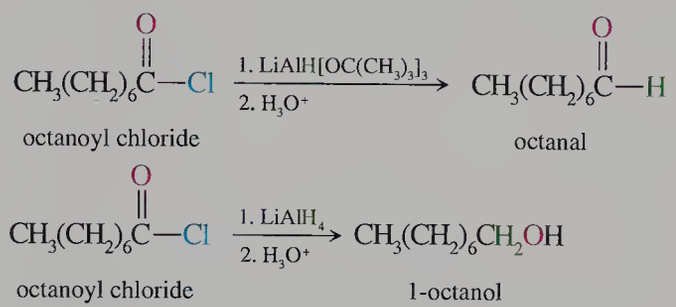


Acid chlorides can also be converted to aldehydes with lithium tri(*tert*-butoxy)aluminum hydride. This is the currently preferred reagent for the reduction. The

reagent is prepared by reacting lithium aluminum hydride with three equivalents of *tert*-butyl alcohol.

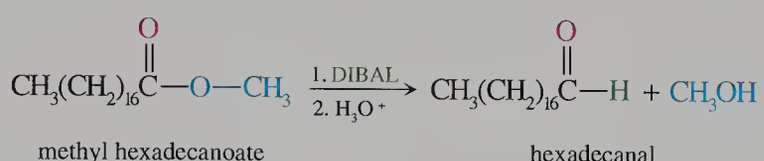
$$LiAlH_4 + 3\,(CH_3)_3COH \longrightarrow Li^+\,AlH[OC(CH_3)_3]_3^- + 3H_2$$

The electron-withdrawing *tert*-butoxy groups decrease the hydridic character of the Al—H bond. As a consequence, lithium tri(*tert*-butoxy)aluminum hydride will displace a chloride ion from an acyl chloride, but will not reduce the carbonyl group of the aldehyde. By contrast, lithium aluminum hydride reduces acyl chlorides to primary alcohols.

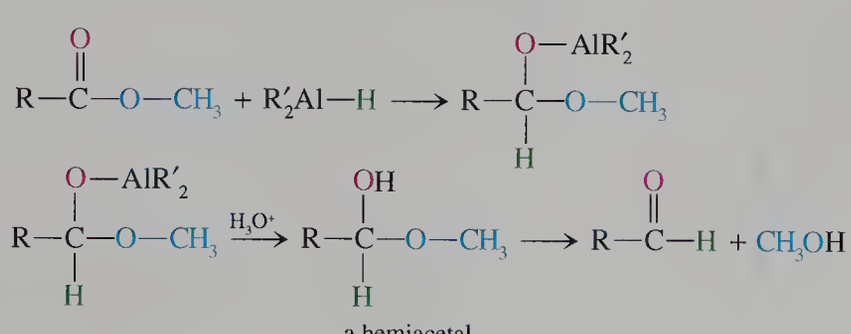


Reduction of Esters

The reduction of an ester either by lithium aluminum hydride or by catalytic hydrogenation at high temperatures under a high pressure of hydrogen yields a primary alcohol. Any aldehyde intermediate that forms is much more easily reduced than the ester. Diisobutylaluminum hydride, $[(CH_3)_2CHCH_2]_2AlH$, is less reactive than lithium aluminum hydride. At −78 °C in toluene, the reagent, known as DIBAL, reduces esters to aldehydes.

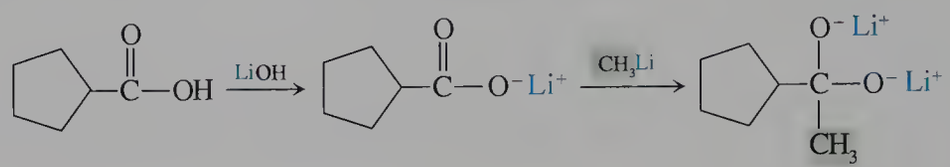


No aldehyde results from the first step. Instead, an aluminate forms by addition of aluminum to the carbonyl oxygen atom and hydrogen to the carbonyl carbon atom. Subsequent hydrolysis yields a hemiacetal, which decomposes to give the aldehyde. The hemiacetal is not converted to an aldehyde in the presence of DIBAL, so it is not reduced to an alcohol. The steps in the mechanism are

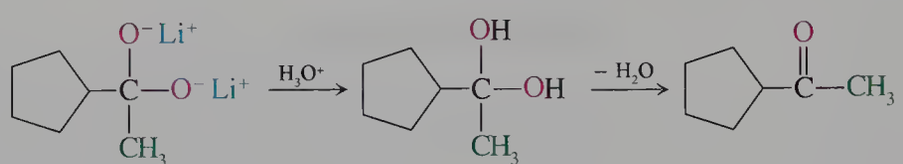


Reactions of Acid Derivatives with Organometallic Reagents

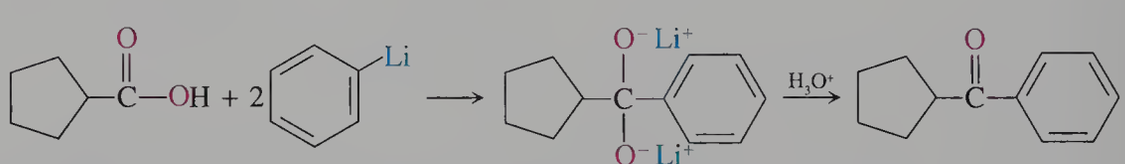
We recall that Grignard reagents add to aldehydes and ketones to give alcohols. We will also learn that Grignard reagents add to the carbonyl group of esters (Chapter 22). Organolithium compounds are more reactive than Grignard reagents and add to carbonyl groups. In fact, they are so reactive that they add to carboxylate anions even though the negative charge of a carboxylate anion makes its carbonyl carbon atom far less electrophilic than other carbonyl carbon atoms. For example, adding an organolithium reagent such as methyllithium to a carboxylate anion gives a dianion.



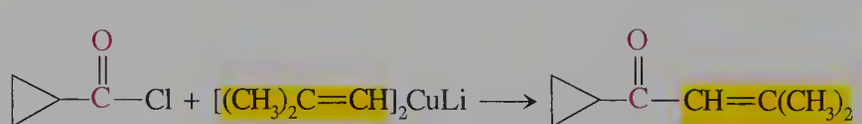
The dianion is treated with aqueous acid, yielding an unstable geminal diol. As we will learn in the next chapter, geminal diols spontaneously eliminate water to give carbonyl compounds. Thus, adding an organolithium reagent to a carboxylate anion gives a ketone in which the groups bonded to the carbonyl carbon atom are derived from both the carboxylic acid and the organolithium reagent.



When the organolithium reagent is inexpensive, as in the case of phenyllithium, it is customary to add two equivalents of the reagent directly to the carboxylic acid. The first equivalent reacts with the carboxylic acid to form the lithium carboxylate salt. The second equivalent reacts with the carbonyl carbon atom of the carboxylate ion.

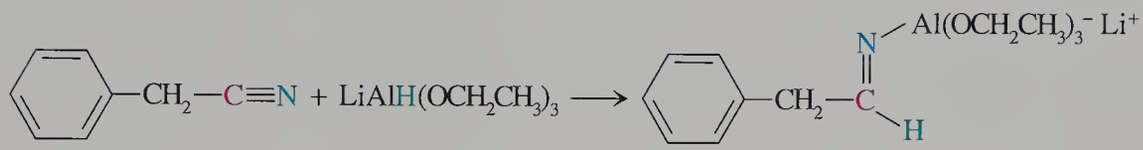


The carbonyl group of an acid chloride reacts with a nucleophilic carbanion of the Gilman reagent (Section 8.8), lithium dialkyl copper. This reagent reacts with acid chlorides and aldehydes, but only very slowly with ketones. Esters of carboxylic acids do not react at all. Thus, another synthesis of ketones using a carbonyl compound and an organometallic reagent has been developed using acid chlorides and the Gilman reagent. The resulting ketone product does not react further with the Gilman reagent under the reaction conditions.

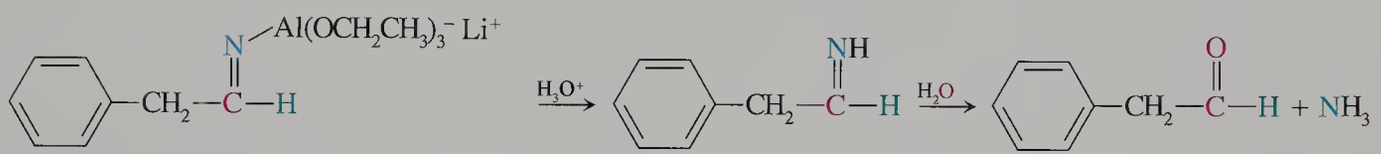


Formation of Carbonyl Compounds from Nitriles

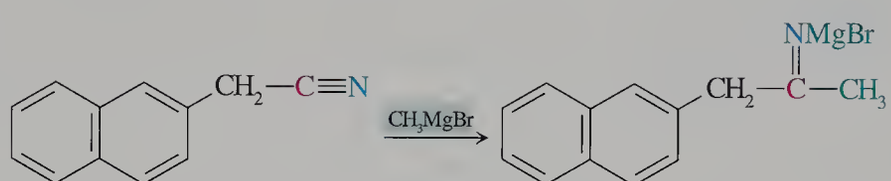
Nitriles can be reduced to amines by either catalytic hydrogenation or by lithium aluminum hydride. However, the modified hydride reagent lithium triethoxyaluminum hydride adds to the C≡N bond only once to give an imine anion derivative.



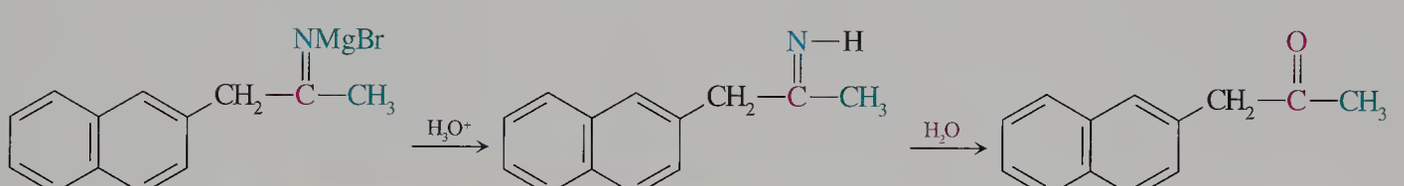
When treated with aqueous acid, it is hydrolyzed to an imine that is rapidly converted to an aldehyde. We will discuss the relative stabilities of imines and carbonyl groups in the next chapter.



Grignard reagents add to the triple bond of a nitrile to give an imine anion complexed with magnesium. Note that the intermediate imine anion has a double bond, which might add a second equivalent of the Grignard reagent. However, this addition reaction does not occur under the reaction conditions.

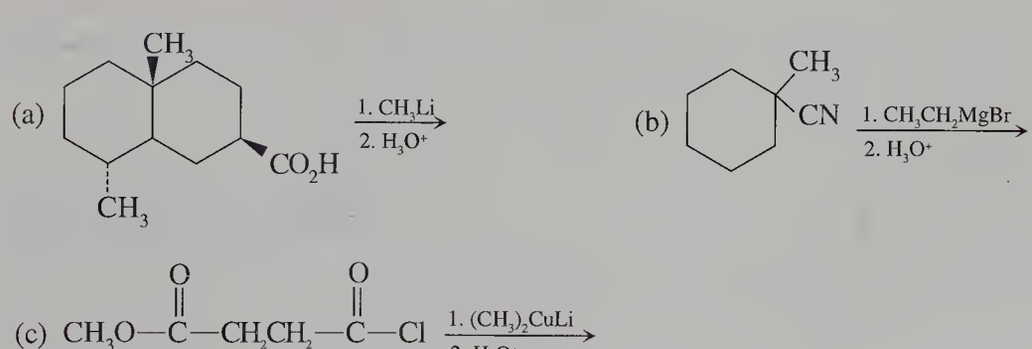


When the magnesium salt of the imine is treated with aqueous acid, it reacts rapidly with water to give the more stable ketone.



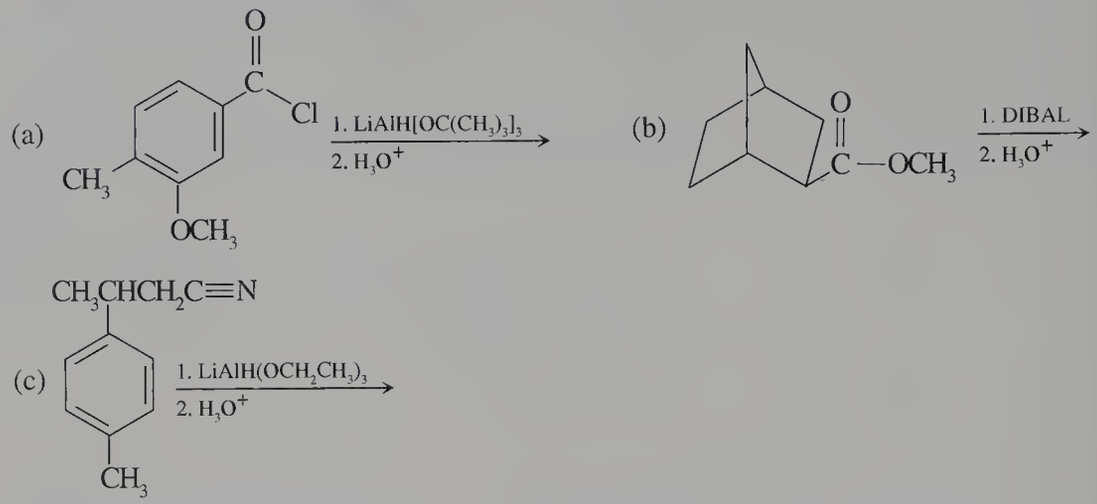
Problem 18.15

Draw the structure of the product of each of the following reactions.



Problem 18.16

Draw the structure of the product of each of the following reactions.



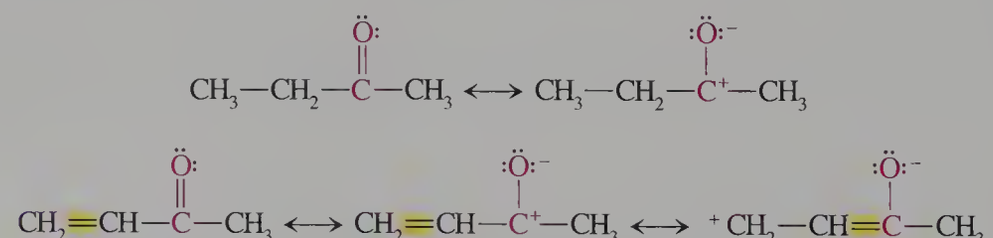
18.8 Spectroscopy of Aldehydes and Ketones

Infrared Spectroscopy

The C=O stretching absorption is one of the most important and characteristic absorptions because it varies predictably as a result of differences in structure. The absorption, which is extremely intense, occurs in the vicinity of 1700 cm^{-1}. Because the C=O bond is stronger than the C=C bond, the carbonyl absorption occurs at higher wavenumber.

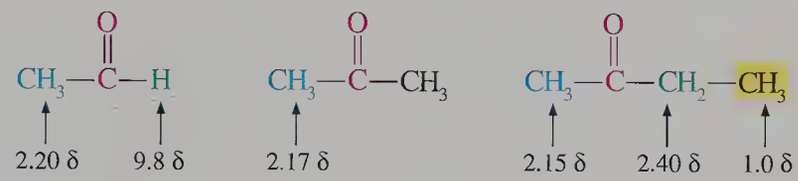
Simple ketones absorb at 1710–1715 cm^{-1}; simple aldehydes absorb at 1720–1725 cm^{-1}. In addition, aldehydes have a characteristic absorption near 2710 cm^{-1} for the aldehydic C—H bond. Cyclohexanones have carbonyl absorptions at the same position as simple acyclic ketones. However, decreased ring size results in shifts to higher wavenumber. Cyclopentanone, cyclobutanone, and cyclopropanone absorb at 1745, 1780, and 1850 cm^{-1}, respectively.

Compounds with carbon–carbon double bonds or aromatic rings in conjugation with the carbonyl group have absorptions at lower wavenumber than unconjugated carbonyl compounds. For example, the carbonyl absorptions of 3-buten-2-one and acetophenone occur at 1670 and 1685 cm^{-1}, respectively, whereas the carbonyl absorption of 2-butanone occurs at 1715 cm^{-1}. The decreased energy required to stretch the carbonyl group in a conjugated compound reflects the increased importance of contributing dipolar resonance structures. The carbonyl group of a conjugated compound has more single bond character illustrated by a second contributing dipolar resonance form of 3-buten-2-one compared to 2-butanone.



Proton NMR Spectroscopy

In both aldehydes and ketones, the protons on the carbon atoms adjacent to the carbonyl carbon atom—the α-protons— have NMR absorptions in the 2.0–2.5 δ region depending on the degree of substitution of the α carbon atom. The absorption of the aldehydic hydrogen atom occurs in the 9.5–10 δ region. This strong deshielding effect is a consequence of the contribution of π electrons of the carbonyl group as well as the inductive effect of the carbonyl oxygen atom. The indicated NMR absorptions of ethanal, propanone, and 2-butanone illustrate typical data obtained for aldehydes and ketones.



Carbon NMR Spectroscopy

The absorption of the α carbon atom of aldehydes and ketones occurs in the 30–50 δ region with the usual effects of increased substitution resulting in absorptions at lower field. Other carbon atoms with a variety of functional groups in the proximity also absorb in this region. Therefore absorptions in this region cannot be used to unambiguously assign the structure of a carbonyl compound.

The most characteristic absorption of aldehydes and ketones is due to the carbonyl carbon atom itself and occurs in the 190–220 δ range. (It is often necessary to show such absorptions as an offset inserted on the remaining high-field portion of the spectrum.) This very low field position is due to both the effect of π electrons and the inductive effect of the electronegative oxygen atom. The absorption of the carbonyl carbon atom of an aldehyde is a doublet as a result of coupling with the aldehydic hydrogen atom but a singlet in ketones, which have no hydrogen atoms bonded directly to the carbonyl carbon atom. As previously noted (Section 15.8), the intensity of carbon-13 NMR resonances is not directly proportional to the number of carbon atoms. In the case of carbonyl carbon atoms, the absorption is very weak.

Problem 18.17

How could IR spectroscopy be used to distinguish between the isomers of each of the following pairs?

(a) 2-methylcyclopentanone and 2-ethylcyclobutanone
(b) 3-cyclohexenone and 2-cyclohexenone
(c) 4-methylbenzaldehyde and 4-methoxybenzaldehyde
(d) 2-methylcyclohexanone and cyclohexanecarbaldehyde

Problem 18.18

Suggest a reason why the IR absorption of the carbonyl group of a ketone is at lower wavenumber than that of the carbonyl group of an aldehyde.

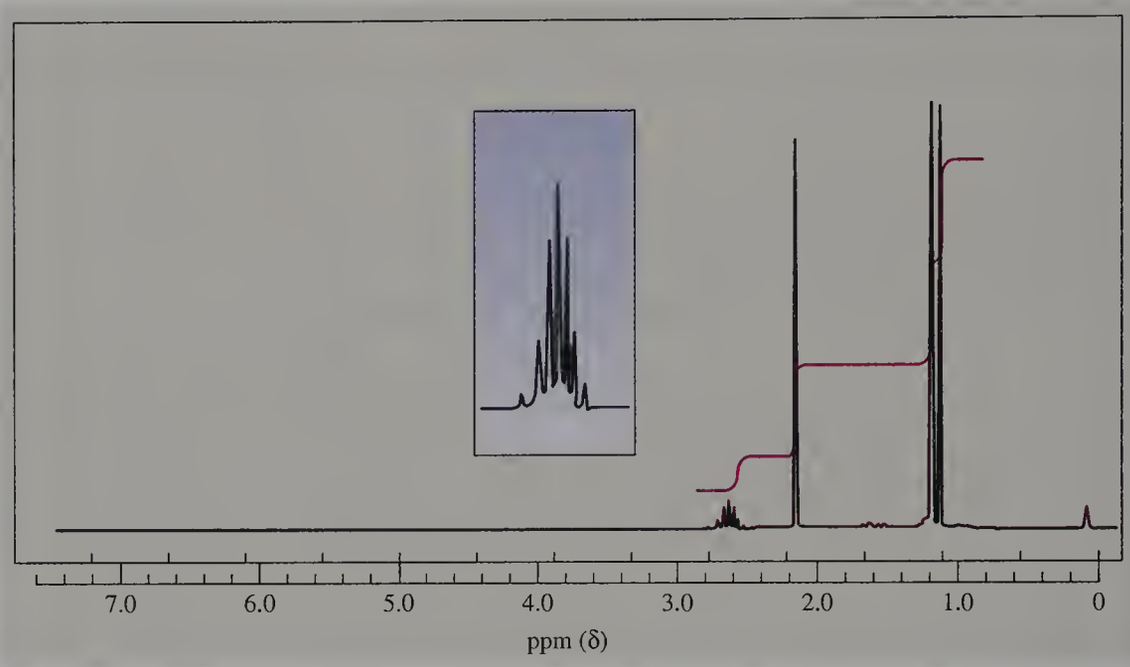
Problem 18.19

Deduce the structure of isomeric compounds having the molecular formula C_4H_8O based on the following carbon NMR data.

(a) 7.6 ppm, 28.8 ppm, 36.4 ppm, 206.3 ppm
(b) 13.3 ppm, 15.7 ppm, 45.7 ppm, 201.6 ppm

Problem 18.20

Deduce the structure of a compound with the molecular formula $C_5H_{10}O$ based on the following hydrogen NMR spectrum.



EXERCISES

Nomenclature of Aldehydes and Ketones

18.1 Write the structure for each of the following compounds.
(**a**) 2-methylbutanal (**b**) 3-ethylpentanal (**c**) 2-bromopentanal
(**d**) 3,4-dimethyloctanal (**e**) 1-bromocyclobutanecarbaldehyde

18.2 Write the structure of each of the following compounds.
(**a**) 3-bromo-2-pentanone (**b**) 2,4-dimethyl-3-pentanone (**c**) 4-methyl-2-pentanone
(**d**) 3,4-dimethyl-2-pentanone (**e**) 2-methyl-1,3-cyclohexanedione

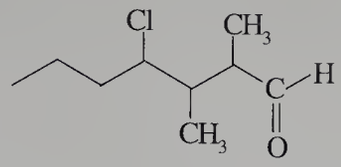
18.3 Give the IUPAC name for each of the following compounds.

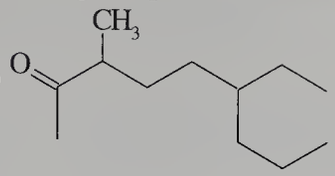
(**a**) $CH_3CH_2CH_2CHO$ (**b**) $CH_3C(CH_3)_2CH_2CHO$ (**c**) $CH_3CH(CH_3)CHO$ (**d**) $CH_3CH_2CH(CH_2CH_3)CHCHO$

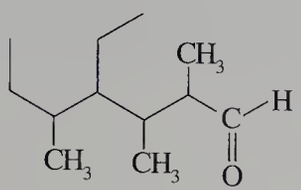
18.4 Give the IUPAC name for each of the following compounds.

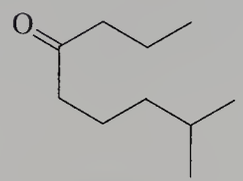
(**a**) $CH_3CH_2C(=O)CH_2CH_3$ (**b**) $CH_3C(=O)C(CH_3)_2CH_3$ (**c**) $CH_3CH(CH_3)C(=O)CH_2CH_3$ (**d**) $CH_3CH(CH_3)CH_2C(=O)CH_2CH_3$

18.5 Give the IUPAC name for each of the following compounds.

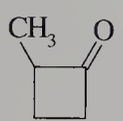
(a) 

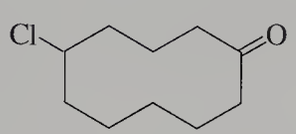
(b) 

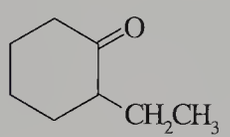
(c) 

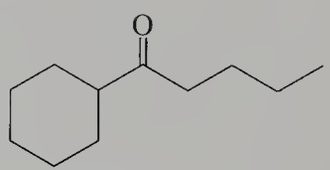
(d) 

18.6 Give the IUPAC name for each of the following compounds.

(a) 

(b) 

(c) 

(d) 

18.7 Many aldehydes and ketones are better known by their common names. Draw the structural formula of each of the following carbonyl compounds. Their common names are given within parentheses.

(a) 2,2-dimethylpropanal (pivaldehyde)
(b) 2-hydroxy-1,2-diphenyl-1-ethanone (benzoin)
(c) 2-propenal (acrolein)
(d) 4-methyl-3-penten-2-one (mesityl oxide)
(e) 5,5-dimethyl-1,3-cyclohexanedione (dimedone)

18.8 Draw the structural formula of each of the following carbonyl compounds. The common name of each compound is given within parentheses.

(a) 3,3-dimethyl-2-butanone (pinacolone)
(b) 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol)
(c) (*E*)-2-butenal (crotonaldehyde)
(d) 1,3-diphenyl-2-buten-1-one (dypnone)
(e) 2,3-butanedione (biacetyl)

Properties of Aldehydes and Ketones

18.9 The H—C—H bond angle of formaldehyde is 116.5°. The H—C—C bond angle of acetaldehyde is 117.2°. Explain this difference.

18.10 The C=C bond length in alkenes and the C=O bond length in aldehydes are 134 and 123 pm, respectively. Explain this difference.

18.11 The dipole moments of acetone and isopropyl alcohol are 2.7 and 1.7 D, respectively. Explain this difference.

18.12 The dipole moments of propanal and propenal are 2.52 and 3.12 D, respectively. Consider the resonance forms of these compounds and explain the difference in their dipole moments.

18.13 The boiling points of butanal and 2-methylpropanal are 75 and 61 °C, respectively. Explain this difference.

18.14 The boiling points of 2-heptanone, 3-heptanone, and 4-heptanone are 151, 147, and 144 °C, respectively. What is responsible for this trend?

18.15 The boiling points of 2-hydroxy- and 3-hydroxybenzaldehydes are 197 and 240 °C, respectively. Suggest a reason for this difference.

18.16 The boiling points of 2-hydroxy- and 3-hydroxyacetophenones are 218 and 296 °C, respectively. Suggest a reason for this difference.

18.17 The solubilities of butanal and 1-butanol in water are 7 and 9 g/100 mL, respectively. Explain this difference.

18.18 The solubilities of butanal and 2-methylpropanal in water are 7 and 11 g/100 mL, respectively. Explain this difference.

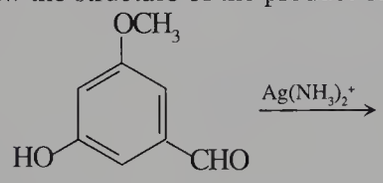
Oxidation and Reduction of Carbonyl Compounds

18.19 What is observed when an aldehyde reacts with Benedict's solution? What is observed when an aldehyde reacts with Tollens's reagent?

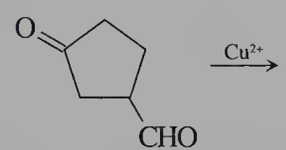
18.20 What class of compounds results from the reduction of ketones with sodium borohydride? What class of compounds results from the reduction of aldehydes by lithium aluminum hydride?

18.21 Draw the structure of the product of each of the following reactions

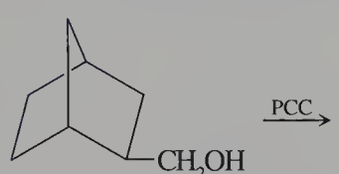
(a)



(b)

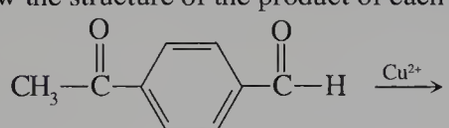


(c)

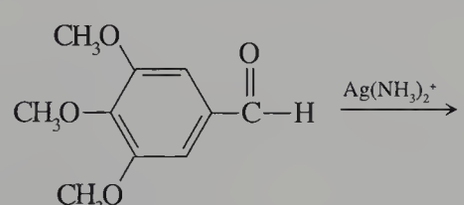


18.22 Draw the structure of the product of each of the following reactions.

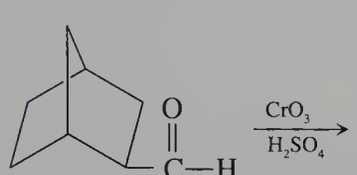
(a)



(b)

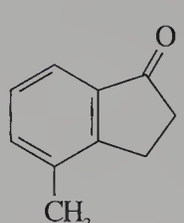


(c)

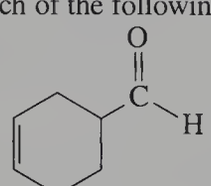


18.23 What is the product when each of the following reacts with lithium aluminum hydride?

(a)



(b)



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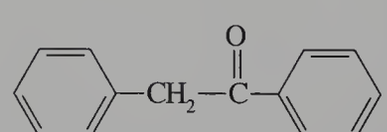
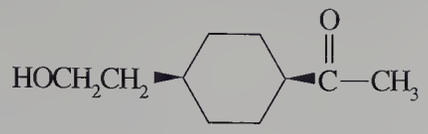
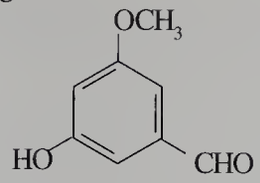
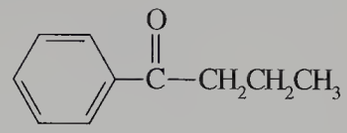


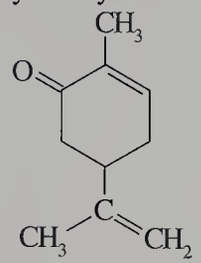
18.24 What is the product when each of the following reacts with sodium borohydride?

(a) 

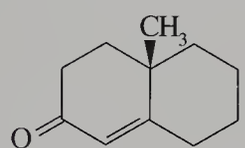
(b) 

(c) 

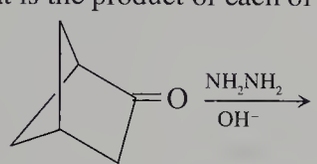
18.25 The reduction of carvone by lithium aluminum hydride yields two products. Explain why.

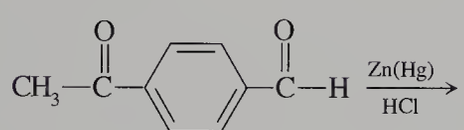


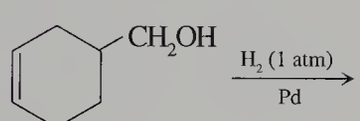
18.26 The reduction of the following compound by sodium borohydride yields two products. Explain why.



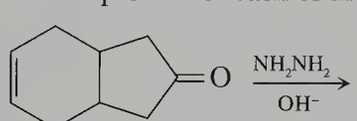
18.27 What is the product of each of the following reactions?

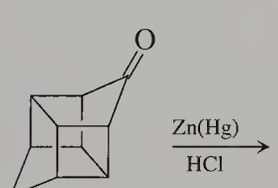
(a) 

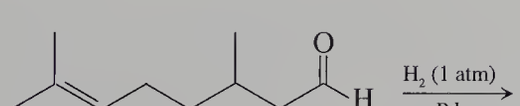
(b) 

(c) 

18.28 What is the product of each of the following reactions?

(a) 

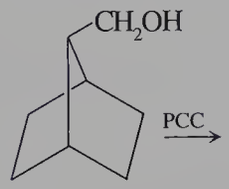
(b) 

(c) 

Synthesis of Carbonyl Compounds

18.29 What is the product of each of the following reactions?

(a)



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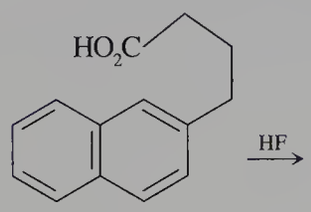

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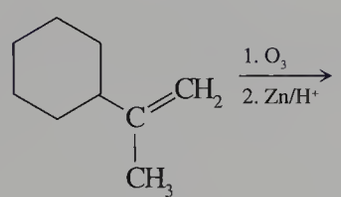

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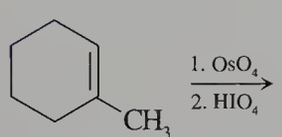
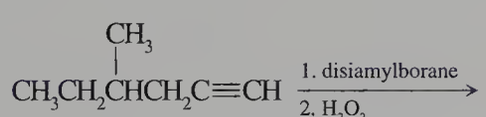
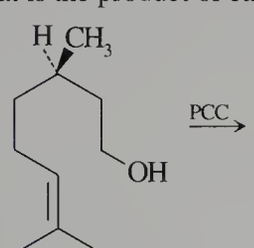


(e)

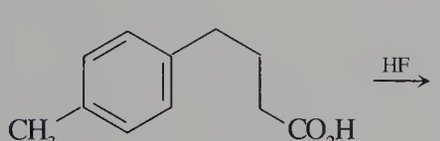


18.30 What is the product of each of the following reactions?

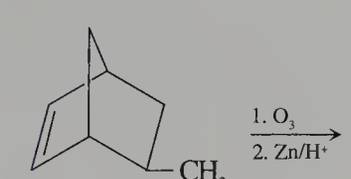
(a)



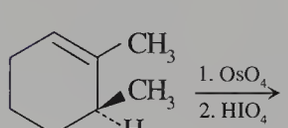
(b)

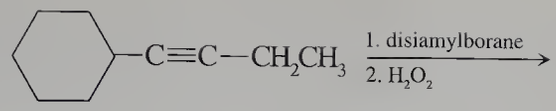


(c)

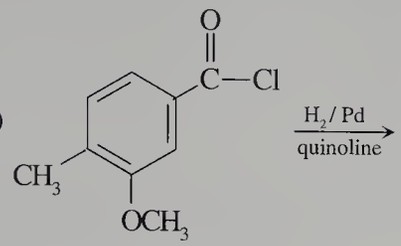


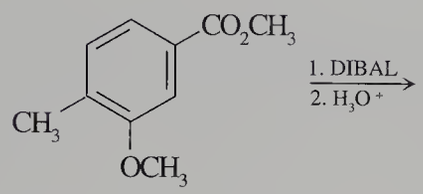
(d)

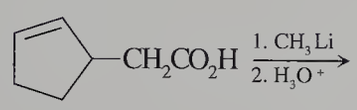


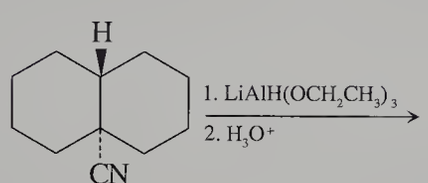
(e) 

18.31 What is the product of each of the following reactions?

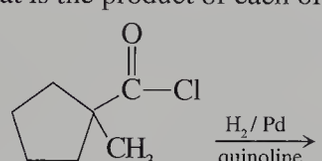
(a) 

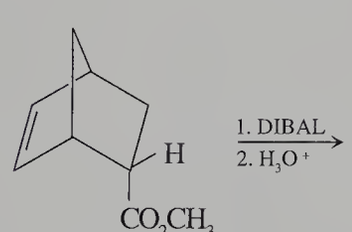
(b) 

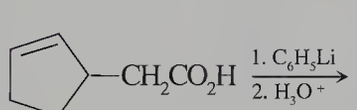
(c) 

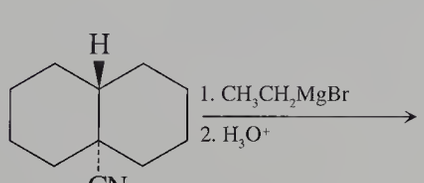
(d) 

18.32 What is the product of each of the following reactions?

(a) 

(b) 

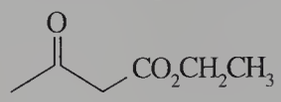
(c) 

(d) 

Biological Reductions

18.33 Reduction of 5-chloro-2-pentanone by NADPH in an enzyme-catalyzed reaction yields (*S*)-5-chloro-2-pentanol. From which face does the hydrogenation occur?

18.34 Reduction of the ketone group of the following keto ester occurs stereospecifically at the *re* face using NADH in an enzyme-catalyzed reaction. Draw the structure of the product and assign its configuration.



Spectroscopy of Aldehydes and Ketones

18.35 Explain why the IR absorption of the C=C bond of 1-butene (1642 cm^{-1}) is at higher wavenumber than the C=C bond absorption of 3-buten-2-one (1613 cm^{-1}).

18.36 Explain why the carbonyl stretching absorption of cyclohexanones are shifted approximately 20 cm^{-1} to higher wavenumber when a bromine atom is substituted in the equatorial position at the α carbon atom.

18.37 Based on the following carbon NMR data, deduce the structures of isomeric compounds having the molecular formula C_4H_8O.

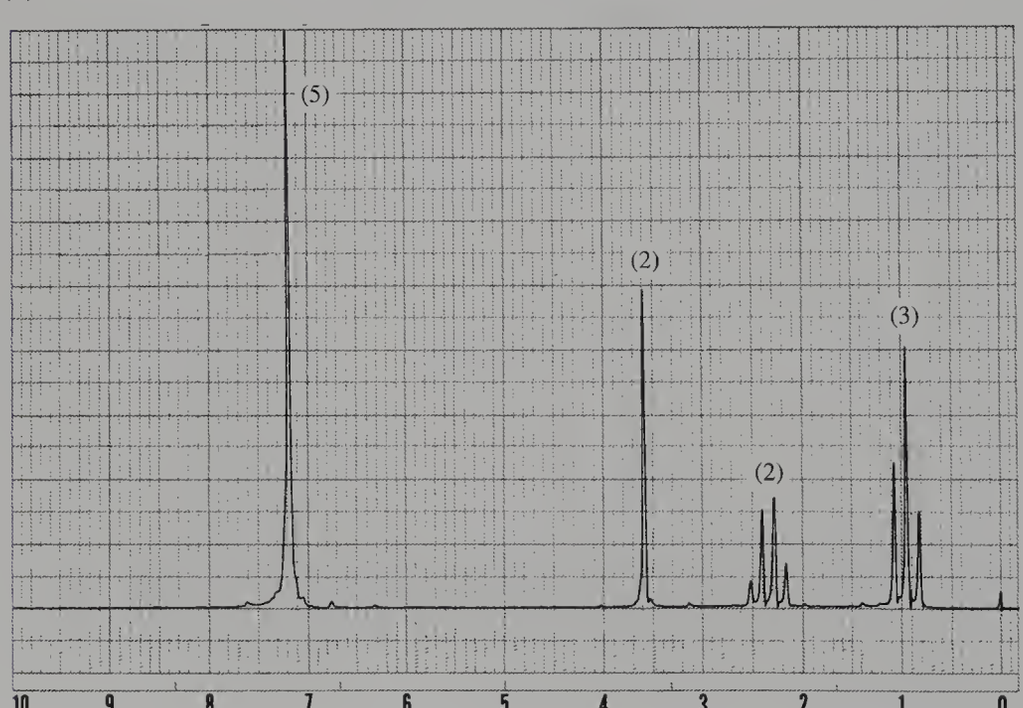
(**a**) 25.7 ppm, 68.0 ppm
(**b**) 15.5 ppm, 41.0 ppm, 204.9 ppm
(**c**) 7.9 ppm, 29.4 ppm, 36.9 ppm, 209.2 ppm
(**d**) 13.7 ppm, 15.7 ppm, 45.8 ppm, 207.6 ppm

18.38 Based on the following carbon NMR data, deduce the structures of isomeric ketones having the molecular formula $C_5H_{10}O$.

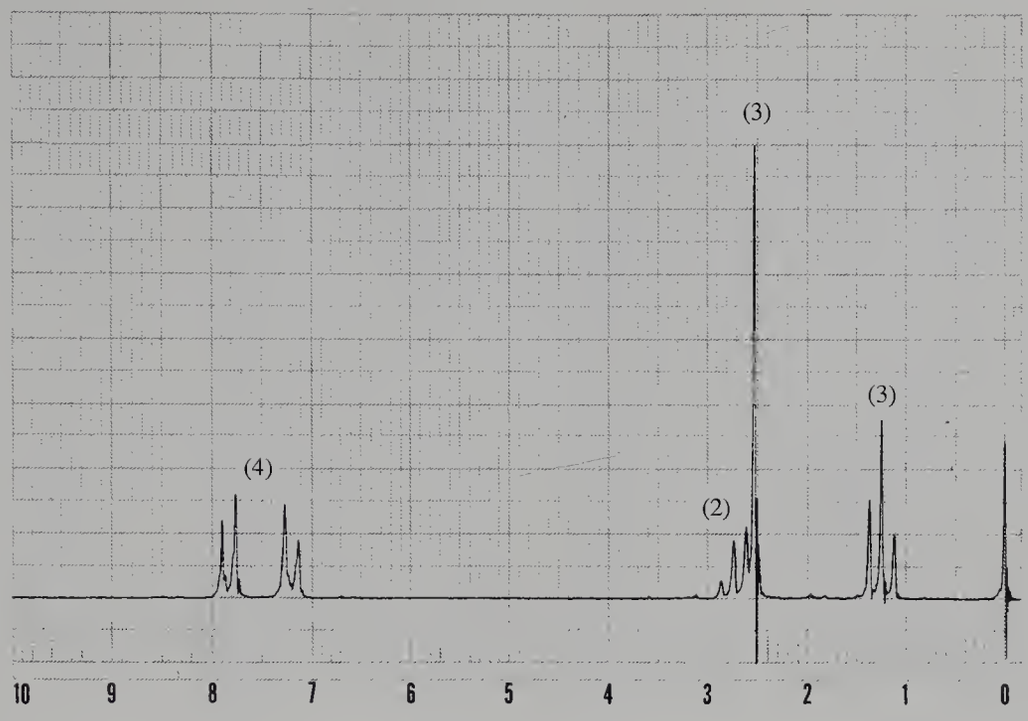
(**a**) 18.1 ppm, 27.3 ppm, 41.5 ppm, 211.7 ppm
(**b**) 13.5 ppm, 17.5 ppm, 29.3 ppm, 45.2 ppm, 206.6 ppm
(**c**) 7.3 ppm, 35.3 ppm, 209.3 ppm

18.39 Deduce the structure of isomeric ketones having the molecular formula $C_{10}H_{12}O$ based on the following hydrogen NMR spectra. The relative intensities are given within parentheses.

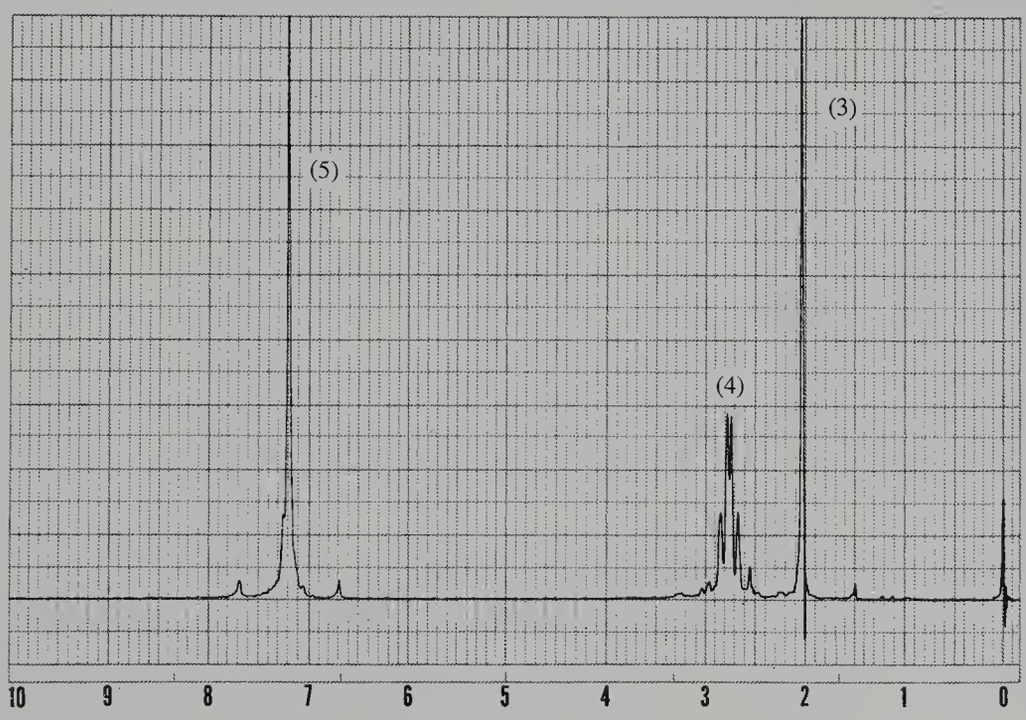
(**a**)



(b)

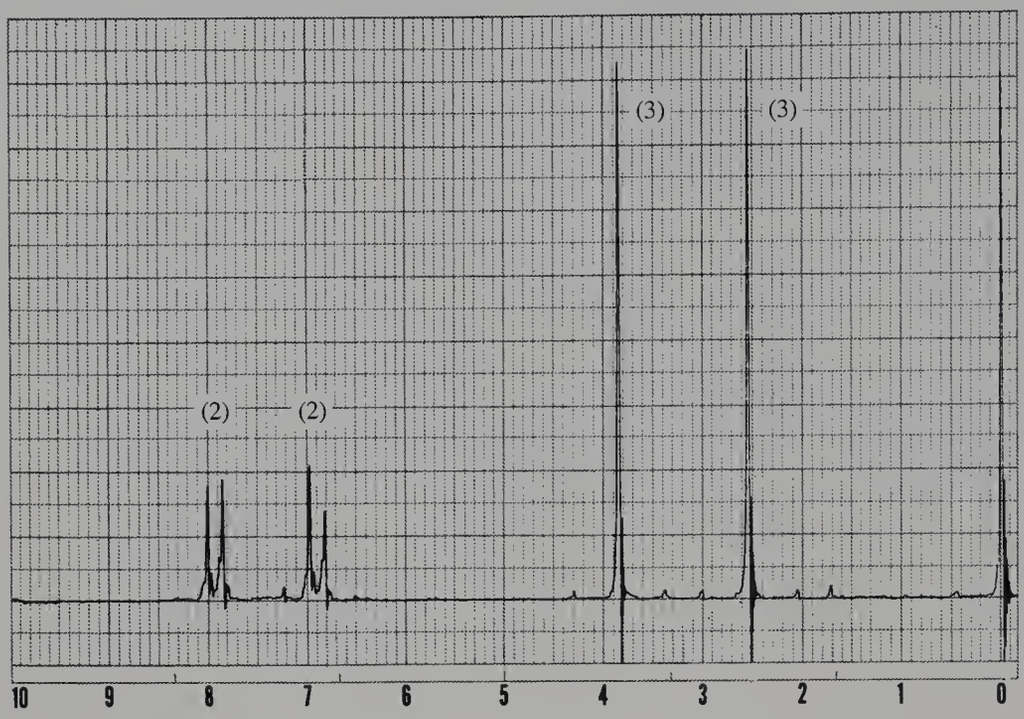


(c)



18.40 Deduce the structures of isomeric compounds having the molecular formula $C_9H_{10}O_2$ based on the following hydrogen NMR spectra. The relative intensities are given within parentheses.

(a)



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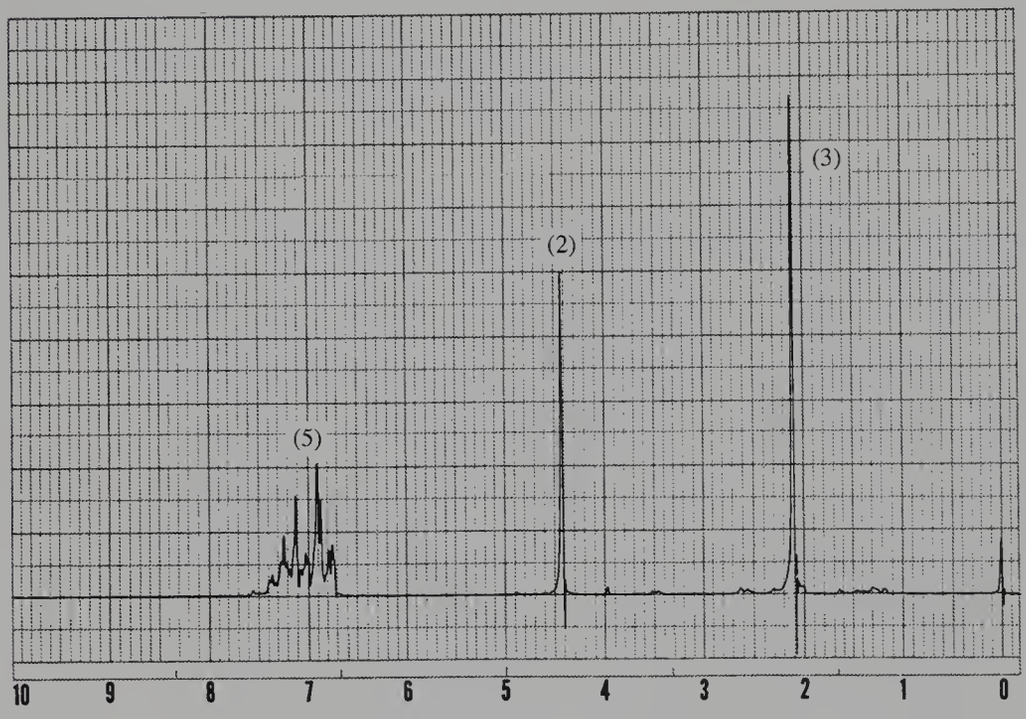
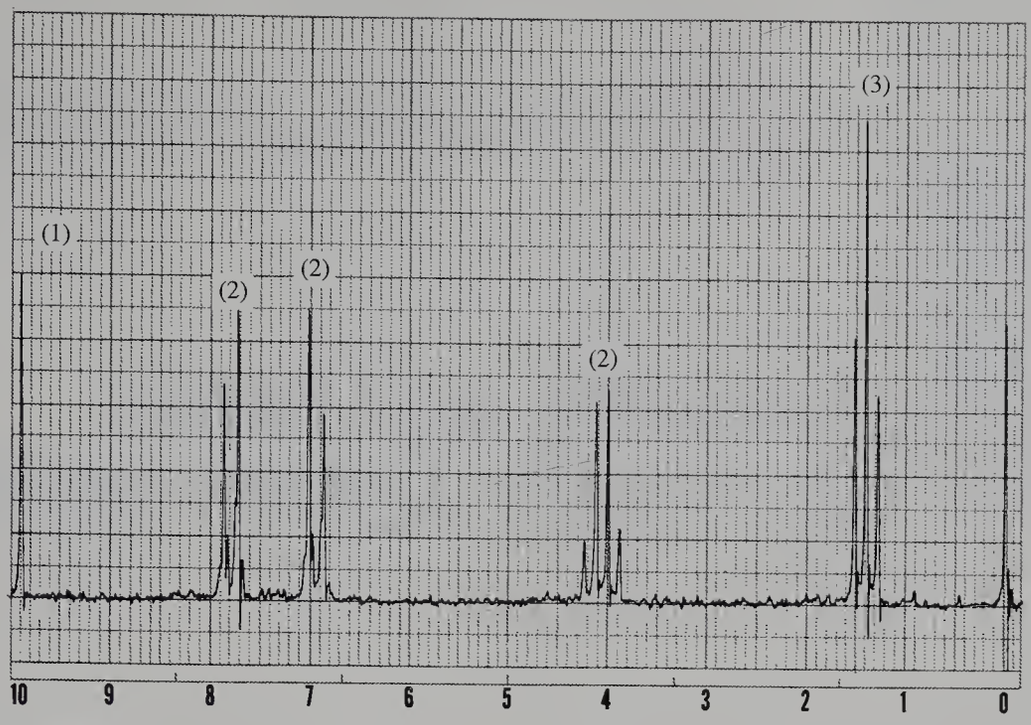
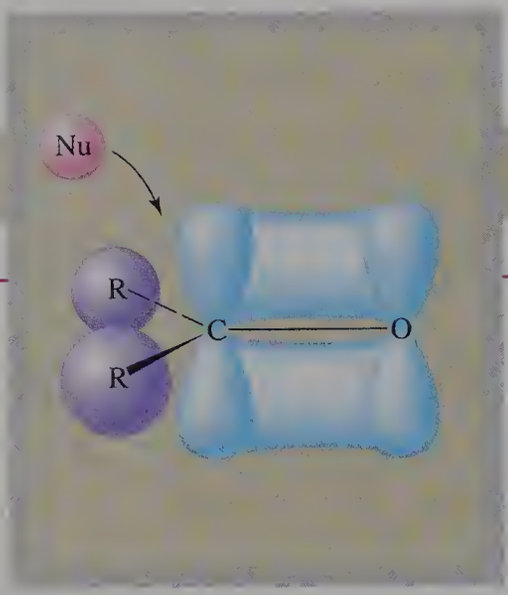


(c)



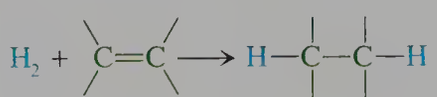


19

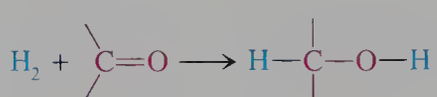
Aldehydes and Ketones: Nucleophilic Addition Reactions

19.1 Thermodynamic Considerations

In Section 7.1, we showed that the standard enthalpy changes (ΔH°_{rxn}) for addition reactions of the carbon–carbon double bond are all negative. We also showed that the energy released in the addition reaction decreases in the order $H_2 > Br_2 > HBr > H_2O$. Only in the case of addition of water is the reaction close to being reversible. In contrast, the standard enthalpy changes for adding these reagents to the carbon–oxygen double bond of aldehydes and ketones differ greatly from the enthalpy changes for adding them to a carbon–carbon double bond. For example, the reaction of H_2 with a carbonyl group is exothermic, but substantially less so than the reaction of H_2 with a carbon–carbon double bond.



$\Delta H^\circ_{rxn} = -118$ kJ mole^{-1}



$\Delta H^\circ_{rxn} = -29$ kJ mole^{-1}

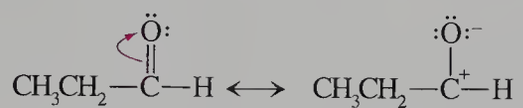
The major reason for the smaller heat of reaction for the carbonyl compound is the greater stability of the π bond of a carbonyl compound compared to the π bond of an alkene. We estimate this factor by subtracting the bond dissociation energy of a single bond from the bond dissociation energy of a double bond. The energy difference between the C—C and C=C bonds is 250 kJ mole^{-1} (60 kcal mole^{-1}). For the C—O and C=O bonds, the difference is 365 kJ mole^{-1} (90 kcal mole^{-1}), substantially larger.

The hydrogenation of an alkene is the most exothermic of the reactions for the various reagents we studied. As a result, we expect the additions of other reagents such as HBr or H_2O to carbon–oxygen double bonds to be either very slightly exothermic or even endothermic reactions. We recall that addition reactions have an unfavorable ΔS°_{rxn}. Hence, when we study the addition reactions of carbonyl compounds,

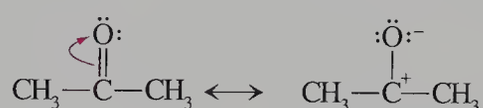
we must pay careful attention to the specific details of the structures of the reactants to determine whether a reaction is favorable or not. Manipulating the experimental conditions when $\Delta G^{\circ}_{rxn} \approx 0$ can shift the position of an equilibrium.

Stability of Aldehydes and Ketones

We will see in this chapter that the relative stabilities of carbonyl groups account for the difference between the equilibrium constants for addition reactions. If a reactant is stable, a reaction that destroys its structure is less likely to take place. Ketones are more stable compounds than aldehydes. The greater stability of ketones compared to aldehydes is related to the stability of carbocations. A carbonyl compound has two resonance forms. One of them has a positive charge on the carbonyl carbon atom and a negative charge on the carbonyl oxygen atom. We recall that alkyl groups stabilize carbocations. Thus, the dipolar resonance form of propanal (propionaldehyde) is not as stable as the dipolar resonance form of propanone (acetone). This increase in stability resembles the increase in stability between a secondary carbocation and a primary carbocation. The dipolar resonance form of an aldehyde is a primary oxycarbocation, whereas the dipolar resonance form of a ketone is a secondary oxycarbocation.



dipolar resonance form of an aldehyde



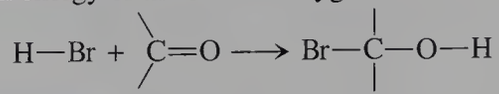
dipolar resonance form of a ketone

The importance of the dipolar resonance forms is reflected in the heats of formation of isomeric carbonyl compounds. The heats of formation of propanal and propanone are -190 kJ mole^{-1} (-45.5 kcal mole^{-1}) and -217 kJ mole^{-1} (-51.9 kcal mole^{-1}), respectively. A difference of approximately 27 kJ mole^{-1} (6.4 kcal mole^{-1}) would change an equilibrium constant by a factor of approximately 10^5 for a reaction converting these isomeric carbonyl compounds to the same product. However, isomeric carbonyl compounds are seldom converted to the same product. For addition reactions, two isomeric products with different heats of formation are also formed. So we also have to consider how the alkyl groups affect the stability of the products. Alcohols result from the hydrogenation of both compounds. The heats of formation of 1-propanol and 2-propanol are -256 kJ mole^{-1} (-61.2 kcal mole^{-1}) and -272 kJ mole^{-1} (-65.1 kcal mole^{-1}), respectively. The stabilities of the two alcohols differ by approximately 16 kJ mole^{-1} (3.9 kcal mole^{-1}). Therefore only part of the difference in the relative energies of propanal and propanone results from stabilization of the dipolar resonance forms by alkyl groups. The stabilization is approximately 11 kJ mole^{-1}, the difference between 27 kJ mole^{-1} and 16 kJ mole^{-1}. This stabilization energy can change an equilibrium constant for a reaction converting a carbon–oxygen double bond into a single bond by a factor of 10^2 at room temperature. Consequently, we can expect addition reactions of carbonyl compounds to be strongly affected by differences in the structure of the carbonyl compound and to a lesser extent by the differences in the structure of the addition prod-

ucts. We conclude that because ketones are more stable than aldehydes, the addition reactions of ketones are thermodynamically less favored than addition reactions of aldehydes.

Problem 19.1

Calculate the ΔH°_{rxn} for the addition of HBr to a carbonyl compound, using 735 kJ mole^{-1} as the bond dissociation energy of the carbon–oxygen double bond.

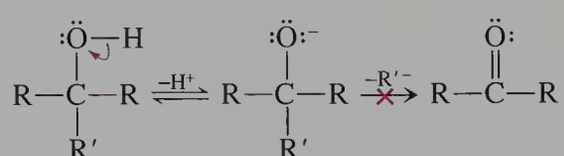


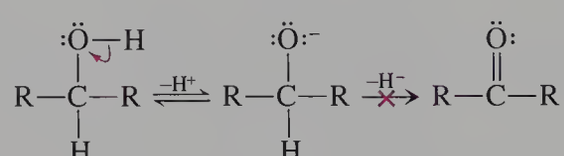
Problem 19.2

The heat of formation of pentanal is –228 kJ mole^{-1} (–54.5 kcal mole^{-1}). Estimate the heat of formation of 2-pentanone.

19.2 Irreversible and Reversible Addition Reactions

We have previously examined two examples of addition reactions of carbonyl compounds that are essentially irreversible, and thus useful synthetic reactions. The first example is the reduction of a carbonyl compound by hydrogen gas. This addition reaction gives an alcohol with the same carbon skeleton as the carbonyl compound (Section 16.9). The second example is addition of a Grignard reagent to a carbonyl compound to give an alcohol with a more complex structure (Section 16.10). These reactions have large equilibrium constants, and the reactions are irreversible. Both a carbanion and a hydride ion are strong nucleophiles with a high attraction for the carbonyl carbon atom. Furthermore, an alkoxide ion has no tendency to eject a hydride ion or a carbanion in a reverse reaction.

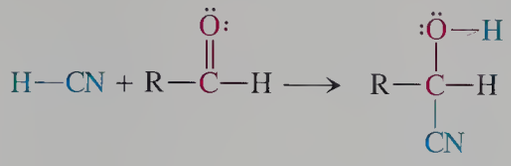




The Nucleophile as a Leaving Group

A nucleophilic addition reaction to a carbonyl group is potentially reversible if the carbon–nucleophile bond is weak and the nucleophile is a good leaving group. We recall that the best leaving groups are the conjugate bases of strong acids. Because an alkane is a very weak acid, an alkyl carbanion is a very strong base, and therefore a poor leaving group. This fact accounts for the irreversible character of the addition of a Grignard reagent to a carbonyl group. Now let's consider the cyanide ion, a species with a negatively charged carbon atom, which is a substantially better leav-

ing group than an alkyl carbanion. Hydrogen cyanide can add to an aldehyde to give a compound called a **cyanohydrin**.



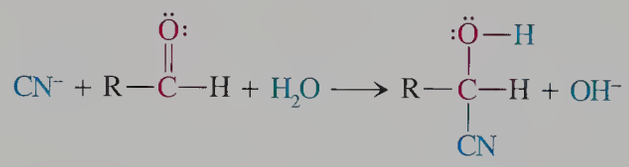
(a cyanohydrin)

The ΔH°_{rxn} for formation of a cyanohydrin is about −25 kJ mole^{-1} (−6 kcal mole^{-1}). Although ΔH°_{rxn} is favorable, the ΔS°_{rxn} is not because two moles of reactants give only one mole of product. Thus, the enthalpy and entropy terms tend to balance each other.

Thermodynamic Versus Kinetic Control of Addition Reactions

The addition reactions of carbon–carbon double bonds are irreversible. The product distribution in these reactions depends on the relative rates of reaction, which in turn reflect the relative energies of the starting materials and the transition state structures. We call this feature **kinetic control**. Many nucleophilic addition reactions to the carbon–oxygen double bond presented in this chapter are reversible, so the products formed respond to different factors than for the addition reactions of alkenes. For nucleophilic addition reactions of carbon–oxygen double bonds, the product distribution often depends on the relative stabilities of the products. We call this feature **thermodynamic control**.

If we change experimental conditions, reversing the direction of an addition reaction, an elimination reaction results. We recall from Section 8.16 that we can make a desired reaction occur by coupling it with a second reaction so that the sum of the two reactions has $\Delta H^\circ_{rxn} < 0$. The net effect is a subtle but important change in the stoichiometry of the reaction. Thus, an elimination reaction can occur by a different pathway than an addition reaction. Let's consider how to reverse the addition reaction of HCN to a carbonyl group by determining whether the following addition reaction readily occurs in the indicated direction.



We can obtain this equation by adding the equation for the addition reaction of HCN to a carbonyl group to the following equation.

$$CN^- + H_2O \rightleftharpoons HCN + OH^- \qquad K_b = 2 \times 10^{-5}$$

What do we know about this reaction? It is the equation for the hydrolysis of cyanide ion, and K_b is much less than 1.0. Thus, the reaction in question for adding CN^- to an aldehyde is not spontaneous. We conclude that under basic conditions, the elimination reaction of a cyanohydrin would readily occur. Increasing the concentration of hydroxide ion drives the equilibrium for the elimination reaction to the right. We also learn that the addition of HCN to an aldehyde is favored under acidic conditions.

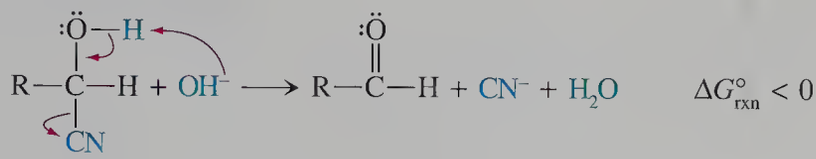


Table 19.1
Equilibrium Constants for Cyanohydrin Formation

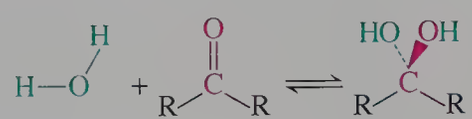
Compound	K_{eq}
acetaldehyde	10,000
acetone	30
3,3-dimethyl-2-butanone	1
benzaldehyde	210
p-methoxybenzaldehyde	30
acetophenone	0.8
cyclopentanone	500
cyclohexanone	10,000

Table 19.1 lists equilibrium constants for the formation of several cyanohydrins. These equilibrium constants largely reflect the differences between the structures of the carbonyl compounds, a subject that we will consider in the next section. These data and those of other addition reactions to be considered in the next section indicate the following trends.

1. Addition reactions with aldehydes occur more readily than addition reactions with ketones.
2. Addition reactions occur less readily when groups bonded to the carbonyl carbon atom donate electrons by resonance.
3. Addition reactions are favored by groups that are located near the carbonyl carbon atom and withdraw electron density from the carbonyl carbon by an inductive effect.

19.3 Hydration of Carbonyl Compounds

The equilibrium constant for an addition reaction of carbonyl compounds depends on both steric and electronic factors. Let's examine the reaction of carbonyl compounds with water to form hydrates. This reaction illustrates the effect of the structure of the reactant and product on the equilibrium constant for the addition reaction.



gem diol
(a hydrate)

The equilibrium constant can be expressed using water as a reactant, but it is more convenient to define K_{hydrn}, which incorporates the molar concentration of water (55 M) in the constant. This expression gives a direct measure of the ratio of hydrate and carbonyl compound at equilibrium..

$$K_{eq} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}]\,[\text{water}]}$$

$$K_{hydrn} = K_{eq}[\text{water}] = \frac{[\text{hydrate}]}{[\text{carbonyl compound}]}$$

Table 19.2
Equilibrium Constants for Hydration Reaction

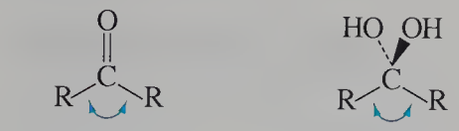
Compound	K_{hydrn}
formaldehyde	2,200
acetaldehyde	1
chloroacetaldehyde	40
acetone	0.0014
benzaldehyde	0.008
acetophenone	0.0000066

The K_{hydrn} values listed in Table 19.2 show the same trends found for the addition of HCN to a carbonyl group. These data show that aldehydes with low molecular weights readily form hydrates. Formaldehyde is over 99% hydrated. Its hydrate is called formalin, a 37% by weight solution of formaldehyde in water formerly used to preserve biological specimens. Other aldehydes are substantially less hydrated. Ketones are normally hydrated less than 1%. The hydrates of aldehydes and ketones usually cannot be isolated, and exist only in solution.

Steric Effects on Addition Reactions

The addition reactions of ketones occur less readily than the addition reactions of aldehydes because ketones are more stable (Section 19.1). A second factor is the larger steric size of the groups bonded to the original sp^2-hybridized carbon atom. In the carbonyl compound the two groups are 120° apart. The two groups bonded to the original carbonyl carbon atom in the product are approximately 109° apart. As a consequence, there is more crowding in the product than in the reactant. Thus, increasing the size of the groups attached to the carbonyl carbon atom decreases the

equilibrium constant for hydration of a carbonyl compound. This steric effect generally occurs only for groups larger than methyl.



120° bond angle keeps groups apart.

109° bond angle moves groups closer.

Inductive Effects on Addition Reactions

The equilibrium constants for the addition reactions of acetone and hexafluoroacetone are dramatically different. There is very little difference in the steric effect of a CH_3 and a CF_3 group because the van der Waals radii of hydrogen and fluorine are similar (Section 4.12). However, the CH_3 and CF_3 groups have different effects on the stability of the carbonyl group. The CF_3 group withdraws electron density from the carbonyl carbon atom and therefore destabilizes the carbonyl group. The CF_3 group has a much smaller destabilizing effect on the addition product. Therefore, the electron-withdrawing CF_3 group increases the equilibrium constant for the addition reaction (Figure 19.1).

destabilized resonance form

stabilized resonance form

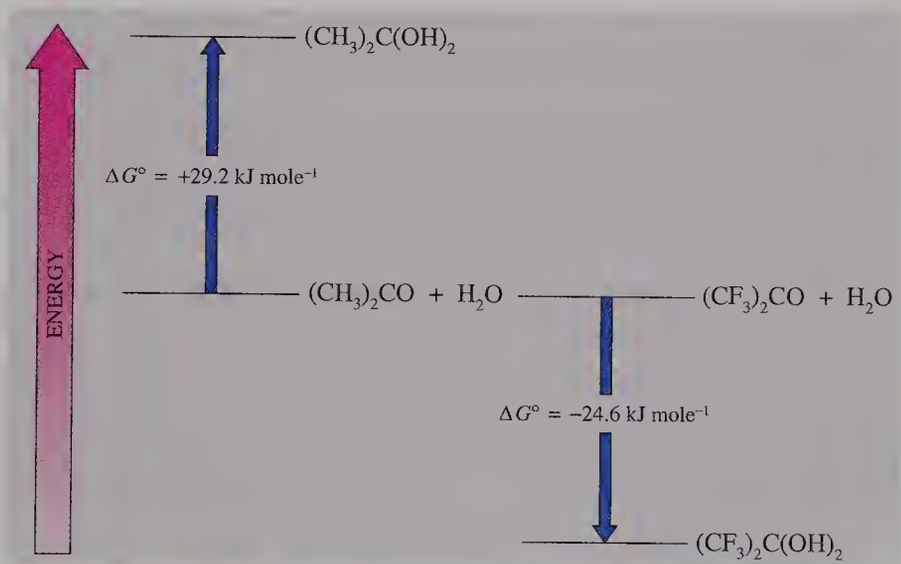


FIGURE 19.1 Inductive Effect on the Equilibrium of Hydration Reactions
The relative energies of acetone and hexafluoroacetone are arbitrarily set as equal. The free energy of hydration of acetone is positive, whereas the free energy of hydration of hexafluoroacetone is negative.

Problem 19.3

The equilibrium constants for the formation of cyanohydrins of benzaldehyde and *p*-methoxybenzaldehyde are approximately 210 and 30, respectively. Is this difference due to a steric effect or an electronic effect?

Problem 19.4

The equilibrium constant for the hydration of trichloroethanal (trichloracetaldehyde) is 3×10^4. Explain why this value differs significantly from the equilibrium constant for ethanal (acetaldehyde).

Sample Solution

The combined electron-withdrawing inductive effect of three chlorine atoms bonded to a carbon atom adjacent to the carbonyl carbon atom destabilizes the polar resonance con-

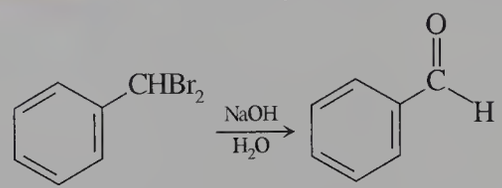
tributor to the structure of the carbonyl compound. The less stable the carbonyl compound, the greater is the driving force for the reaction.

Problem 19.5

The equilibrium constants for the addition of HCN to acetaldehyde and acetone under comparable conditions are 1×10^4 and 30, respectively. What structural features account for the differences between these two values?

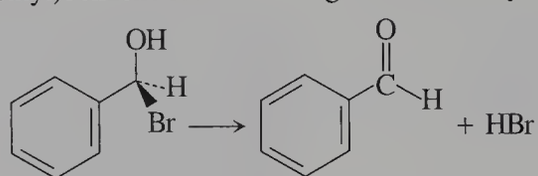
Problem 19.6

Explain why the S_N2 reaction of (dibromomethyl)benzene with NaOH yields benzaldehyde.



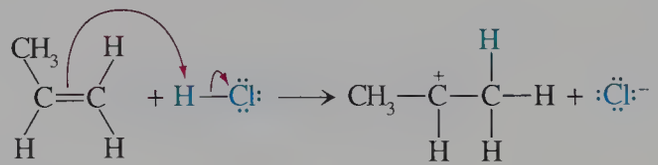
Sample Solution

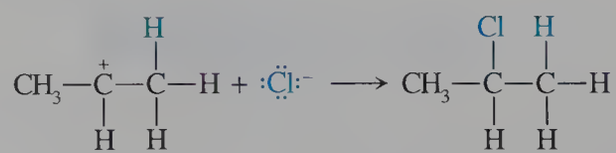
Displacement of the first bromide ion by hydroxide ion yields a benzyl alcohol with the remaining bromine bonded to the benzyl carbon atom. This compound is the potential addition product of hydrogen bromide with benzaldehyde. As indicated in Section 19.1 and illustrated by the calculation in Problem 19.1, the formation of the addition product has $\Delta H^\circ_{rxn} \approx 0$. Moreover, we know that ΔS°_{rxn} is unfavorable for the addition reaction. Thus, the elimination reaction is favored, and the intermediate bromo alcohol formed in the S_N2 reaction of (dibromomethyl)benzene loses HBr to give benzaldehyde.



19.4 Mechanism of Addition Reactions of Carbonyl Compounds

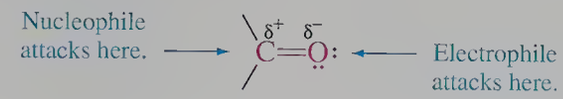
We recall from our discussion of alkenes in Chapter 6 that unsymmetrical reagents such as HCl add to π bonds. In these reactions, the electrophilic proton reacts with the π bond to give an intermediate carbocation whose stability determines the position of electrophilic attack on the double bond. This carbocation subsequently reacts with a nucleophile to give the addition product.



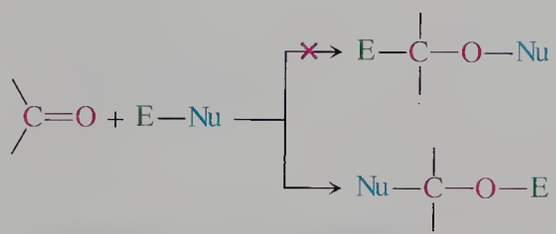


Aldehydes and ketones also contain a π bond. They too react with unsymmetrical reagents to give addition products. The carbonyl bond is polar, and a reagent

reacts so that the electrophilic part bonds to the carbonyl oxygen atom and the nucleophilic part bonds to the carbonyl carbon atom.

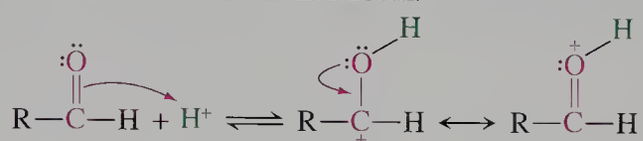


The reaction is regiospecific: only one compound forms.

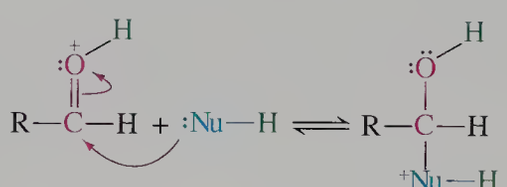


Many reagents that add to carbonyl compounds can be represented by H—Nu. The electrophilic part of the reagent is H^+; the nucleophilic part is $Nu:^-$ (the reagent also may have lone pair electrons, represented H—Nu:). The addition reaction occurs in several steps. The order of the steps depends on whether acid or base catalyzes the reaction. For the acid-catalyzed reaction:

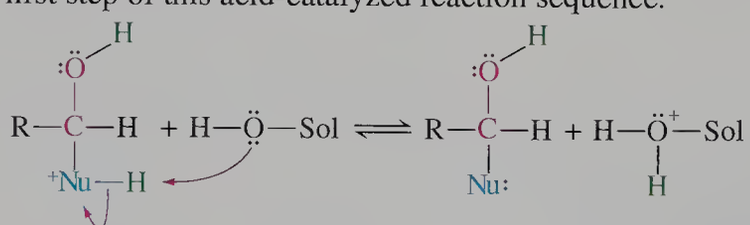
1. A proton (an electrophile and an acid) reacts with the carbonyl oxygen atom (a nucleophilic site or Lewis base) to produce a carbocation, an oxonium ion in the alternate resonance form.



2. The carbocation, which has a vacant $2p$ orbital and therefore acts as a Lewis acid, reacts with the lone pair electrons of H—Nu: functioning as a Lewis base.

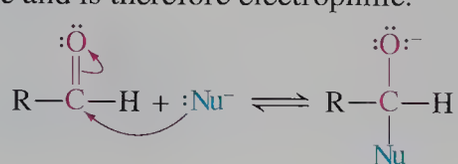


3. An acid–base reaction with a hydroxylic solvent, represented by Sol—O—H, transfers a proton. The transferred proton is now available for the first step of this acid-catalyzed reaction sequence.

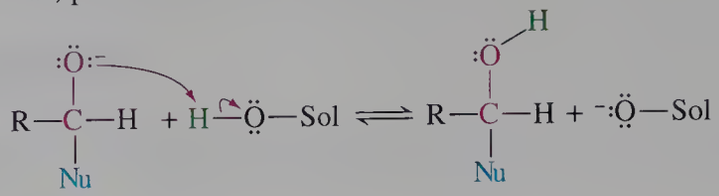


The sequence of steps differs for a base-catalyzed reaction:

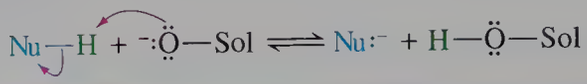
1. The nucleophile, $Nu:^-$, attacks the carbonyl carbon atom, which has a partial positive charge and is therefore electrophilic.



2. An acid–base reaction with a hydroxylic solvent, represented as Sol—O—H, protonates the alkoxide ion.



3. The conjugate base of the solvent removes a proton from H—Nu to regenerate $Nu:^-$.



Problem 19.7

Write the steps for the acid-catalyzed hydration of CH_3CHO in aqueous solution.

19.5 Kinetic Effects in Addition Reactions

Although addition of a nucleophile to carbonyl compounds may be reversible, we still want to know how fast the reactions occur. We can use Le Châtelier's principle to adjust the reaction conditions to "drive" the reaction toward the products, but the time required to reach equilibrium remains important.

Nucleophiles react faster with aldehydes than with ketones for electronic and steric reasons. First, we consider electronic effects. Two alkyl groups attached to the carbonyl carbon atom of the ketone donate electron density to the carbonyl carbon atom and stabilize its partial positive charge. The carbonyl carbon atom of an aldehyde is bonded to only one alkyl group. Therefore, the carbonyl carbon atom of an aldehyde has a larger partial positive charge than that of a ketone. As a consequence, nucleophiles react faster with aldehydes than with ketones.

less stabilization
more reactive

more stabilization
less reactive

Next, let's consider the role of steric effects, the sizes of groups, in the reactivity of aldehydes and ketones. Because a ketone has two alkyl groups attached to the carbonyl carbon atom, it is sterically hindered relative to the carbonyl carbon atom of an aldehyde, which has only a hydrogen atom and one alkyl group bonded to it. Hence, a nucleophile can approach the carbonyl group of an aldehyde more readily, leading to a faster reaction (Figure 19.2).

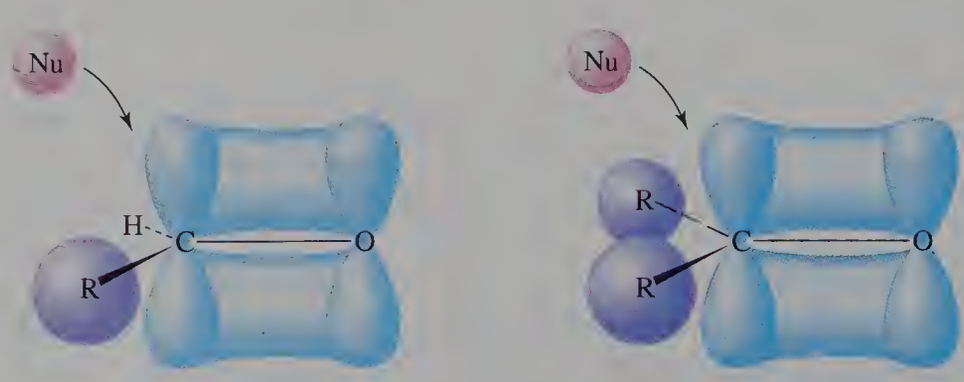
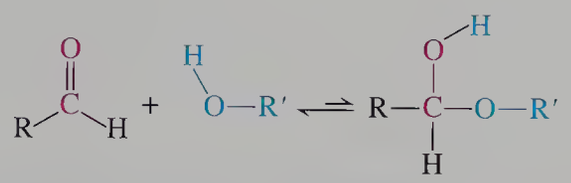


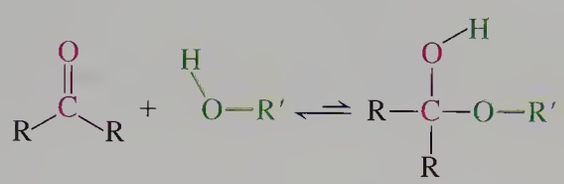
FIGURE 19.2 Effect of Steric Hindrance on Addition Reactions
The reaction of a nucleophile with a carbonyl carbon atom depends on the number and size of the groups bonded to that atom. Aldehydes have only one alkyl group and react faster than ketones that have two alkyl groups.

19.6 Addition of Alcohols to Carbonyl Compounds

We have seen that water adds to carbonyl compounds to give unstable hydrates that exist in equilibrium with the reactants. Alcohols also react with carbonyl compounds. In the case of an aldehyde, a **hemiacetal** results. A ketone forms a **hemiketal**. Both classes of compounds have a hydroxyl group and an alkoxy group bonded to the same carbon atom.



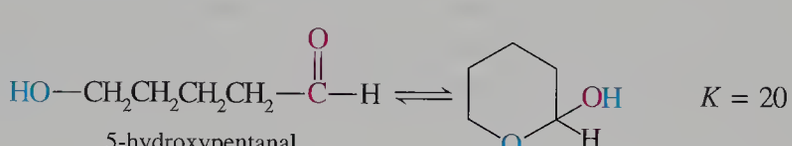
(a hemiacetal)



(a hemiketal)

These structurally related compounds differ slightly. The hemiacetal has a hydrogen atom and an alkyl group attached to the original carbonyl carbon atom, whereas the hemiketal has two alkyl groups attached. The IUPAC has adopted the term hemiacetal to represent both types of compounds. However, hemiacetal and hemiketal remain in common usage because they remind us of a structural difference reflected in the magnitude of the equilibrium constants for reactions of these compounds.

Hemiacetals and hemiketals are often unstable compounds. That is, the equilibrium constant for formation of either a hemiacetal or a hemiketal is less than 1, and the equilibrium positions for the reactions favor the reactants. However, when both the carbonyl group and the alcohol are part of the same molecule, the reaction gives a cyclic compound. The equilibrium constant for formation of a cyclic hemiacetal is greater than 1, as shown for 5-hydroxypentanal.

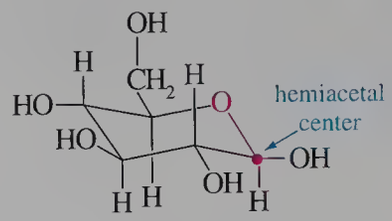


5-hydroxypentanal

$K = 20$

The ΔH°_{rxn} for the intramolecular reaction is approximately the same as for an intermolecular reaction. The reason for the difference in the two equilibrium constants lies in ΔS°_{rxn} for the intramolecular reaction compared to ΔS°_{rxn} for the intermolecular reaction. In the intermolecular reaction, two molecules combine to yield a single molecule of product, ΔS°_{rxn} is negative, and the reaction is not favored. The intramolecular reaction transforms one molecule into a single, isomeric product molecule. The ΔS°_{rxn} for the intramolecular reaction may be slightly negative because of some restriction of rotational freedom in the cyclic hemiacetal. However, ΔS°_{rxn} for an intramolecular reaction is much less negative than ΔS°_{rxn} for an intermolecular reaction. In the intermolecular reaction, the entropy term outweighs the enthalpy term and the hemiacetal does not form. In contrast, the enthalpy term in the intramolecular reaction dominates and the hemiacetal forms. In fact, carbohydrates

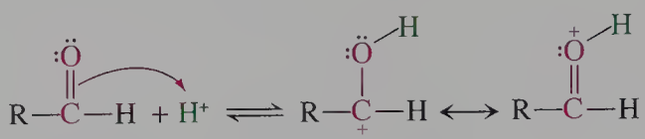
such as glucose (Chapter 20), which contain both carbonyl and hydroxyl groups, exist mainly as cyclic hemiacetals or hemiketals and only to a small extent as open-chain molecules.



a cyclic form of glucose

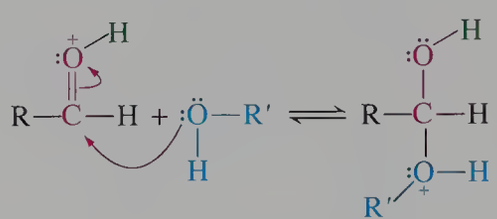
Mechanism of Acid-Catalyzed Addition of Alcohols

The acid-catalyzed reaction adding an alcohol to an aldehyde or ketone occurs in several steps. The first is protonation of the carbonyl oxygen atom (an electron pair donor, or Lewis base) to produce a carbocation.

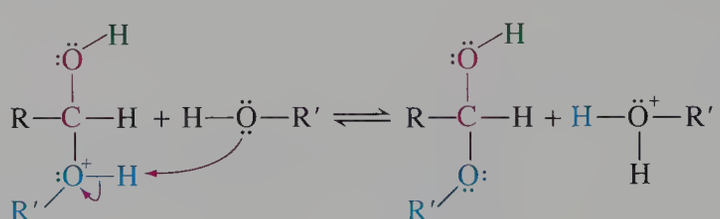


carbocation

The carbocation, which has a vacant $2p$ orbital and therefore acts as a Lewis acid, then reacts with the lone pair electrons of the oxygen atom of the alcohol (R´—OH).



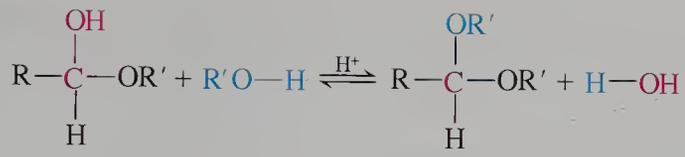
Finally, an acid–base reaction with another R´—OH transfers a proton. The transferred proton becomes available for the first step of the reaction sequence, acting as an acid catalyst for the reaction.



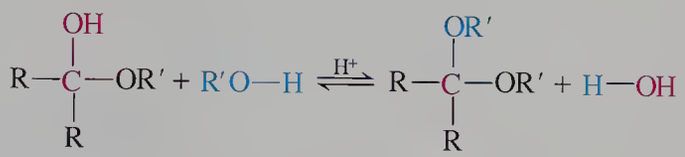
(a hemiacetal)

19.7 Formation of Acetals and Ketals

In the reaction we considered above, one molecule of aldehyde or ketone reacts with one molecule of alcohol to give a hemiacetal or hemiketal. In an excess of alcohol, a hemiacetal or hemiketal reacts to form an equilibrium mixture of an acetal or ketal, respectively. An alkoxy group (—OR) replaces the —OH group in either a hemiacetal or a hemiketal. The reactions are shown below.

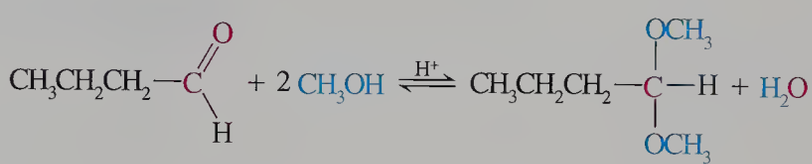


(an acetal)

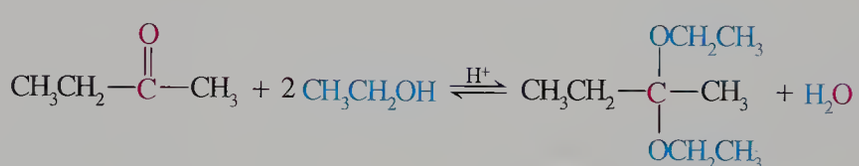


(a ketal)

Note that both **acetals** and **ketals** have two alkoxy groups (—OR′) attached to the same carbon atom. An acetal has a hydrogen atom and an alkyl group attached to the carbon atom, whereas the ketal has two alkyl groups attached. The formation of an acetal or a ketal requires two molar equivalents of alcohol per mole of the original carbonyl compound.

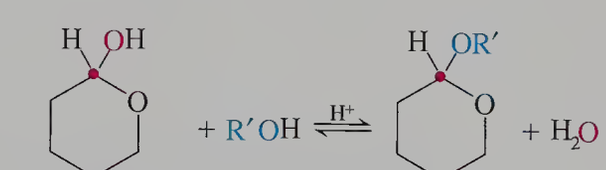


methyl acetal of butanal



ethyl ketal of butanone

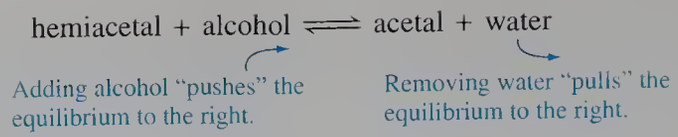
The acetal and ketal shown in the above reactions are acyclic compounds. However, some hemiacetals and hemiketals have cyclic structures and react with alcohols to produce cyclic acetals and cyclic ketals. Consider the cyclic hemiacetal of 5-hydroxypentanal. Its ring oxygen atom was originally the 5-hydroxyl oxygen atom. When this cyclic hemiacetal reacts with the alcohol (R′—OH), the product is a cyclic acetal. The oxygen atom in the —OR′ group of the acetal originated in the alcohol. We will see this reaction again when we consider carbohydrates in Chapter 20.



cyclic hemiacetal cyclic acetal

Reactivity of Acetals and Ketals

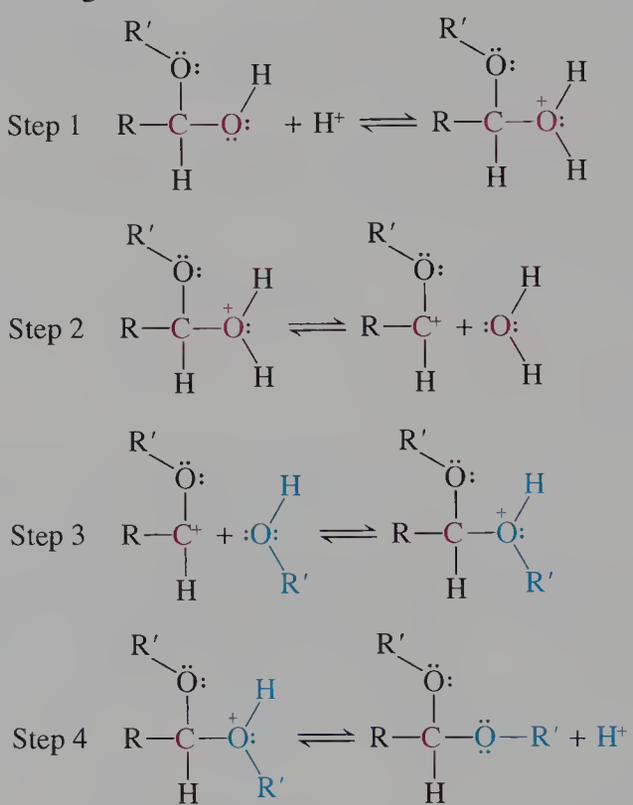
The conversion of a hemiacetal to an acetal and the conversion of a hemiketal to a ketal are reversible in acid solution. Removing the water formed in the reaction or increasing the concentration of alcohol shifts the position of the equilibrium to the right, toward formation of an acetal or ketal.



The reverse reaction, acid-catalyzed hydrolysis of acetals or ketals, occurs readily in the presence of water. Acetals and ketals react with water in a hydrolysis reaction to give a carbonyl compound and the alcohol. However, acetals and ketals do not react in neutral or basic solution. The reason for this difference becomes evident when we examine the proposed mechanism.

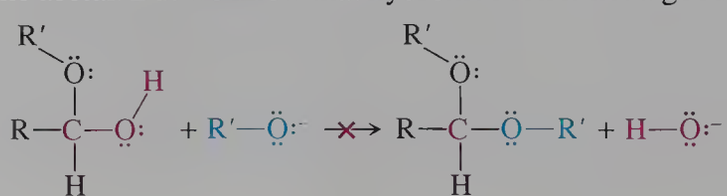
Mechanism of Acetal and Ketal Formation

The conversion of hemiacetals and hemiketals to acetals and ketals occurs in four reversible acid-catalyzed steps. These steps are shown for the conversion of a hemiacetal to an acetal. In step 1, the acid protonates the oxygen atom of the hydroxyl group. In step 2, water leaves, and a carbocation forms. In step 3, the carbocation combines with the alcohol. In step 4, the proton bonded to the oxygen atom leaves, giving an acetal. Note that H^+ acts as a catalyst: It starts the reaction by protonating the hemiacetal and is regenerated in the last step when the acetal forms.

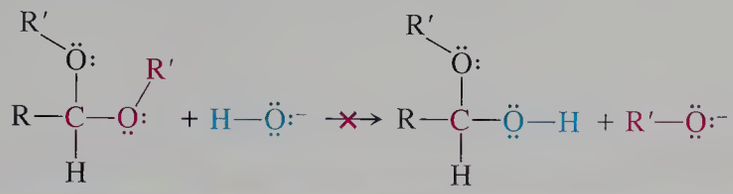


Step 2 occurs readily for two reasons. First, the OH group is protonated to form water, a better leaving group than hydroxide ion. Second, the oxygen atom's lone pair electrons resonance stabilize the carbocation formed in this S_N1 reaction.

Base catalyzes neither acetal formation nor the reverse reaction, called acetal hydrolysis. An S_N2 displacement of hydroxide by alkoxide would be required in the formation of the acetal. But we know that hydroxide ion is not a good leaving group.

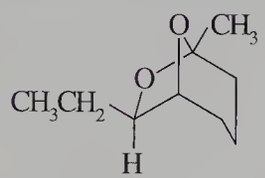


Similarly, the hydrolysis of an acetal by base would require an S_N2 displacement of an alkoxide ion, and this reaction does not occur either.



Problem 19.8

Identify the functional group of brevicomin, the sex attractant of a species of pine beetle.



Problem 19.9

Write the structure of the acetal or ketal formed by each of the following pairs of compounds.

(a) cyclopentanone and methanol

(b) 3-pentanone and ethanol

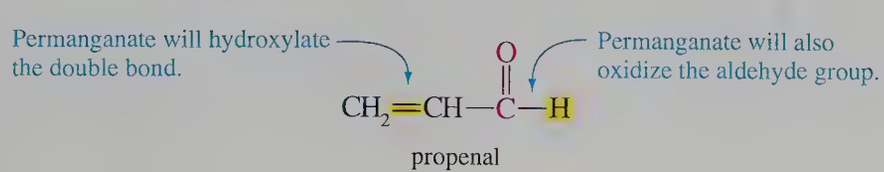
(c) benzaldehyde and 1-propanol

19.8 Acetals as Protecting Groups

Synthetic transformations at one functional group in a molecule containing two or more functional groups are often complicated by interfering reactions at the other reactive sites. To eliminate the complications of reactions at undesired sites, we use **protecting groups**. These convert a functional group to an unreactive form that can be converted back to the original functional group after we achieve other synthetic goals. A protecting group is selected so that it is easy to make and easy to remove at the end of the synthesis. Both reactions should occur in high yield.

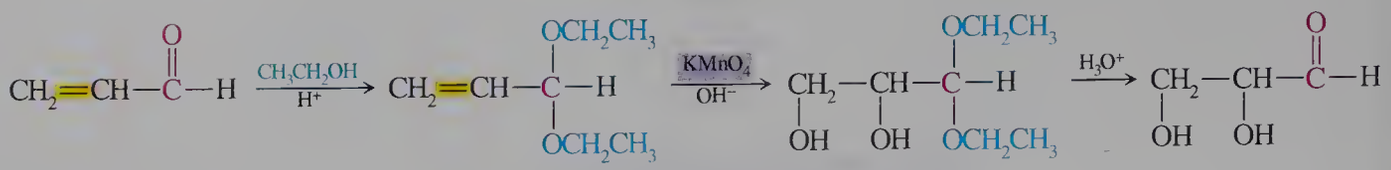
The formation of acetals (or ketals) followed by their hydrolysis at a later stage in a synthetic sequence is a useful technique to protect the carbonyl group. With the exception of acid-catalyzed hydrolysis, acetals are unreactive. We recall that ethers, which resemble acetals, are unreactive toward bases, oxidizing agents, and reducing agents. They are so unreactive they are used as solvents for the Grignard reagent. Acetals are also unreactive toward the same reagents. Thus, the very reactive aldehyde (or ketone) can be protected or "masked" to prevent its reaction with reagents required to transform other functional groups in the same molecule. Finally, an acid-catalyzed reaction releases the carbonyl functional group. When we select conditions for the reactions of other functional groups, we must avoid acidic conditions because the acetal will hydrolyze.

Let's first consider the use of an acetal to protect the aldehyde of propenal when the goal is to oxidize the carbon–carbon double bond using basic potassium permanganate. This reagent would also oxidize an aldehyde group.



propenal

The aldehyde group is first protected by converting it to an acetal using an alcohol such as ethanol. Because the dihydroxylation using permanganate occurs under basic conditions, the acetal is stable, and the aldehyde remains protected. The acetal is hydrolyzed in a final step using a mildly acidic aqueous solution.

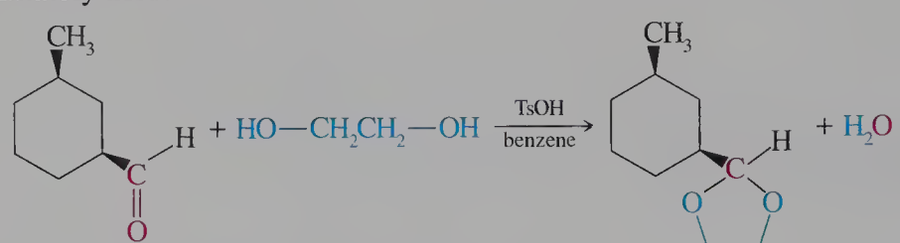


Synthesis of Cyclic Acetals

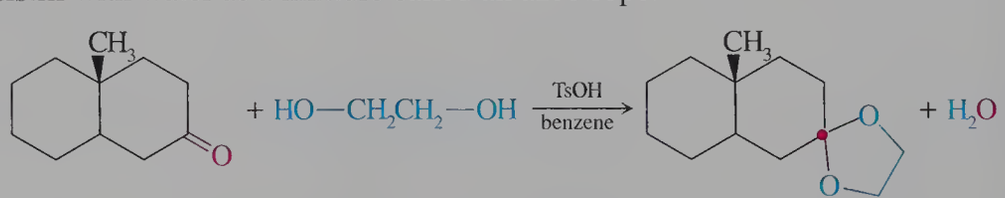
The balanced equation for the formation of an acetal with an alcohol such as ethanol, shown below, suggests one disadvantage to the use of alcohols as protecting groups. The reaction converts three molecules into two, and as a consequence ΔS°_{rxn} is negative. Therefore, it is harder to drive the reaction to the right, even when using excess alcohol and removing the water formed. Consider the reaction of an aldehyde with ethanol using *p*-toluenesulfonic acid (TsOH) as the acid catalyst.

$$RCHO + 2\,CH_3CH_2OH \underset{}{\overset{TsOH}{\rightleftharpoons}} RCH(OCH_2CH_3)_2 + H_2O \qquad \Delta S^\circ_{rxn} < 0$$

The simple expedient of using a diol to form the acetal eliminates this unfavorable entropy term. The most common diol used is 1,2-ethanediol (ethylene glycol). In this reaction, two molecules of reactant yield two molecules of product, and the ΔS°_{rxn} is approximately zero.



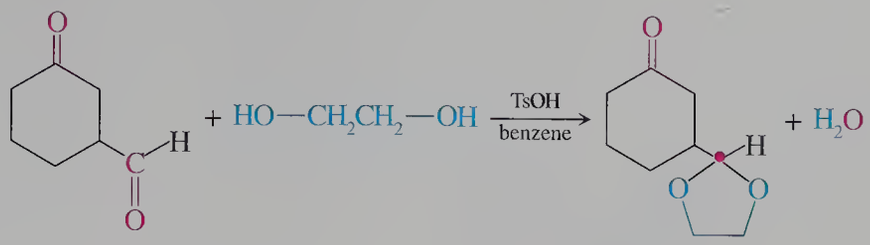
For most ketones, the equilibrium position for ketal formation using simple alcohols is so far on the side of the reactants that highly specialized conditions are required. However, as a result of eliminating the unfavorable entropy term, ethylene glycol reacts with ketones to give good yields of ketals. Distillation with toluene or benzene drives the position of the equilibrium toward products. These substances codistill with water as a mixture called an azeotrope.



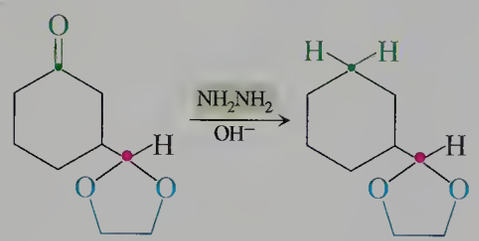
Selective Acetal Formation

If there are substantial differences in the equilibrium constants for acetal formation of two carbonyl groups, it may be possible to form one acetal in preference to another. Selective acetal formation occurs in the competition between an aldehyde and

a ketone. For example, 3-oxocyclohexanecarbaldehyde reacts with one equivalent of ethylene glycol to give a protected aldehyde group.



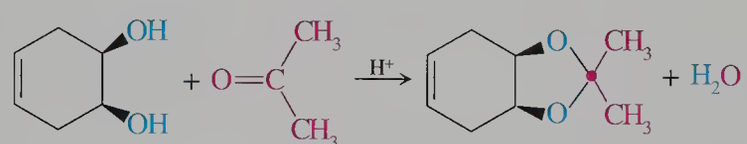
As a consequence, functional group transformations of the ketone group are now possible without competitive reactions that would occur in the original unprotected compound. For example, the Wolff–Kishner reduction can reduce the ketone to a methylene group.

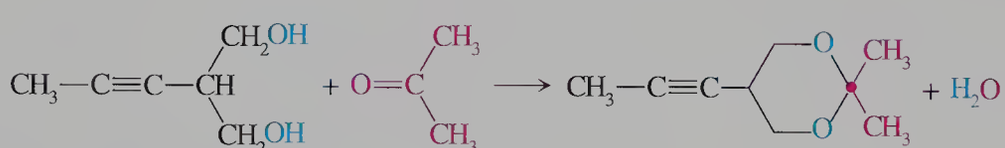


Note that a Clemmensen reduction would fail because it uses HCl. This reagent would unprotect the aldehyde, and thus both carbonyl groups would be reduced.

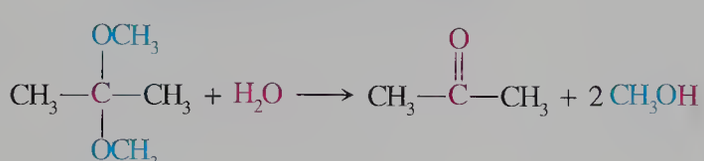
Protection of Alcohols by Acetal Formation

If alcohols can be used to protect carbonyl compounds by formation of an acetal (or ketal), then the same method can protect an alcohol using a carbonyl compound. For example, vicinal diols can be protected by forming a cyclic five-membered ketal with acetone. Similarly, 1,3-diols react with acetone to form cyclic six-membered ketals.



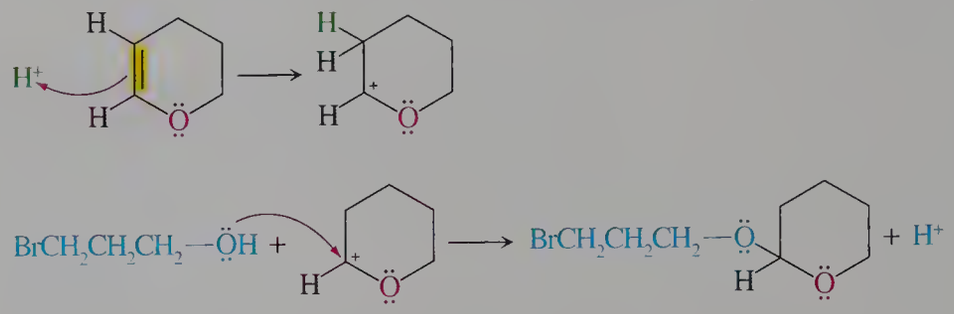


2,2-Dimethoxypropane drives such reactions to completion. It is an unstable ketal that reacts with the water generated by the reaction of the diol with acetone.



Both enthalpy and entropy considerations strongly favor the hydrolysis of the methyl ketal of acetone, and the acetone formed helps to drive the reaction of the diol to form the cyclic ketal.

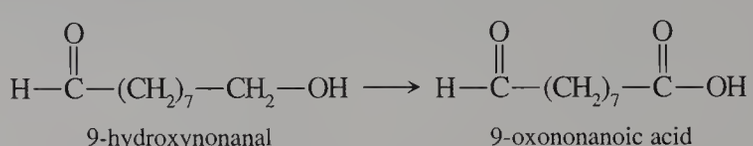
Alcohols containing only one hydroxyl group can also be protected by forming an acetal. However, we recall that ΔS°_{rxn} strongly disfavors the reaction of two moles of an alcohol with a carbonyl compound. Therefore, a special technique is used to form the acetal protecting group. Alcohols react regiospecifically with dihydropyran in an acid-catalyzed addition reaction. The carbocation formed is resonance stabilized by the lone pair electrons of the ring oxygen atom. Subsequent attack of the carbocation by the nucleophilic oxygen atom of the alcohol followed by deprotonation yields an alkoxy-substituted tetrahydropyran known as a THP derivative.



Although the addition of an alcohol to the double bond forms an ether linkage, the THP derivative is not an ether. Two oxygen atoms are bonded to a common carbon atom, making the compound an acetal. The THP derivative is stable unless it is exposed to aqueous acid. Therefore the original alcohol is protected at the hydroxyl group. The THP derivative is hydrolyzed with dilute acid to regenerate the hydroxyl group after other synthetic transformations have been carried out.

Problem 19.10

The following reaction cannot be accomplished directly using potassium permanganate as the oxidizing agent. Explain why not, and outline a method to obtain the product using appropriate protecting groups.



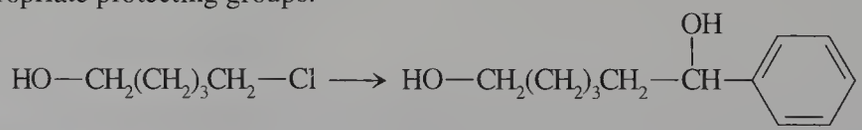
9-hydroxynonanal 9-oxononanoic acid

Sample Solution

Aldehydes are oxidized even by mild oxidizing agents. Potassium permanganate is a strong oxidizing agent that will oxidize the hydroxy aldehyde to form a dicarboxylic acid. The aldehyde group must first be protected by forming an acetal. Although alcohols such as methanol or ethanol could be used, the equilibrium constant for formation of a cyclic acetal makes ethylene glycol the reagent of choice. In the subsequent oxidation of the alcohol, the acetal remains intact. Finally, hydrolysis with dilute acid liberates the free aldehyde group, and the desired product results.

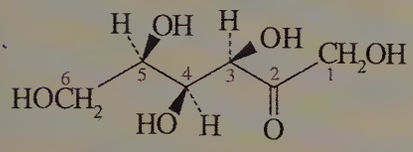
Problem 19.11

The following reaction cannot be accomplished by preparing a Grignard reagent and reacting it with benzaldehyde. Explain why not, and outline a method to obtain the product using appropriate protecting groups.

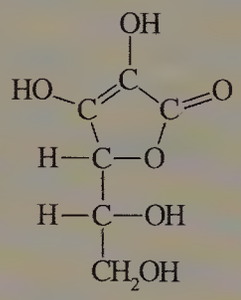


Vitamin C Synthesis

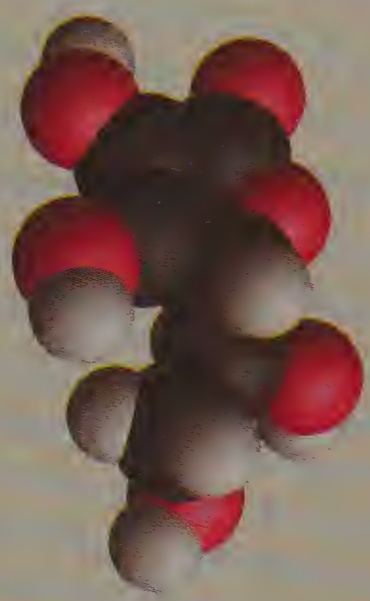
The commercial demand for vitamin C as a food additive as well as in vitamin supplements has led to an industrial-scale synthesis of this compound. Virtually all commercial vitamin C is synthetic. The synthesis uses sorbose, a carbohydrate that is isomeric with other better known carbohydrates such as fructose and glucose.



sorbose

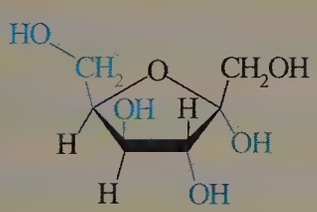


vitamin C

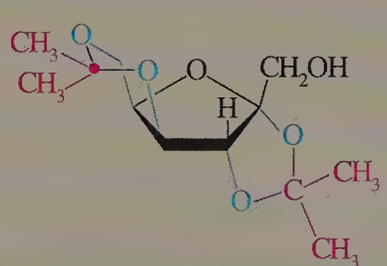


vitamin C

Selective oxidation of the primary hydroxyl group at C-1 to give a carboxylic acid is required. Competitive oxidation at the primary hydroxyl group at C-6 as well as at the secondary hydroxyl groups must be avoided. Sorbose exists primarily as a cyclic hemiacetal formed between the C-2 carbonyl group and the C-5 hydroxyl group. Thus, the compound exists as a tetrahydrofuran with cis C-2 and C-3 hydroxyl groups. In addition, the C-4 hydroxyl group and the C-6 atom with its attached hydroxyl group are also cis. Reaction with propanone (acetone) forms two cyclic ketals within the structure. A five-membered ketal forms at C-2 and C-3 and a six-membered ketal at C-4 and C-6.

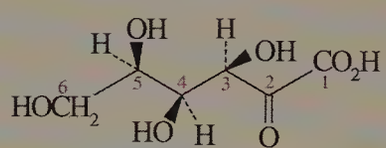


cyclic form of sorbose

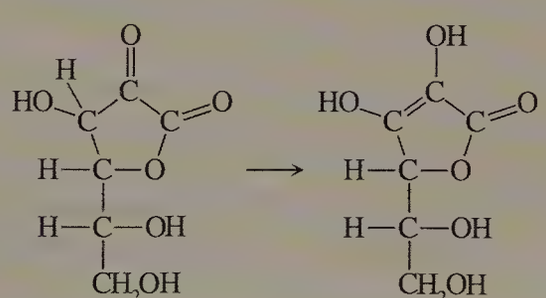


diacetonide of sorbose

With the exception of the C-1 hydroxyl group, all other hydroxyl groups are protected. Oxidation of the protected sorbose followed by release of the hydroxyl groups in an acid-catalyzed hydrolysis reaction gives the desired carboxylic acid.

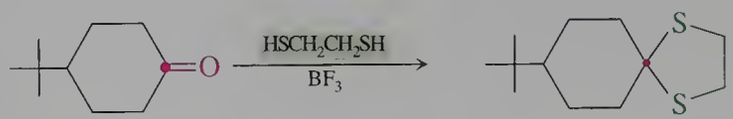


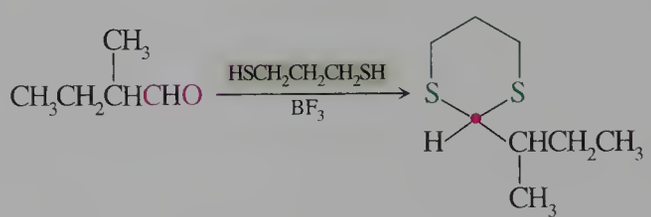
The cyclic ester formed by reaction of the carboxylic acid with the C-4 hydroxyl group is vitamin C. The "ketone" actually exists as an enol tautomer that allows conjugation between the carbon–carbon double bond and the carbonyl group of the ester.



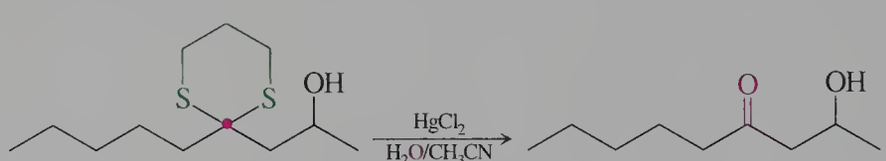
19.9 Thioacetals and Thioketals

Thiols are the sulfur analogs of alcohols (Section 16.11). The sulfur atom of a thiol is a better nucleophile than the oxygen atom of an alcohol. Thus, thiols react with aldehydes or ketones to form thioacetals or thioketals by a mechanism similar to that described for acetals and ketals. These sulfur derivatives form in high yield because the equilibrium constant for thioacetal formation is much greater than that for acetal formation. We use Lewis acids such as BF_3 or $ZnCl_2$, rather than protic acids, to catalyze the formation of the thioacetal. Both 1,2-ethanedithiol and 1,3-propanedithiol are used to form cyclic thioacetals and thioketals.

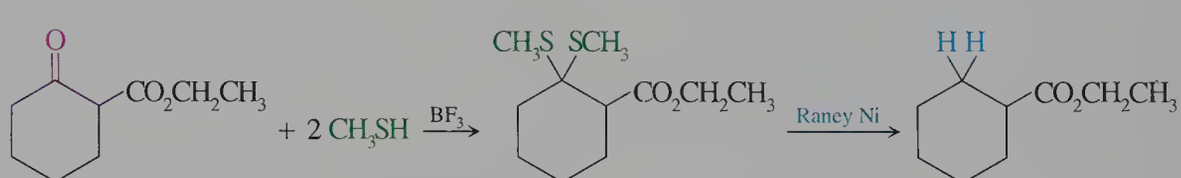




Like acetals, thioacetals are stable in basic solution. However, thioacetals also survive under the acidic conditions that would hydrolyze an acetal. Thus, they protect a carbonyl group and allow us to react many other functional groups under acidic or basic conditions. Because thioacetals are stable in acid, their hydrolysis requires use of mercuric chloride in aqueous acetonitrile. The formation of an insoluble mercury(II) sulfide provides the driving force for the reaction.



Thioacetals are valuable intermediates for organic synthesis in their own right. For example, thioacetals are desulfurized by Raney nickel to give the corresponding hydrocarbon.



The formation of a thioacetal followed by desulfurization corresponds to the net reduction of a carbonyl group to a methylene group. Therefore, this method complements the Wolff–Kishner and Clemmensen reductions and has the advantage that the desulfurization reaction requires neither acid nor base.

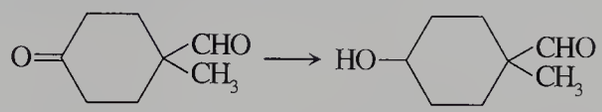
Problem 19.12

Draw the structures of the products of each of the following combination of reagents.
(a) cyclohexanone and methanethiol

(b) 2-butanone and 1,2-ethanedithiol
(c) cyclohexanecarbaldehyde and 2-thioethanol

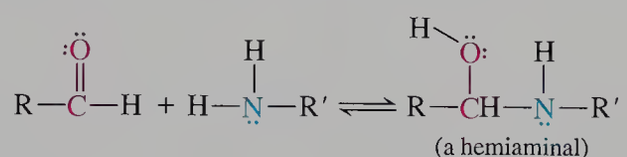
Problem 19.13

Outline the steps required to accomplish the following transformation using a thioacetal derivative in one of the steps.



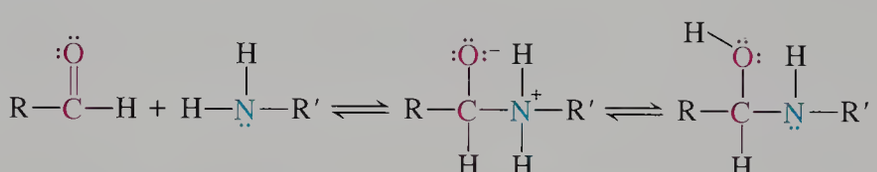
19.10 Addition of Nitrogen Compounds

Ammonia and amines of the general formula RNH_2 may be considered nitrogen analogs of water and alcohols, respectively. They are more nucleophilic than the oxygen analogs (Section 10.1) and react faster with carbonyl groups of aldehydes and ketones. In these reactions, a nitrogen analog of a hemiacetal, called a **hemiaminal**, forms.

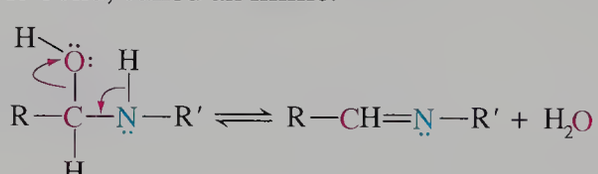


(a hemiaminal)

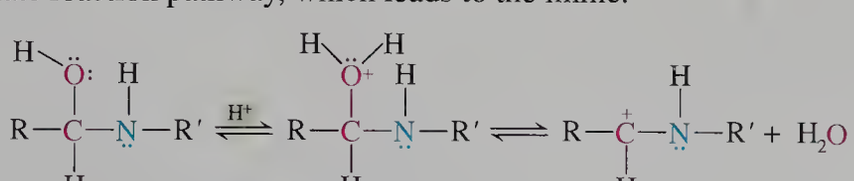
A hemiaminal forms by nucleophilic attack of nitrogen on the carbonyl carbon atom, followed by loss of a proton from the nitrogen atom and the gain of a proton by the oxygen atom. These are intermolecular acid–base proton reactions between the various species in the solution.



The hemiaminal does not react with a second mole of amine to form the nitrogen analog of an acetal because it readily loses water to form a compound with a carbon–nitrogen double bond, called an **imine**.

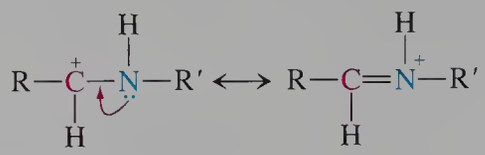


The mechanism for this dehydration resembles that of the conversion of a hemiacetal to a carbonyl compound (Section 19.6). Although protonation of the more basic nitrogen atom of the hemiaminal does occur, this reaction leads only to the reverse of the reaction that formed it. However, protonation of the hydroxyl group opens up an alternate reaction pathway, which leads to the imine.



(an oxonium ion)

The carbocation formed by loss of water is resonance stabilized by the lone pair electrons of nitrogen in the same way that the lone pair electrons of oxygen stabilize the oxocarbocation intermediate in the formation of acetals. However, nitrogen is more effective in stabilizing the carbocation because it is less electronegative than oxygen and is better able to supply electron density by resonance. (We observed the same order of electron-donating properties of nitrogen and oxygen in Section 14.5 when we considered substituent effects on electrophilic aromatic substitution reactions.)

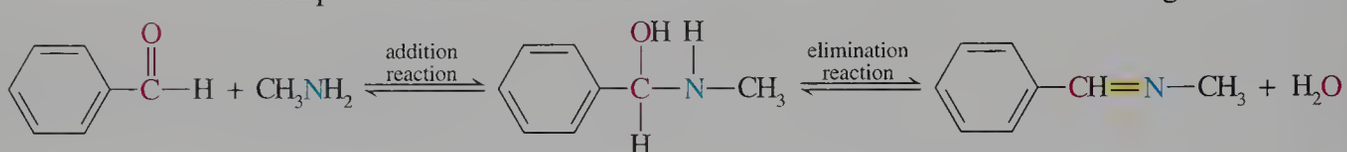


(more stable)

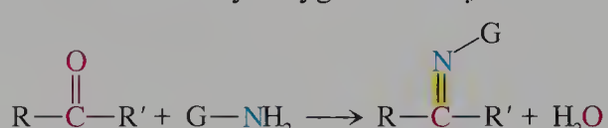
resonance forms of an iminium ion

Loss of a proton from the iminium ion gives the imine product. Note that all reactions leading to imine are reversible. Therefore, an imine may be hydrolyzed to form an amine and a carbonyl compound. Le Châtelier's principle allows us to predict the conditions required to drive the reaction in the given direction. Removing water as it forms favors formation of the imine. Adding excess water favors imine hydrolysis.

The overall reaction of a carbonyl compound with an amine is called an **addition–elimination reaction**. In the addition step, the nitrogen atom bonds to the carbonyl carbon atom and a hydrogen atom bonds to the carbonyl oxygen atom. The initial addition product then loses a molecule of water in an elimination reaction to give an imine.

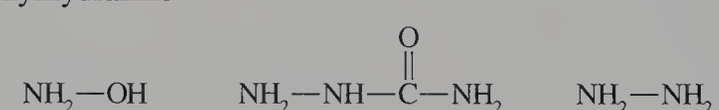


The net result of reacting an aldehyde or ketone with GNH_2, where G represents any group, is replacement of the carbonyl oxygen atom by G—N=.

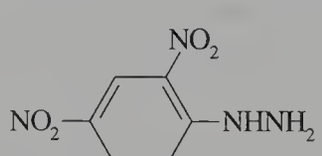


Stable Imine Derivatives

Some compounds in which a nitrogen atom bonds directly to electronegative groups with lone pair electrons form stable imine derivatives. These compounds include hydroxylamine, semicarbazide, hydrazine, and substituted hydrazines, such as 2,4-dinitrophenylhydrazine.



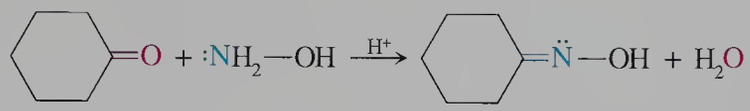
hydroxylamine semicarbazide hydrazine



2,4-dinitrophenylhydrazine

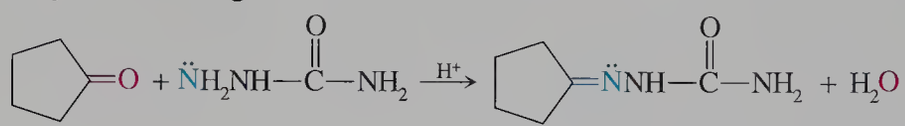
Many liquid carbonyl compounds react with these compounds to give solid derivatives. For example, cyclohexanone reacts with hydroxylamine to give a solid oxime

that melts at 91 °C. An "unknown" carbonyl compound may be identified by comparing the melting point of its derivative with the melting points of derivatives of known carbonyl compounds. In this way, the identity of the "unknown" compound is established as cyclohexanone if its oxime melts at 91 °C and the melting points of other derivatives also match known values.



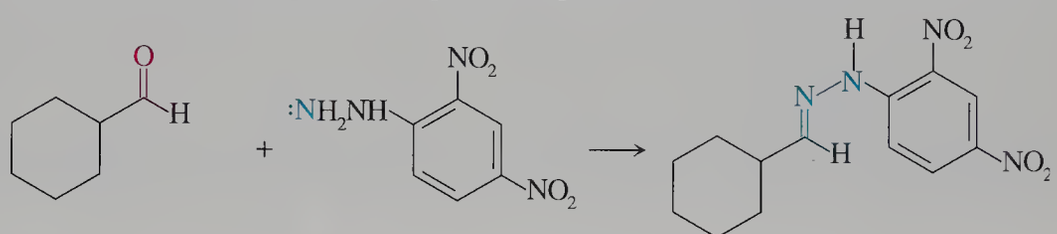
cyclohexanone oxime
(mp 91 °C)

The reaction of carbonyl compounds with semicarbazide yields semicarbazones. The reaction occurs at only one of the two possible NH_2 groups. The lone-pair electrons of the NH_2 group bonded to the carbonyl are less nucleophilic than those of the other NH_2 group because the carbonyl carbon atom decreases the electron density at that nitrogen atom.



cyclopentanone semicarbazone

An aldehyde reacts with 2,4-dinitrophenylhydrazine to give a bright, yellow-to-orange crystalline solid called a **2,4-dinitrophenylhydrazone** (2,4-DNP). Chemists used the melting points of these derivatives to identify "unknown" compounds before the development of spectroscopic methods.



cyclohexanecarboxaldehyde

cyclohexanecarboxaldehyde 2,4-DNP

Problem 19.14

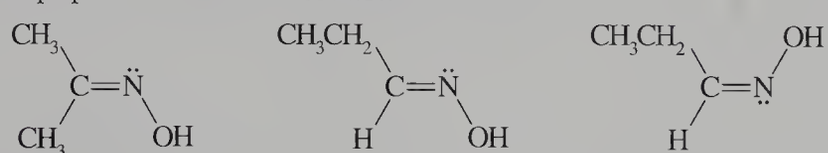
Two equivalents of benzaldehyde react with hydrazine to give a compound with molecular formula $C_{14}H_{12}N_2$. Draw the structure of the compound.

Problem 19.15

Two isomers of propanal oxime exist, but only one of propanone oxime. Consider the hybridization of the nitrogen atom in an oxime and the geometry of the molecules, and explain this fact.

Sample Solution

Because the nitrogen atom is sp^2-hybridized, propanol oxime has a C=N—O angle of 120° and, like an alkene, can exist as cis-trans isomers. In the case of propanone oxime the two methyl groups preclude cis-trans isomers.



propanone oxime

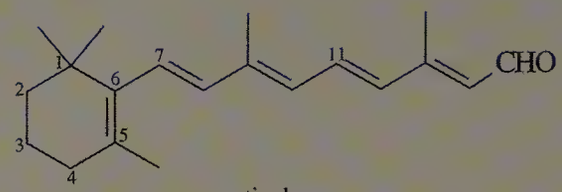
(*E*)-propanal oxime

(*Z*)-propanal oxime

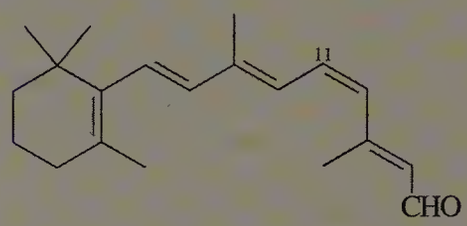
Addition Reactions and Vision

We learned at our mothers' knees that "carrots are good for us". This homely injunction is true because carrots contain β-carotene, which mammals require for vision.

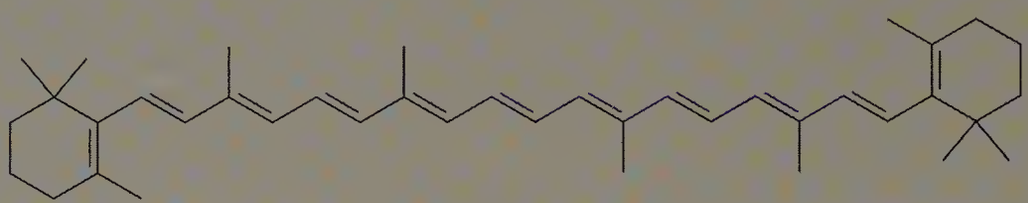
β-Carotene is a pigment largely responsible for the color of carrots. Persons who do not have adequate β-carotene in their diets—it is available in egg yolk, liver, and various fruits and vegetables in addition to carrots—suffer from *night blindness*. Mammals have a liver enzyme system that splits β-carotene in half to give two molecules of an aldehyde named retinal. Retinal has a series of alternating single and double bonds. Geometric isomers can exist around each of the double bonds. The all-trans compound and the isomer with a cis orientation around the C-11 and C-12 atoms play an important role in vision.



retinal



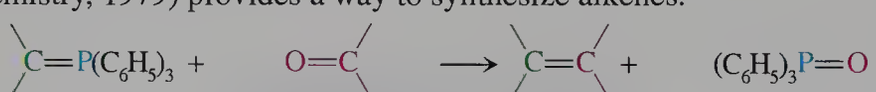
cis-11-retinal



β-carotene

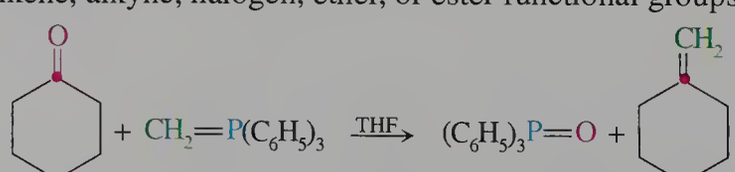
19.11 The Wittig Reaction

Carbonyl compounds react with phosphorus ylides to yield alkenes according to the following general equation. This reaction, discovered by Georg Wittig (Nobel Prize in chemistry, 1979) provides a way to synthesize alkenes.

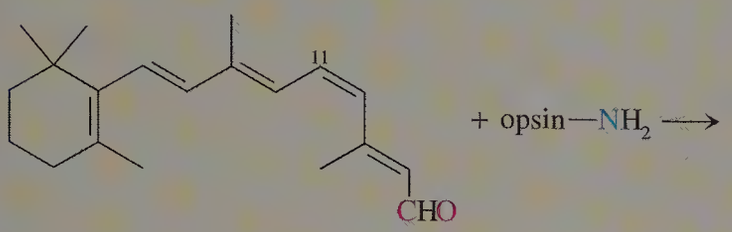


(ylide) (aldehyde or ketone) (alkene) triphenylphosphine oxide

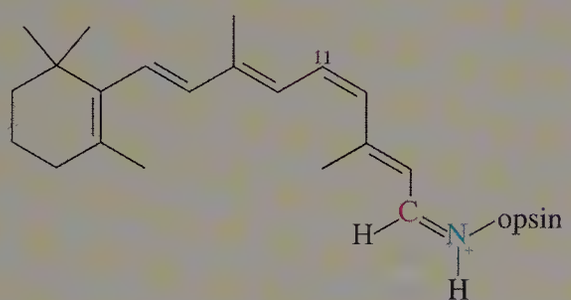
The Wittig reaction is regiospecific. The double bond forms between the carbonyl carbon atom and the carbon atom bonded to the phosphorus atom of the ylide. However, the reaction is not stereospecific. Thus, if geometric isomers are possible for appropriate combinations of groups bonded to the sp^2-hybridized carbon atom, both isomers form. The Wittig reaction uses polar aprotic solvents such as diethyl ether, tetrahydrofuran, or dimethyl sulfoxide. The Wittig reaction can be carried out in the presence of alkene, alkyne, halogen, ether, or ester functional groups.



cis-11-Retinal undergoes an addition reaction with a protein in the retina called opsin to form a substance called rhodopsin. The aldehyde group of *cis*-11-retinal reacts with a specific amino group in the protein to form an imine. The shape of the imine adduct of *cis*-11-retinal allows it to "fit" into the protein.



cis-11-retinal



rhodopsin

Rhodopsin absorbs visible light, acting in the retina as a visual receptor. Light strikes rhodopsin, isomerizing the *cis* double bond at C-11 to a *trans* double bond, a process called photoisomerization. The resulting all-*trans* isomer no longer fits into the opsin, the imine spontaneously hydrolyzes, and the all-*trans* retinal is released from opsin. This process occurs in less than one millisecond. The reaction generates a nerve impulse, which travels to the brain. Millions of nerve impulses combine to form a visual image.

If *cis*-11-retinal cannot bind opsin to give rhodopsin, vision is impaired. We recall from earlier discussions that formaldehyde, produced by the oxidation of methyl alcohol, can cause blindness. Blindness occurs because formaldehyde reacts faster than does *cis*-11-retinal with the reactive amine group of opsin. If no rhodopsin forms, then no "light-induced" messages reach the brain.

Formation of Phosphorus Ylides

Phosphorus ylides are usually obtained from alkyl halides and triphenylphosphine in a two-step sequence. We recall that the nucleophilicity of third-row elements such as sulfur and phosphorus is greater than that of second-row elements, because the atoms are more polarizable (Section 10.1). The phosphorus atom of triphenylphosphine is an effective nucleophile. Because it is also a weak base, competing elimination is not important, and bimolecular substitution of primary and secondary alkyl halides gives good yields. In the first step, the halide ion of the alkyl halide is displaced in an S_N2 reaction to yield an alkyltriphenylphosphonium salt.

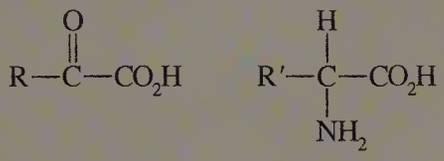
The alkyltriphenylphosphonium salts are stable and can be isolated, crystallized, and stored until needed. In a separate second step, the alkyltriphenylphosphonium salt is deprotonated using a strong base such as sodium hydride or butyllithium. The proton on the carbon atom bonded to phosphorus is weakly acidic because the positively charged phosphorus inductively withdraws electrons.

$$(C_6H_5)_3P^+—CH_3\ I^- \xrightarrow{\text{butyllithium}} (C_6H_5)_3P^+—CH_2^- \longleftrightarrow (C_6H_5)_3P{=}CH_2$$

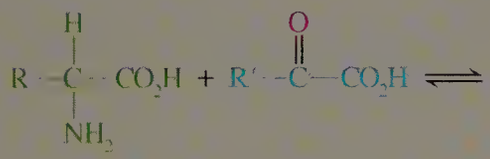
Two resonance forms depict the structure of the ylide. The dipolar resonance form is generally used to show the mechanism of the Wittig reaction. This resonance form

Vitamin B_6 and Transamination via Imines

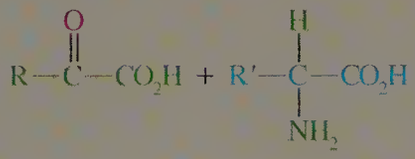
Two types of carboxylic acids play different but equally important roles in cells. The α-keto acids are important intermediates in energy-producing metabolic reactions, such as the citric acid cycle, that derive energy for the cell. Amino acids are the "building blocks" of proteins, including the enzymes that control virtually all chemical reactions in an organism.



α-keto acid amino acid



amino acid I α-keto acid II



α-keto acid I amino acid II

Two different R groups are shown in the reaction of an amino acid and an α-keto acid. The interconversion of an amino acid to its related α-keto acid or vice versa occurs to meet the needs of the cell. The net reaction that accomplishes this transformation is known as **transamination**.

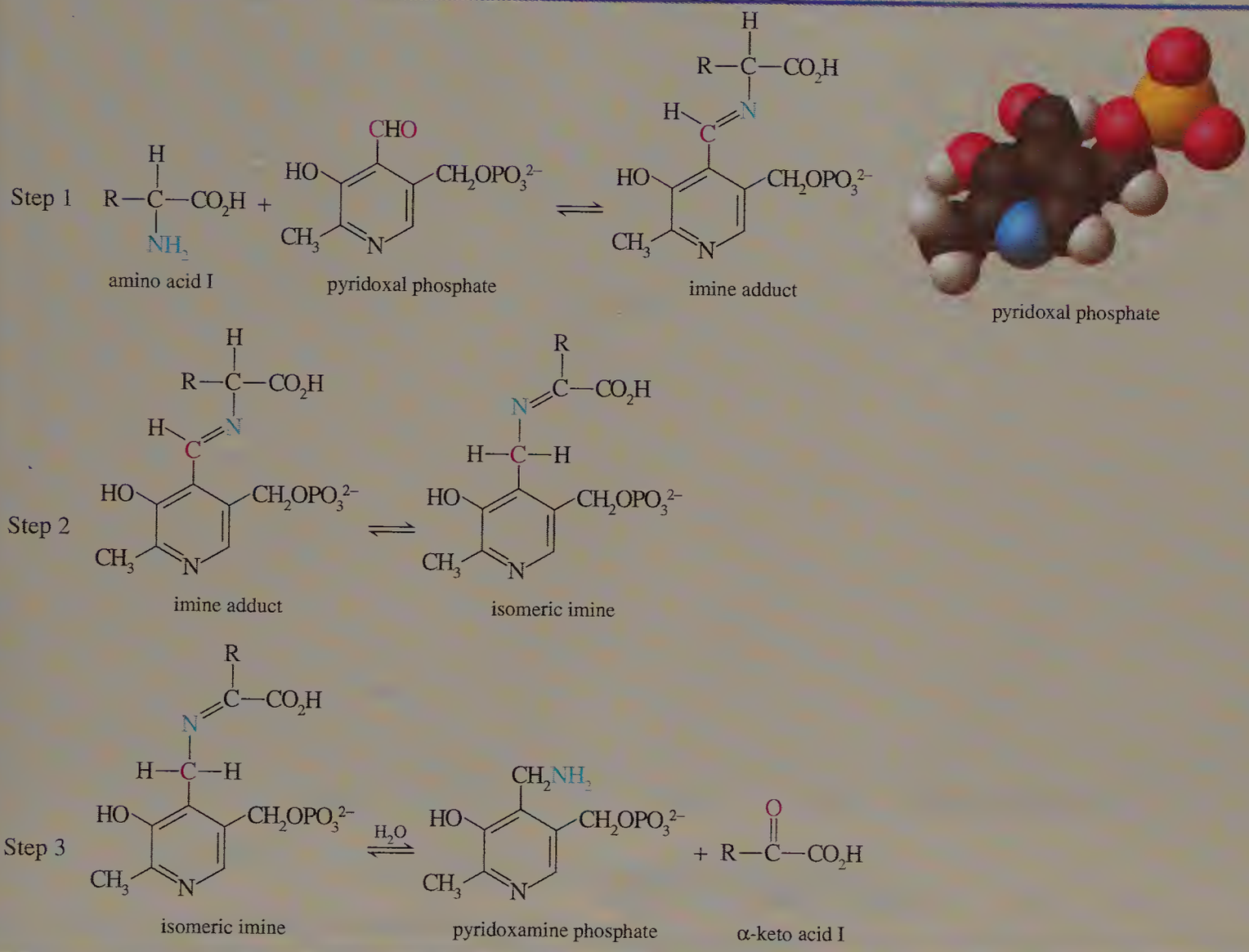
Transamination requires one of the two forms of vitamin B_6 and occurs in three steps. In step 1, the amino acid forms an imine with the carbonyl group of pyridoxal phosphate, one of the forms of vitamin B_6. In step 2, an isomerization reaction occurs to form an isomeric imine. In step 3, the isomeric imine hydrolyzes to yield the α-keto acid and another form of vitamin B_6 called pyridoxamine phosphate.

Thus, the reaction converts the amino acid into an α-keto acid by transferring its amino group to the vitamin for storage. Because all the reactions shown at right are reversible, a different α-keto acid can be converted to its related amino acid by the reverse of this three-step sequence using the amino group stored in pyridoxamine phosphate. In this way, an amino acid with an R group is converted to an α-keto acid with an R group and an α-keto acid with an R′ group is converted into an amino acid with an R′ group. This is the net reaction called transamination.

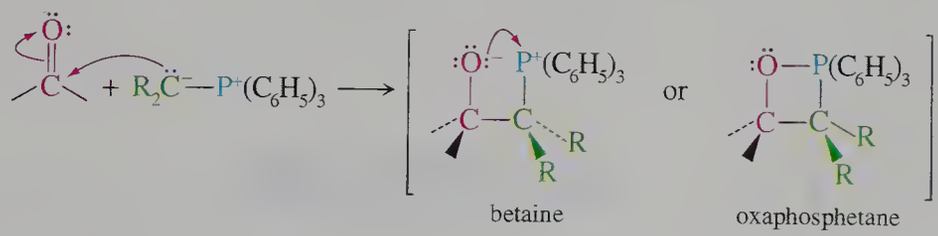
has a single bond between the phosphorus and carbon atoms. Although charges are located on two atoms, this form is the major contributor to the ylide structure. The uncharged resonance form has a double bond between the phosphorus and carbon atoms, so the phosphorus atom has ten electrons in its valence shell. Although expansion of the valence shell occurs for third-row elements by using empty 3*d* orbitals, the 3*d*–2*p* π bond formed between a third- and a second-row element is weak because of ineffective overlap of atomic orbitals. We recall that a similar argument accounts for the diminished capacity of the halogen atoms to donate electrons in electrophilic aromatic substitution of aromatic rings (Section 14.6). The importance of the dipolar resonance form accounts for the strongly nucleophilic character of the carbon atom of the ylide and its reactivity with a carbonyl carbon atom in the Wittig reaction.

Mechanism of the Wittig Reaction

The first step in the Wittig reaction may be the direct formation of an oxaphosphetane or alternatively preliminary formation of phosphorus betaine, which yields an



oxaphosphetane. The exact course of the reaction may depend on the type of groups bonded to the carbonyl carbon atom and the type of ylide. Nevertheless, the direction of the addition of the ylide to the carbonyl atoms is the same as for other addition reactions studied in this chapter. The electrophilic carbon atom of the ylide forms a bond to the carbonyl carbon atom and the phosphorus bonds to the oxygen atom.

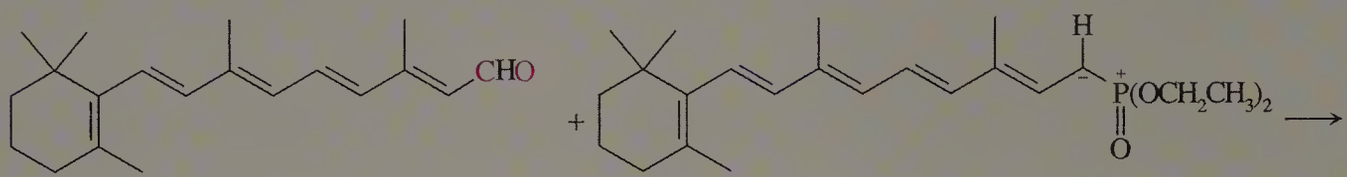


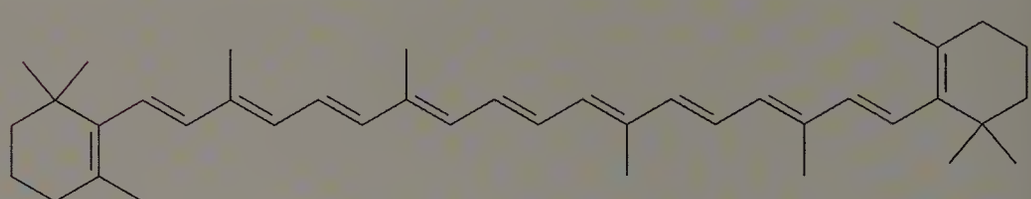
The intermediate phosphorus compound immediately decomposes to yield the alkene and a phosphine oxide. This second step is concerted; all bonds break and form simultaneously in the transition state. The driving force for this reaction is the formation of a very strong phosphorus–oxygen bond. The P—O bond dissociation energy in triphenylphosphine oxide is approximately 550 kJ mole^{-1} (130 kcal mole^{-1}).

Synthesis of β-Carotene

The Wittig reaction is used to prepare alkenes because the reaction does not give isomers with double bonds located at other points in the carbon skeleton. The method is usually superior to elimination reactions. Only the possibility of *E,Z* isomers remains as an impediment to the synthesis of pure alkenes.

When only small-scale reactions are required in a laboratory synthesis of an alkene or in an industrial process to give small quantities of an alkene, the Wittig reaction may be used. However, under the right circumstances of available starting materials and a highly desirable product, the Wittig reaction has been used in large-scale industrial synthesis. One such example is the synthesis of β-carotene, which is used in vitamin pills and as a yellow food-coloring agent. The synthesis uses retinal and a phosphorane derived from retinal. A variation of the Wittig reaction termed the Horner–Emmons method has been used. The phosphorane is derived from a less expensive phosphorus derivative that is more soluble. Although *E,Z* isomers could result about the newly formed double bond, the reaction is stereoselective and only the *E* isomer, β-carotene, is obtained.





β-carotene

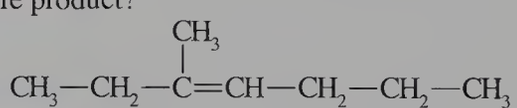
Problem 19.16

What combination of phosphorus ylide and a carbonyl compound could be used to prepare each of the following alkenes?

(a) methylenecyclooctane (b) 1,1-diphenyl-1-propene
(c) 2-methyl-2-pentene (d) ethylidenecyclohexane

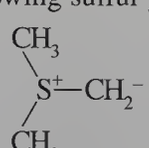
Problem 19.17

Outline two possible syntheses of the following compound. Would you predict any difficulties in obtaining a pure product?



Problem 19.18

Suggest a method to prepare the following sulfur ylide.



EXERCISES

Thermodynamic Calculations

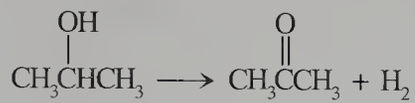
19.1 The bond dissociation energies of H—CN and C—CN are 545 and 510 kJ mole^{-1}, respectively. The O—H bond dissociation energy is 425 kJ mole^{-1}. Calculate the $\Delta H°$ for cyanohydrin formation, that is, addition of HCN to a carbonyl group.

19.2 The bond dissociation energies of H—S and C—S are 345 and 270 kJ mole^{-1}, respectively. The O—H bond dissociation energy is 425 kJ mole^{-1}. Calculate the $\Delta H°$ for addition of H_2S to a carbonyl group.

19.3 Calculate the $\Delta H°_{rxn}$ for the following isomerization reaction.

$$CH_2{=}CHCH_2OH \longrightarrow CH_3CH_2CHO$$

19.4 Using the heats of formation (see Section 19.1) and an approximate value of $\Delta S°_{rxn}$, estimate the minimum temperature (K) at which the following reaction is favorable.



Reactivity of Carbonyl Compounds

19.5 Formaldehyde has been used to disinfect rooms and surgical instruments. Why is this compound so effective compared to other carbonyl compounds?

19.6 Glutaraldehyde is used as a sterilizing solution for instruments that cannot be heated in an autoclave. Explain its action in sterilizing objects.

19.7 Which member of each of the following pairs of compounds reacts faster with sodium borohydride?
(**a**) cyclopropanone or cyclopentanone
(**b**) acetophenone or benzaldehyde
(**c**) acetone or 3,3-dimethyl-2-butanone

19.8 Which member of each of the following pairs of compounds reacts faster with sodium borohydride?
(**a**) benzaldehyde or acetaldehyde
(**b**) cyclopentanone or cyclohexanone
(**c**) *p*-trifluoromethylbenzaldehyde or benzaldehyde

Equilibrium Constants of Hydration Reactions

19.9 The equilibrium constants for the formation of hydrates of acetaldehyde and chloroacetaldehyde are 1 and 37, respectively. Estimate the equilibrium constant for formation of the hydrate of trichloroacetaldehyde.

19.10 The equilibrium constant for formation of a hydrate of acetone is 0.0014. Using the data in Exercise 19.9, estimate the equilibrium constant for formation of a hydrate of 1,3-dichloroacetone.

19.11 Explain why the methoxy group of *p*-methoxybenzaldehyde decreases the equilibrium constant for hydration relative to benzaldehyde whereas the methoxy group of *m*-methoxybenzaldehyde increases the equilibrium constant.

19.12 The equilibrium constants for the formation of hydrates of acetone, acetophenone, and benzophenone are 0.0014, 6.6×10^{-6}, and 1.7×10^{-7}, respectively. Suggest a reason why the second phenyl group of benzophenone has a much smaller effect on the equilibrium constant than the phenyl group of acetophenone compared to acetone.

19.13 Explain why the equilibrium constant for hydration of cyclopropanone is significantly larger than for hydration of cyclopentanone.

19.14 Considering the role of torsional interactions in determining cycloalkane stability, predict the order of the equilibrium constants for hydration of cyclopentanone and cyclohexanone.

Formation of Cyanohydrins

19.15 Hydrogen cyanide (H—C≡N:) reacts with 2-propanone to give a good yield of an addition product, but 2,2,4,4-tetramethyl-3-pentanone gives a poor yield in the same reaction. Why?

19.16 Explain why the equilibrium constant for formation of a cyanohydrin of cyclohexanone is about 20 times larger than the equilibrium constant for formation of a cyanohydrin of cyclopentanone.

19.17 Explain why the equilibrium constant for formation of a cyanohydrin of butanone is about 40 times larger than the equilibrium constant for formation of a cyanohydrin of 3,3-dimethylbutanone.

19.18 Explain why the equilibrium constant for formation of a cyanohydrin of *p*-methoxybenzaldehyde (K_{eq} = 30) is smaller than the equilibrium constant for benzaldehyde.

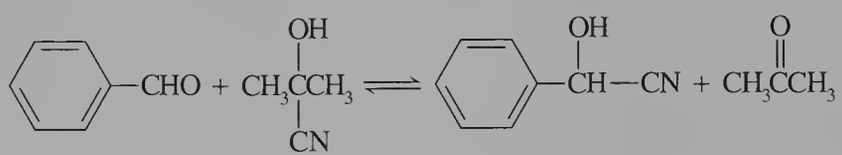
19.19 Is the equilibrium constant for formation of a cyanohydrin of *p*-methylbenzaldehyde larger or smaller than the equilibrium constant for benzaldehyde?

19.20 Is the equilibrium constant for formation of a cyanohydrin of *p*-ethoxybenzaldehyde larger or smaller than the equilibrium constant for *p*-dimethylaminobenzaldehyde?

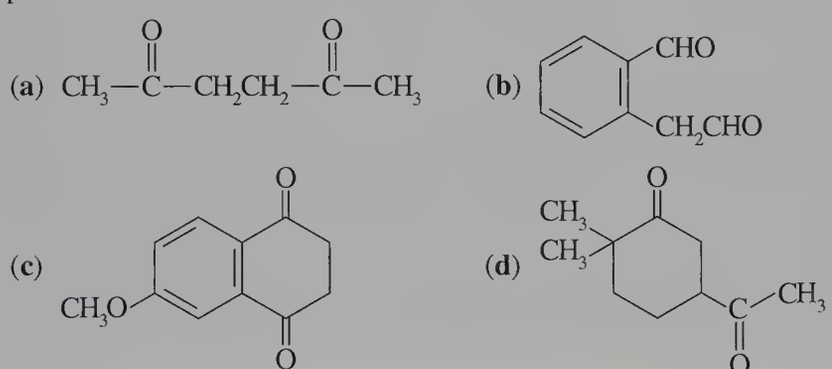
19.21 Explain why the equilibrium constant for the formation of a cyanohydrin of 3,3,5-trimethylcyclohexanone is smaller than the equilibrium constant for cyclohexanone.

19.22 Two cyanohydrins of 4-*tert*-butylcyclohexanone exist. Which is the kinetic product? Which is the thermodynamic product?

19.23 When benzaldehyde is heated with acetone cyanohydrin and a catalytic amount of base, the following reaction occurs. Estimate the equilibrium constant for the reaction. Write a mechanism for the reaction.



19.24 Write the structure of the product for the reaction of one equivalent of HCN with each of the following compounds.



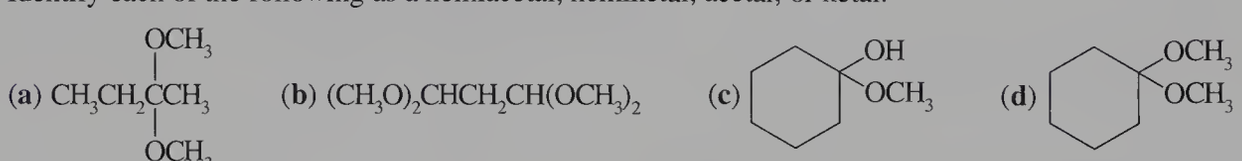
Addition of Alcohols to Carbonyl Compounds

19.25 Identify each of the following as a hemiacetal, hemiketal, acetal, or ketal.

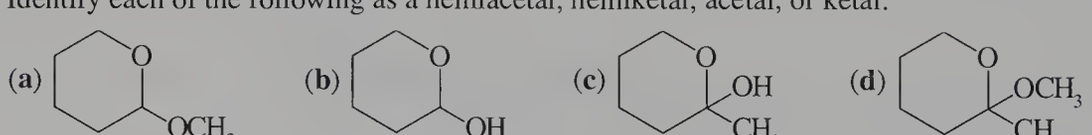
(a) $CH_3CH_2CH(OCH_3)_2$ **(b)** $CH_3CH_2C(OCH_3)_2CH_3$

(c) $CH_3\overset{\displaystyle OCH_2CH_3}{\overset{|}{C}}HOCH_2CH_3$ **(d)** $CH_3CH_2\overset{\displaystyle OCH_3}{\overset{|}{C}}HOH$

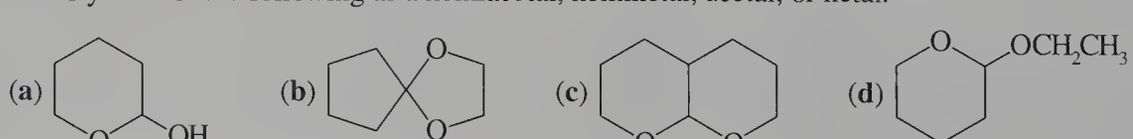
19.26 Identify each of the following as a hemiacetal, hemiketal, acetal, or ketal.



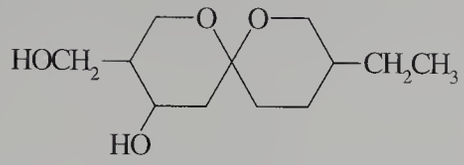
19.27 Identify each of the following as a hemiacetal, hemiketal, acetal, or ketal.



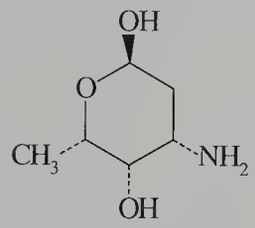
19.28 Identify each of the following as a hemiacetal, hemiketal, acetal, or ketal.



19.29 Identify the functional groups in talaromycin A, a substance found in the fungus that grows in poultry litter.



19.30 Identify the functional groups in daunosamine, a component of Adriamycin, used in cancer chemotherapy.



19.31 Is the equilibrium constant for the following reaction greater than or less than unity?

$$CF_3CHO + CH_3CH(OCH_3)_2 \rightleftharpoons CH_3CHO + CF_3CH(OCH_3)_2$$

19.32 Which compound should exist to the larger extent as a hemiacetal, 4-hydroxybutanal or 5-hydroxypentanal?

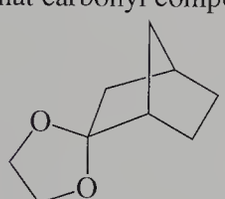
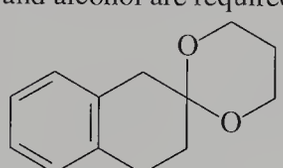
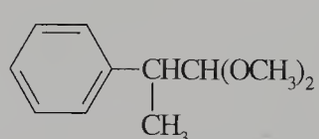
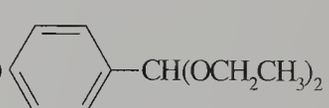
19.33 Benzaldehyde reacts with 1,2-propanediol to give two isomeric acetals. Draw their structures.

19.34 Acetone reacts with 1,2,3-propanetriol (glycerol) to give two isomeric ketals. Draw their structures.

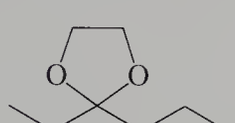
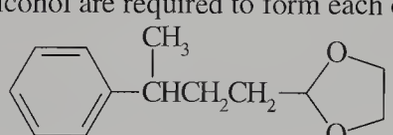
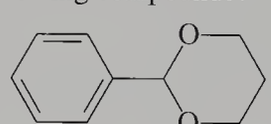
19.35 2-Oxopropanal (pyruvaldehyde) reacts with excess methanol in an acid-catalyzed reaction to give a compound with molecular formula $C_5H_{10}O_3$. Draw its structure.

19.36 2-Oxopropanal (pyruvaldehyde) reacts with excess ethylene glycol in an acid-catalyzed reaction to give a compound with molecular formula $C_7H_{12}O_4$. Draw its structure. What is the difference between the product of this reaction and the product in Exercise 19.35?

19.37 What carbonyl compound and alcohol are required to form each of the following compounds?

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

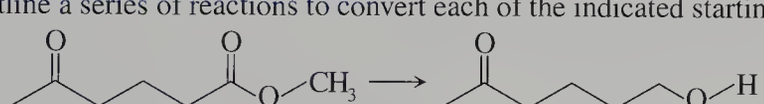
19.38 What carbonyl compound and alcohol are required to form each of the following compounds?

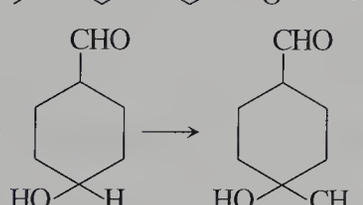
(a)  **(b)**  **(c)** 

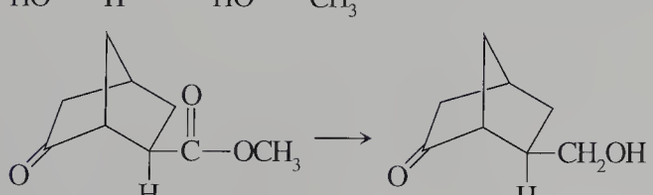
(d) $(CH_3O)_2CHCH_2CH_2CH(OCH_3)_2$

Use of Protecting Groups in Synthesis

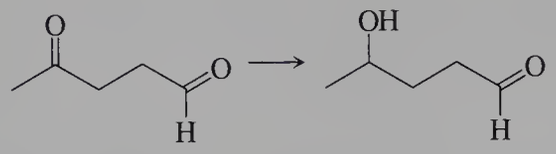
19.39 Outline a series of reactions to convert each of the indicated starting materials to the indicated product.

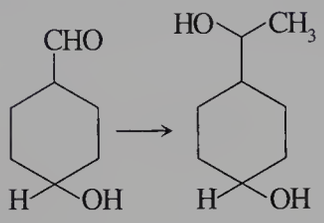
(a) 

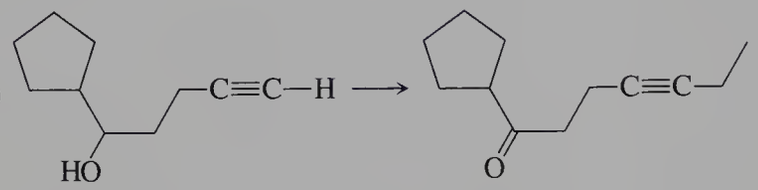
(b) 

(c) 

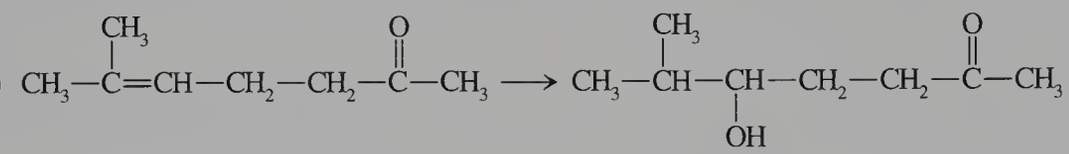
19.40 Outline a series of reactions to convert each of the indicated starting materials to the indicated product.

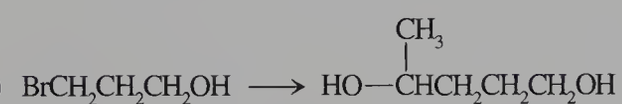
(a) 

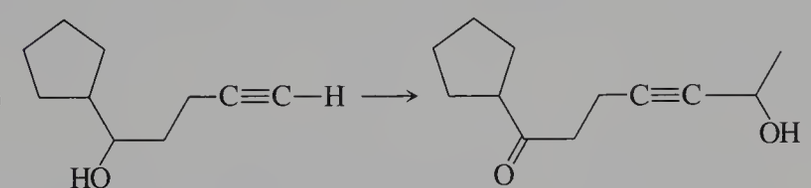
(b) 

(c) 

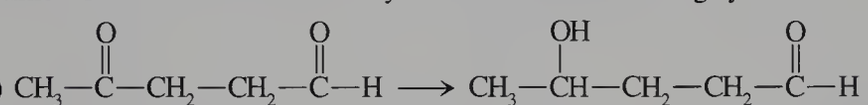
19.41 Outline a series of reactions to carry out the following synthesis.

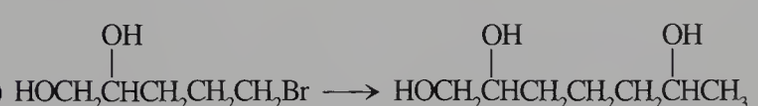
(a) 

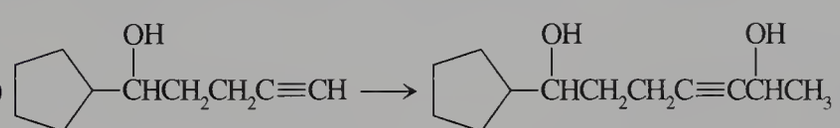
(b) 

(c) 

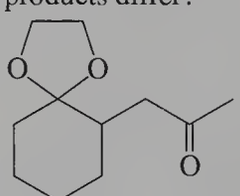
19.42 Outline a series of reactions to carry out each of the following syntheses.

(a) 

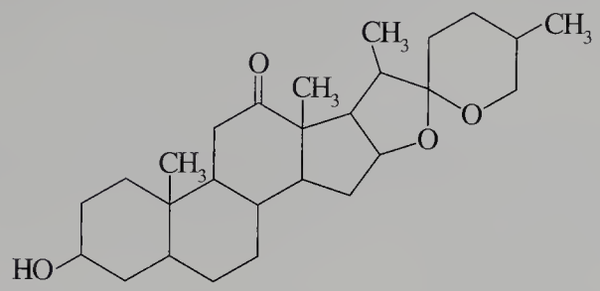
(b) 

(c) 

19.43 Reduction of the following compound by the Wolff–Kishner method gives $C_{11}H_{20}O_2$, but reduction by the Clemmensen method gives C_9H_{18}. Why do the products differ?



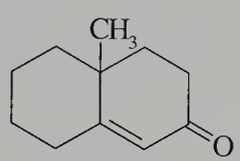
19.44 Draw the structure of the product obtained from the following reactant using Wolff–Kishner conditions. What difference would be observed if Clemmensen conditions were used?

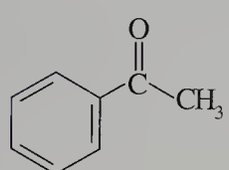


Thioacetals and Thioketals

19.45 Draw the structure of the product of each of the following reactions.

(a) $CH_3(CH_2)_2\overset{\overset{O}{\|}}{C}-H \xrightarrow[H^+]{CH_3CH_2SH}$

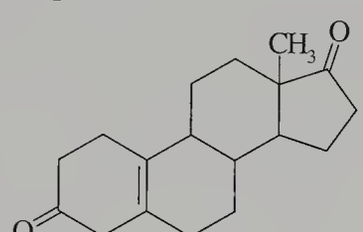
(b)  $+ HSCH_2CH_2SH \xrightarrow{BF_3}$

(c)  $+ HSCH_2CH_2CH_2SH \xrightarrow{BF_3}$

19.46 Thiols react with dihydropyran in an acid-catalyzed reaction to form an addition product. Write the mechanism for the reaction and draw the structure of the addition product.

19.47 Aldehydes and ketones react with 2-thioethanol to give cyclic derivatives. Draw the two possible products from the reaction of 4-*tert*-butylcyclohexanone with this reagent.

19.48 Predict the product of the reaction of one equivalent of 1,2-ethanedithiol with the following steroid.

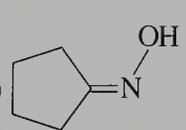


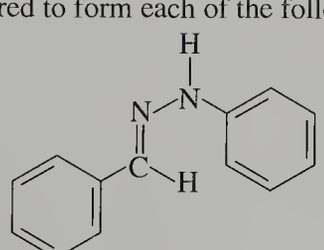
Addition of Nitrogen Compounds

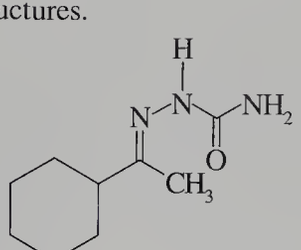
19.49 Write the structure of the product for each of the following combinations of reactants.

(a) ethanal and methylamine
(b) acetone and ethylamine
(c) benzaldehyde and hydrazine
(d) 3-pentanone and hydroxylamine
(e) 1-phenyl-2-propanone and semicarbazide

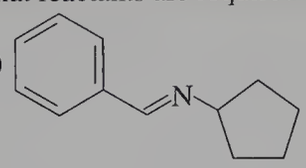
19.50 Identify the reactants required to form each of the following structures.

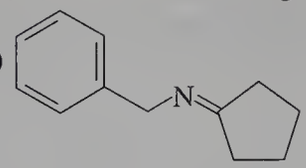
(a) 

(b) 

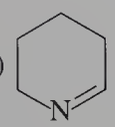
(c) 

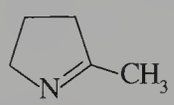
19.51 What reactants are required to produce each of the following isomeric imines?

(a) 

(b) 

19.52 What reactants are required to produce each of the following isomeric imines?

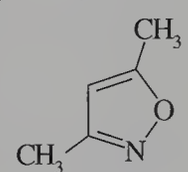
(a) 

(b) 

19.53 Reaction of cyclohexanone with hydroxylamine yields a single product. However, cyclopentanecarbaldehyde yields two isomeric oximes. Explain why.

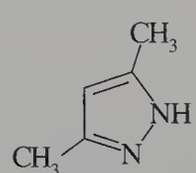
19.54 Draw the structure of the product of reaction of hydrazine with two molar equivalents of benzaldehyde.

19.55 2,4-Pentanedione reacts with hydroxylamine to yield 3,5-dimethylisoxazole. Write a mechanism for the reaction.

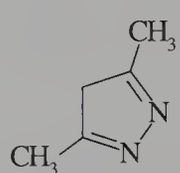


3,5-dimethylisoxazole

19.56 2,4-Pentanedione reacts with hydrazine to yield 3,5-dimethylpyrazole, not an isomeric diimine. Explain why the pyrazole forms.



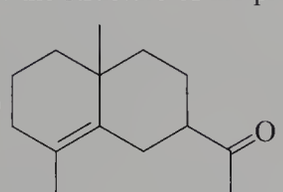
3,5-dimethylpyrazole

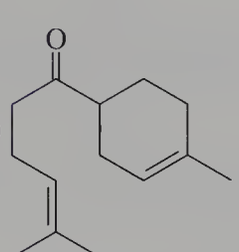


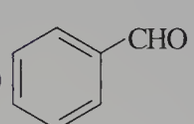
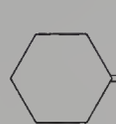
not formed

Ylide Chemistry

19.57 Draw the structure of the product of each of the following reactions.

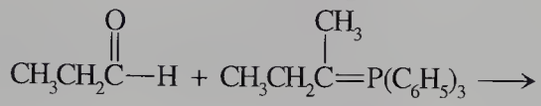
(a)  $+ (C_6H_5)_3P{=}CH_2 \longrightarrow$

(b)  $+ (C_6H_5)_3P{=}CHC_6H_5 \longrightarrow$

(c)  $+$  $=P(C_6H_5)_3 \longrightarrow$

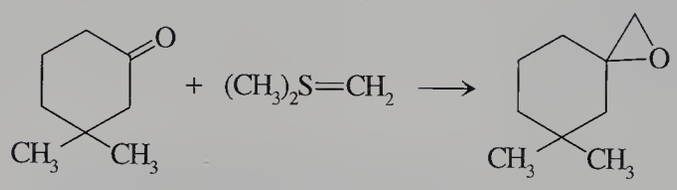
19.58 Outline a synthesis of each of the following compounds using a Wittig reaction.
(**a**) ethylidenecyclopentane (**b**) 2-ethyl-1-pentene (**c**) 4-propyl-3-heptene

19.59 Draw the structure of the two products formed in the following reaction.



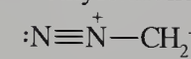
19.60 Draw the structure of the ylide formed by reacting 1-bromo-2-butyne with triphenylphosphine followed by reaction with sodium ethoxide. Explain why such a relatively weak base is sufficient to generate the ylide.

19.61 Suggest a mechanism for the following reaction of a sulfur ylide with a ketone.



dimethylsulfonium
methylide

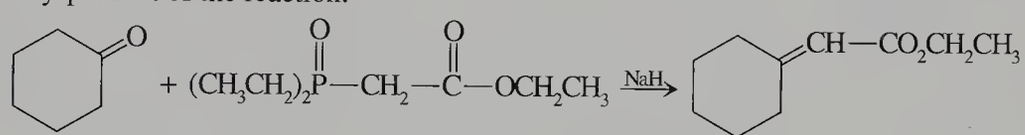
19.62 Acetone reacts with diazomethane to yield 2,2-dimethyloxirane. Write a mechanism for this reaction.

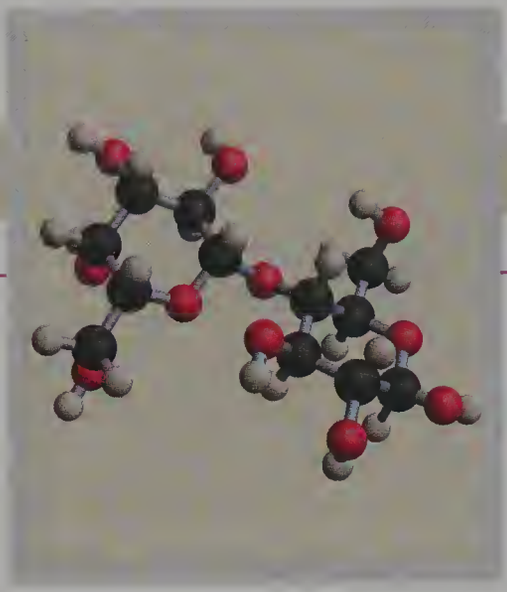


diazomethane

19.63 The reaction of dimethylsulfonium methylide, $(CH_3)_2S{=}CH_2$, with 4-*tert*-butylcyclohexanone could yield two isomeric epoxide products. Draw their structures. What factors may control the relative amounts of the two compounds formed?

19.64 Suggest a mechanism for the following reaction of cyclohexanone with triethylphosphonoacetate. Draw the structure of the by-product of the reaction.





20

Carbohydrates

20.1 Carbohydrates and Energy

If the importance of biological molecules were measured by abundance, carbohydrates would hold first prize. They are the most abundant molecules in the biological world (except for water). The term "hydrates of carbon" was suggested for the class of compounds with the generic formula $(CH_2O)_n$ in 1844. Although the name remains, many compounds classified as carbohydrates today do not have the empirical formula $(CH_2O)_n$. The name **carbohydrates** now includes a wide range of structures—from simple molecules with as few as three carbon atoms to very large molecules consisting of thousands of five- or six-carbon atom subunits. Carbohydrates are polyhydroxy aldehydes or ketones, or compounds that can be hydrolyzed to form polyhydroxy aldehydes or ketones. Their functions are as varied as their structures. They provide a major source of metabolic energy to animals and are important structural components in many cells.

Because carbohydrates are so plentiful in the biological world, we use a host of names for them, including sugars, starches, and cellulose. The roots, stems, and leaves of plants contain many carbohydrates with very complex structures. These molecules result from endothermic reactions whose ultimate energy source is the sun.

Carbohydrates can be regarded as a form of "stored sunlight". The sun pours about 1×10^{23} kJ of radiant energy onto the Earth each year. Dust and clouds reflect (absorb and immediately reradiate) one-third of this energy back into space. The Earth absorbs and slowly reradiates most of the rest back into space as heat. Plants temporarily trap less than 0.05% of the solar energy reaching the Earth in a process called photosynthesis. Organisms store this energy in organic chemical bonds. During photosynthesis, plants convert carbon dioxide and water into glucose and oxygen by a very complex series of reactions, using light energy to drive the reactions. (The oxygen we breathe is a by-product of about two billion years of photosynthesis.) Cells subsequently synthesize cellulose or starch from glucose subunits.

$$6\,CO_2 + 6\,H_2O \xrightarrow{\text{light}} 6\,O_2 + \underbrace{C_6H_{12}O_6}_{\text{glucose}} \longrightarrow \text{cellulose or starch} + H_2O$$

The starch stored in plants forms a source of metabolic energy for the plant itself and for animals that eat the plants. Animals break down starch and re-link glucose subunits into a substance closely related to starch called glycogen to store metabolic energy. Although terrestrial plants contribute significantly to our source of carbohydrates, phytoplankton in the oceans contribute most of the carbohydrates and oxygen on Earth. They convert about 2×10^{11} kg of carbon dioxide into carbohydrates and oxygen each year.

Carbohydrates are a major source of metabolic energy for most life forms. Photosynthetic organisms convert carbon dioxide into organic compounds, which are more reduced than carbon dioxide. These reduced compounds store chemical energy in carbon–hydrogen bonds. Animals eat the reduced carbon compounds, obtaining the stored energy by oxidative metabolic reactions.

$$\text{cellulose or starch} + H_2O \longrightarrow C_6H_{12}O_6$$

$$C_6H_{12}O_6 + 6\,O_2 \xrightarrow{\text{metabolism}} 6\,CO_2 + 6\,H_2O + \text{energy}$$

Humans convert starch into glucose by an enzyme-catalyzed hydrolysis reaction, but humans and most other animals lack the enzyme necessary to hydrolyze cellulose. Some animals—cows and other hoofed animals (ungulates), as well as termites, for example—harbor microorganisms that hydrolyze cellulose to produce glucose. The energy in cellulose thus becomes available to the cows and subsequently moves along the food chain to humans. The difference between the structures of starch and cellulose will be discussed in Section 20.9.

20.2 Classification of Carbohydrates

Carbohydrates fall into three large structural classes: monosaccharides, oligosaccharides, and polysaccharides. **Monosaccharides** cannot be hydrolyzed into smaller molecules. Examples include glucose and fructose.

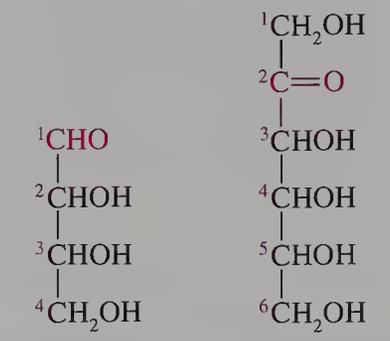
Carbohydrates consisting of a "few" monosaccharides—typically 2 to 10 or so—are called **oligosaccharides**. Hydrolysis of oligosaccharides may yield identical monosaccharides, or two or more different monosaccharides. Oligosaccharides are called **disaccharides**, **trisaccharides**, and so forth, depending on the number of linked monosaccharide units. The disaccharide lactose, or "milk sugar", for example, contains one molecule of glucose and one of galactose. Maltose, another disaccharide, contains two glucose units.

Polysaccharides contain thousands of covalently linked monosaccharides. Those with only one type of monosaccharide subunit are called **homopolysaccharides**. Examples include starch and cellulose made by plants. They yield only glucose when hydrolyzed. Glycogen, sometimes called animal starch, is another homopolysaccharide of glucose. Polysaccharides with more than one type of monosaccharide are called **heteropolysaccharides**.

The monosaccharides in oligo- and polysaccharides are linked by acetal or ketal bonds, called **glycosidic bonds** in carbohydrate chemistry. These bonds link the aldehyde or ketone site of one monosaccharide and a hydroxyl group of another monosaccharide. Hydrolysis of the glycosidic bonds yields the component monosaccharides.

Monosaccharides can be further classified by their most highly oxidized functional group. Monosaccharides are called **aldoses** if their most highly oxidized functional group is an aldehyde and **ketoses** if their most highly oxidized functional

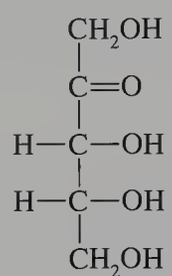
group is a ketone group. The suffix *-ose* indicates that a compound is a carbohydrate. The prefix *aldo-* or *keto-* indicates that the compound is an aldehyde or ketone. The prefixes tri-, tetr-, pent-, and hex- indicate the number of carbon atoms in an aldose or ketose. Aldoses are numbered from the carbonyl carbon atom, whereas ketoses are numbered from the end of the carbon chain closer to the carbonyl carbon atom.



(an aldotetrose) (a ketohexose)

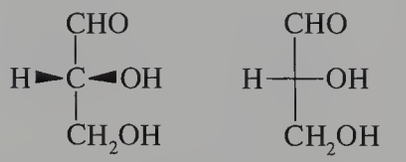
Problem 20.1

D-Ribulose, which has the following structure, is an intermediate in the pentose phosphate pathway that produces ribose, a precursor for nucleic acid biosynthesis. Classify D-ribulose by chain length and its carbonyl group.



20.3 Chirality of Monosaccharides

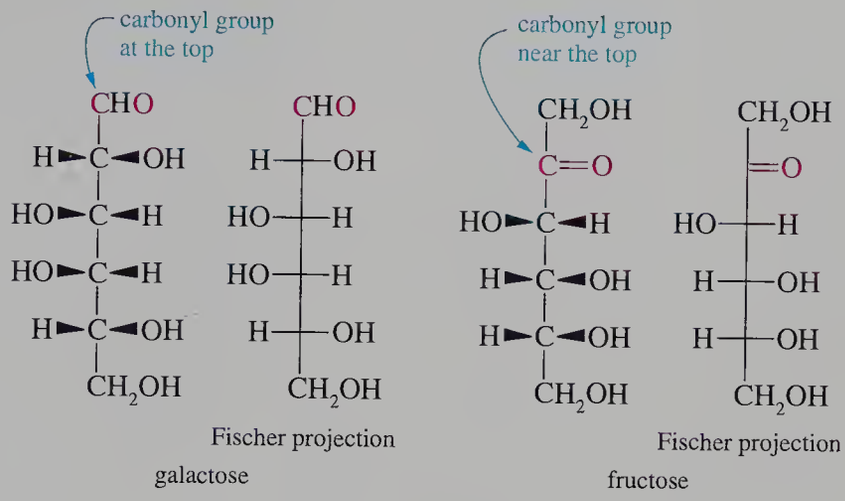
Monosaccharides are conveniently represented by their Fischer projection formulas (Chapter 9). We recall that in a Fischer projection formula, a vertical line represents the carbon chain. Groups attached to the ends of the vertical line represent bonds going into the page, and horizontal lines represent bonds coming out of the page. By convention, the carbonyl carbon atom, the most oxidized carbon atom in these compounds, is placed near the "top" in the Fischer projection formula. The simplest aldose, glyceraldehyde, has three carbon atoms, one of which is a stereogenic center. This aldotriose can exist in two enantiomeric forms. The naturally occurring *R* isomer rotates light in a clockwise direction.



Fischer projection

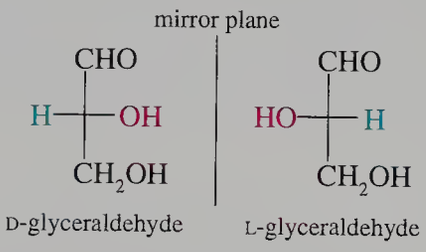
(*R*)-(+)-glyceraldehyde

Monosaccharides with multiple stereogenic centers are arranged with the carbon backbone continually pushed back behind the plane of the page. A curve of atoms in a C-shaped structure results, with the attached hydrogen atoms and hydroxyl groups pointing out from the backbone of the carbon chain.



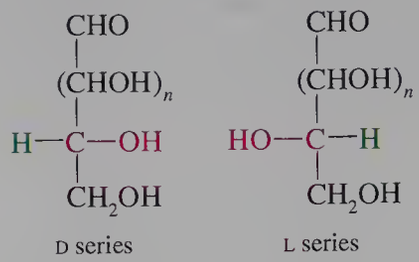
Aldoses

The stereochemistry of each stereogenic center of a monosaccharide can now be indicated by the *R,S* notation. However, the Fischer projection formula, devised late in the 19th century by the German chemist Emil Fischer, remains in common use for carbohydrates and amino acids (Chapter 26). In the Fischer stereochemical system, the configurations of all stereogenic centers depend on their relation to the naturally occurring stereoisomer of glyceraldehyde. This aldotriose has the hydroxyl group on its chiral C-2 atom, located on the right in the projection formula. Its configuration is symbolized D, so the naturally occurring isomer is designated D-glyceraldehyde. Its enantiomer, called L-glyceraldehyde, has the hydroxyl group on the left at the chiral carbon atom in the Fischer projection formula. Fischer was lucky in his arbitrary assignment of the correct stereochemical structure to each of the two forms of glyceraldehyde. He had a 50% chance of being wrong, but his choice turned out to have the correct configuration.



Using the *R,S* notation, D-glyceraldehyde is the *R* enantiomer. The *R,S* configuration of each of the stereogenic centers of longer chain monosaccharides can be used to name the many possible isomers. But Fischer's original system of nomenclature describes the stereogenic centers with respect, first, to one another and, second, to the configuration of one selected center. Here is how it works. The configuration of the highest numbered stereogenic center is used to assign the compound as a member of the D or L series. Because the numbering of the carbon chain

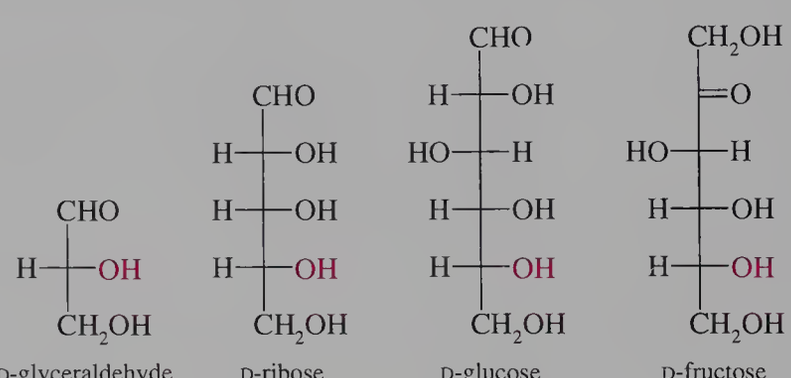
assigns the lowest possible number to the carbonyl carbon atom, the highest numbered stereogenic center is the farthest from the most highly oxidized carbon atom.



D series L series

We recall that diastereomers have different chemical properties. Thus, the second consideration is the configuration of each of the hydroxyl groups of a monosaccharide relative to one another, because this relationship distinguishes the monosaccharide from other diastereomers. For example, the aldopentose with all hydroxyl groups at the three chiral carbon atoms on the same side in the Fischer projection formula is called ribose. The assignment of one enantiomer of ribose to the D or L series is then made by reference to the C-4 atom, the highest numbered chiral carbon atom in a five-carbon compound. The name D-ribose defines the absolute configuration at every stereogenic center in the molecule: the hydroxyl groups at the C-2, C-3, and C-4 atoms are all on the right in the Fischer projection.

This apparently arbitrary method of stereochemical assignments of carbohydrates is based on their biosynthetic origins. Cells synthesize monosaccharides from the three-carbon "building block" D-glyceraldehyde, extending the chain from the C-1 atom. Thus, in an aldotetrose, the C-2 atom is the original C-1 of glyceraldehyde. Extending the chain further, the C-3 atom of an aldopentose was originally C-1 of glyceraldehyde. So, nearly all naturally occurring monosaccharides have the same configuration as D-glyceraldehyde. This biosynthetic relationship explains why the stereogenic carbon atom farthest from the carbonyl group determines whether the compound is D or L.



D-glyceraldehyde D-ribose D-glucose D-fructose

Fischer projections of the aldotetroses, aldopentoses, and aldohexoses of the D series are shown in Figure 20.1. D-Glyceraldehyde, at the top of the "tree", is the parent aldose. When we insert a new stereogenic center (H—C—OH) between the carbonyl carbon atom and the stereogenic center below, the resulting molecules are D aldotetroses. Because the new CHOH group can have its OH group on the right or left, two aldotetroses, D-erythrose and D-threose, are possible. Note that aldotetroses contain two nonequivalent stereogenic centers, so $2^2 = 4$ stereoisomers are possible. The two L aldotetroses are not shown in Figure 20.1. D-Erythrose and L-erythrose are enantiomers, as are D-threose and L-threose.

Inserting a new stereogenic center (H—C—OH), which can have either of two configurations, between the carbonyl carbon atom and the stereogenic center at the

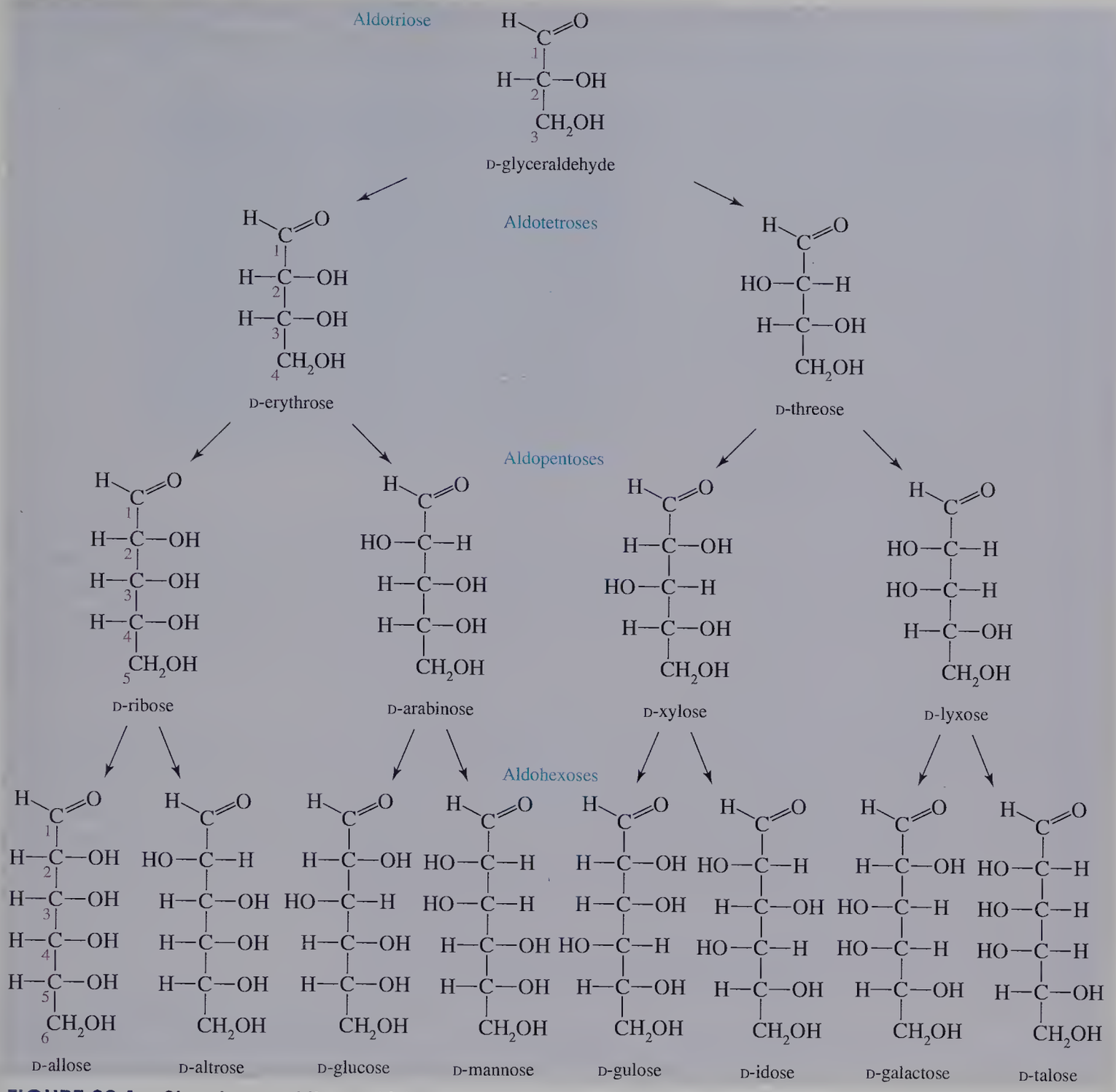


FIGURE 20.1 Structures of the D-Aldoses

C-2 atom in D-erythrose, leads to two D-aldopentoses: D-ribose and D-arabinose. Similarly, inserting a new stereogenic center (H—C—OH) between the carbonyl carbon atom and the stereogenic center at the C-2 atom in D-threose yields D-xylose and D-lyxose. Repeating the process one more time in each of the four D aldopentoses gives a total of eight D aldohexoses. D-Glucose and D-galactose are the most widely found in nature. D-Mannose and D-talose occur in smaller amounts. The others are extremely rare.

The isomeric monosaccharides shown in any group in Figure 20.1 are diastereomers. They are not enantiomers because they are not mirror images. To write the enantiomer of a monosaccharide of the D series, we must reverse the configuration of

each stereogenic center because one molecule must be the mirror image of the other. The enantiomeric relationship of the glucose isomers is shown in Figure 20.2.

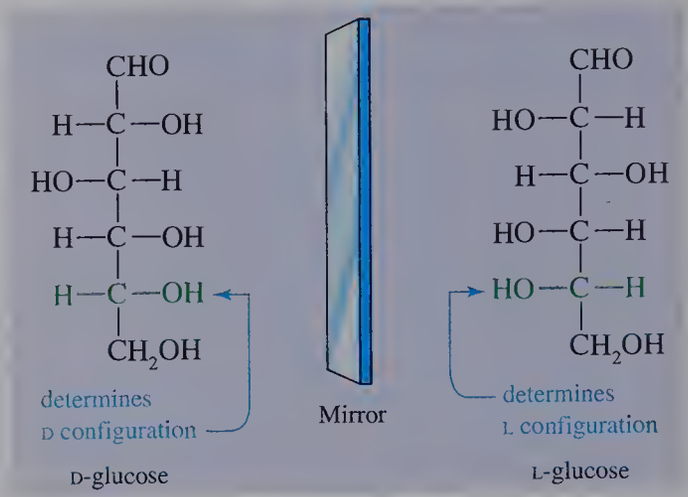


FIGURE 20.2 Enantiomeric Relationship of D and L Monosaccharides

Ketoses

Our focus to this point has been the aldoses, which play an important role in many biological processes. However, several ketoses also play a pivotal role in metabolism. The Fischer projections of the ketotetroses, ketopentoses, and ketohexoses of the D series are shown in Figure 20.3. The "parent" ketose is the ketotriose dihydroxyacetone. We can construct ketoses from dihydroxyacetone by inserting chiral centers (H—C—OH) one at a time between the ketone carbonyl carbon atom and the carbon atom directly below it.

The simplest ketose, dihydroxyacetone, contains no stereogenic carbon atom. This ketose occurs in the metabolism of glucose as a phosphate ester at the C-3 hydroxyl group. Fructose, the most important ketohexose, results from isomerization of glucose during glycolysis, a metabolic pathway that all cells use to degrade glucose and produce energy. The ketopentoses ribulose and xylulose are intermediates in the pentose phosphate pathway, another important metabolic pathway that produces the ribose necessary for ribonucleic acids.

Uncommon Monosaccharides

Most aldoses and ketoses are unbranched compounds with an oxygen functional group at each carbon atom. However, a few structural variations occur in some uncommon monosaccharides. Most of the compounds are named using the more common monosaccharides as the "parent". Most ketoses have the carbonyl carbon atom at C-2 and can isomerize to aldoses (Section 20.4). However, a 3-keto isomer of ribose exists. A more common variation of structure involves replacement of one or more hydroxyl groups by hydrogen. The best known example of such a **deoxy** sugar is 2-deoxyribose.

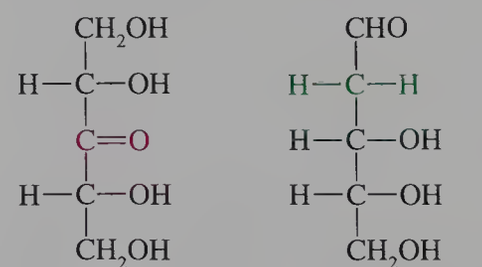
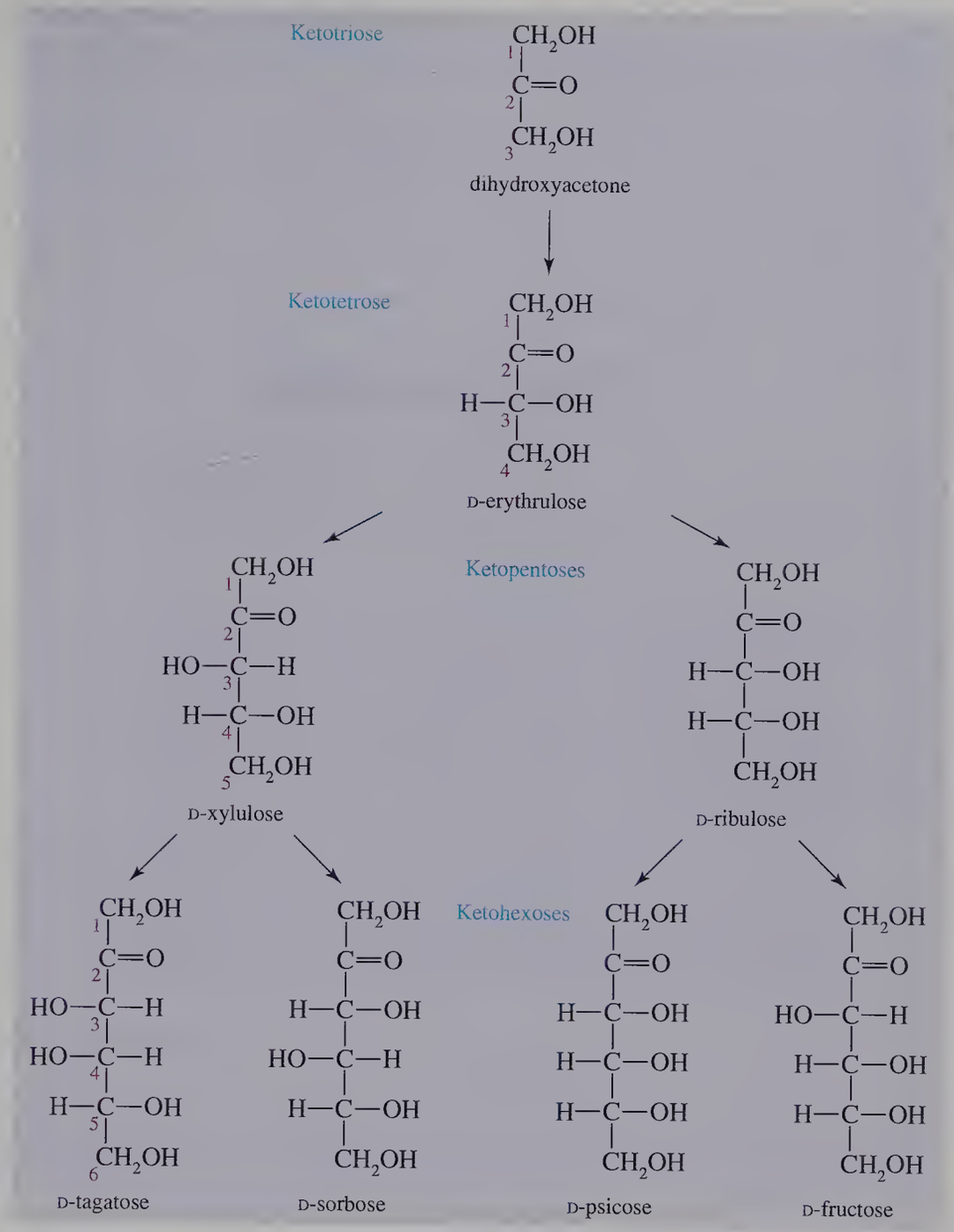
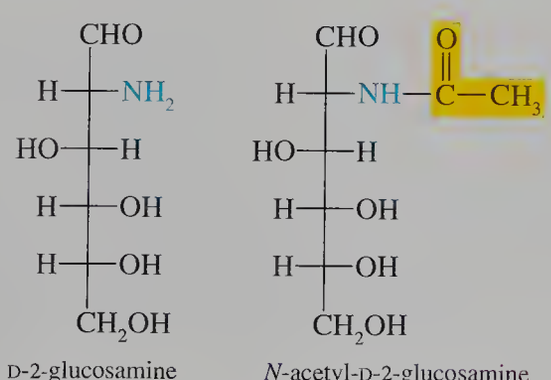


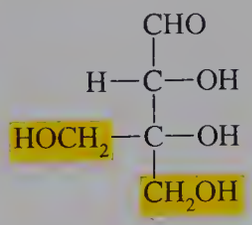
FIGURE 20.3 Structures of the D-2-Ketoses



Another structural variation replaces a hydroxyl group with an amine group and its derivatives. These **amino sugars** are components of some antibiotics. They also occur in polysaccharides contained in the exoskeleton of arthropods and are components of blood group antigens. The polysaccharide found in lobster shells contains the *N*-acetyl derivative of D-2-glucosamine.



A few monosaccharides have branched structures. D-Apiose is an example. Note that C-3 is not a stereogenic center because it is bonded to two hydroxymethyl groups.



D-apiose

Problem 20.2

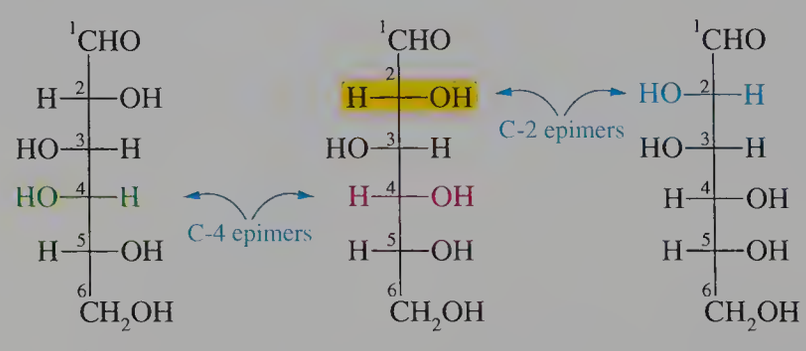
Draw the structure of each of the following monosaccharides.
(a) L-arabinose, the enantiomer of D-arabinose
(b) a 3-ketose structurally related to D-glucose
(c) 6-deoxymannose

20.4 Isomerization of Monosaccharides

The isomerization of a monosaccharide requires an inversion of configuration at a stereogenic center. For compounds that contain two or more stereogenic centers, the inversion at a single stereogenic center changes the physical properties of the molecule. Because there are two or more hydroxyl groups in monosaccharides, the selective inversion of configuration at one stereogenic center usually requires the selective protection of other hydroxyl groups in the form of cyclic acetals. In principle, chemical reactions can invert the configuration at any stereogenic center, but in practice the reaction requires many synthetic steps. Each step involves chemistry that you have already learned, and we will not elaborate on the synthetic details in this text with the single exception of the special case of epimerization.

Epimers

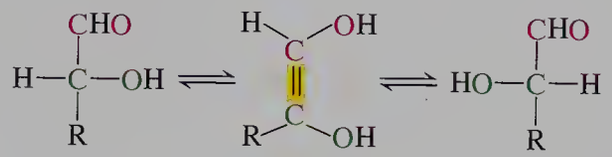
One stereogenic center of a monosaccharide can be easily inverted. We recall that diastereomers are stereoisomers that are not enantiomers. Diastereomers that contain two or more stereogenic carbon atoms but differ in configuration at only one stereogenic center are called **epimers**. For example, the diastereomers D-glucose and D-galactose are epimers because they differ in configuration only at the C-4 atom. D-Glucose and D-mannose are epimers that differ in configuration at the C-2 atom.



D-galactose D-glucose D-mannose

The interconversion of epimers such as D-glucose and D-mannose at the C-2 atom illustrates a chemical reaction described in Chapter 19. The α hydrogen atom

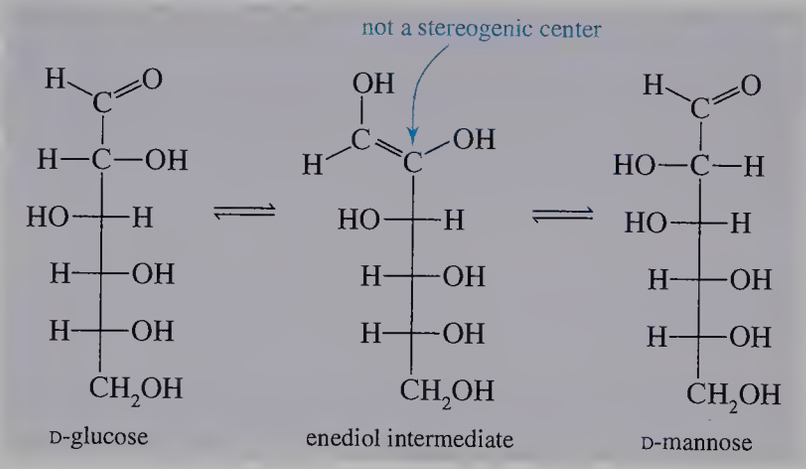
of an aldehyde is enolizable, and in the presence of a weak base it undergoes a keto–enol tautomerization reaction to produce a small amount of an isomeric enol. In an aldose, the α carbon atom is chiral and has a hydroxyl group bonded to it. Tautomerization yields an **enediol** in which the α carbon atom is not chiral. In the reverse reaction, in order to regenerate the aldose, a stereogenic center reforms at the α carbon atom. It can have either of two configurations, and two C-2 epimers result.



epimer 1 (an enediol) (*E* and *Z*) epimer 2

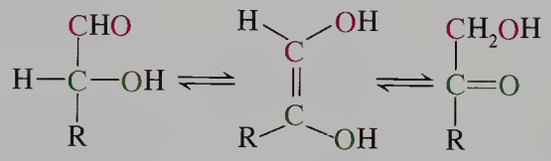
For example, D-glucose can be converted to D-mannose by way of an enediol intermediate (Figure 20.4). A specific epimerase catalyzes this reaction in cells.

FIGURE 20.4 Isomerization of Aldoses via an Enediol Intermediate



Interconversion of Aldoses and Ketoses

An enediol has a hydroxyl group on each double-bonded carbon atom. Hence, it is the enol of a ketose as well as two enantiomeric aldoses. The original C-1 of the aldose becomes a primary alcohol; the C-2 secondary alcohol becomes a ketone.



(an aldose) (an enediol) (a ketose)

Therefore glucose, mannose, and fructose can all be in equilibrium with the same enediol. This isomerization process occurs in biochemical reactions near pH 7 for several aldoses and ketoses in enzyme-catalyzed reactions. The isomerization of glucose and fructose occurs by way of their 6-phosphate esters and is catalyzed by glucose 6-phosphate isomerase. The equilibrium constant for the formation of fructose 6-phosphate from glucose 6-phosphate is approximately 0.3. This reaction is one of the initial steps in glycolysis. The reaction continues because subsequent reactions with favorable equilibrium constants remove the product.

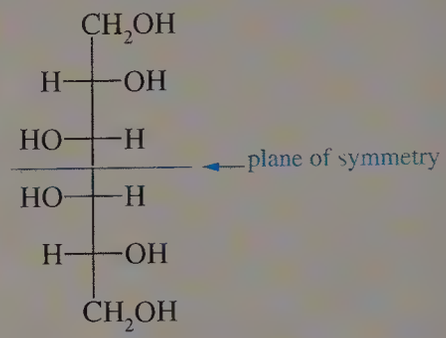
Galactosemia

Epimers are interconverted in cells by enzymes called **epimerases**. For example, an epimerase catalyzes the conversion of D-galactose into D-glucose in an important metabolic process. Some newborn children lack a functional gene for the necessary epimerase. This results in the genetic disease galactosemia.

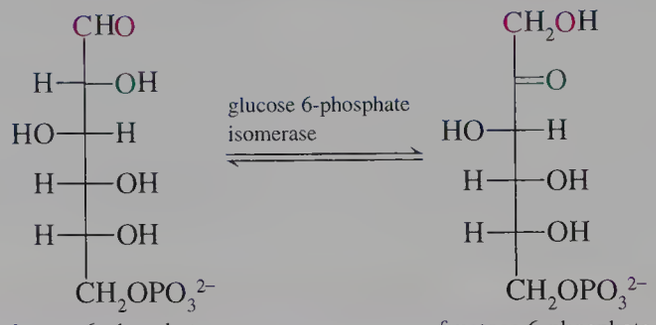
Galactose is a component of the disaccharide lactose. Hydrolysis of lactose produces D-galactose and D-glucose. When the epimerase that converts galactose to glucose is missing, D-galactose accumulates in the body.

Galactose has a C-1 aldehyde group that is reduced to an alcohol called galactitol. Galactitol accumulates in the lens of the eye and causes cataracts. It also causes severe mental retardation. These disastrous consequences can be prevented entirely by a diet free of milk and milk products for affected newborns.

Note that although galactitol has several stereogenic carbon atoms, the molecule as a whole has a plane of symmetry. It is therefore an optically inactive *meso* compound.



galactitol



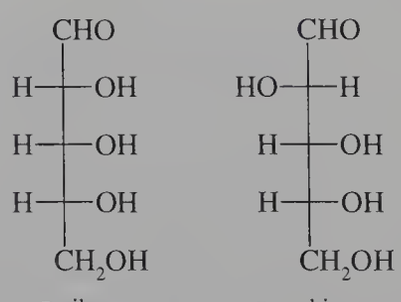
glucose 6-phosphate fructose 6-phosphate

Problem 20.3

Which aldopentose is an epimer of D-ribose at the C-2 atom?

Sample Solution

Consider the structure of D-ribose and examine the configuration at the C-2 atom. The hydroxyl group is on the right side of the formula. Write a structure that has the same configuration at the C-3 and C-4 atoms, but place the hydroxyl group at the C-2 atom on the left side. This compound is D-arabinose.



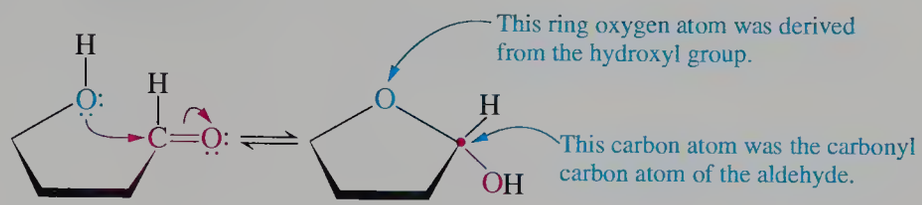
D-ribose D-arabinose

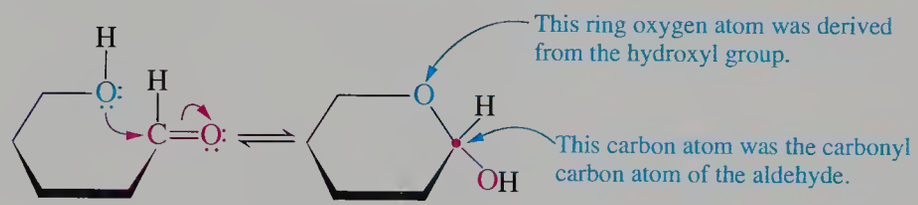
Problem 20.4

Ribulose 5-phosphate is converted to xylulose 5-phosphate in one of the steps of the pentose phosphate pathway. Suggest a mechanism for this reaction.

20.5 Hemiacetals and Hemiketals

We recall that aldehydes and ketones react reversibly with alcohols to form hemiacetals and hemiketals, respectively (Section 19.6). With the hydroxyl group and the carbonyl group in the same molecule, the equilibrium constant for the formation of a cyclic hemiacetal by way of an intramolecular reaction is larger than for an intermolecular reaction. Cyclic hemiacetals containing five or six atoms in the ring are the most common.

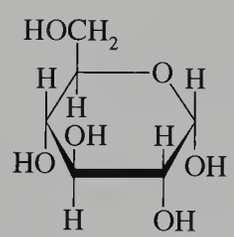




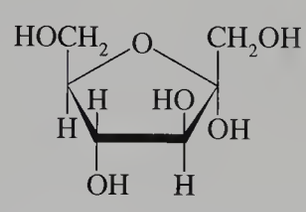
The cyclic hemiacetal or hemiketal forms of aldo- and ketohexoses and aldopentoses are the predominant forms of these sugars, rather than the open-chain structures we have discussed to this point. Cyclic hemiacetals and hemiketals of carbohydrates that contain five-membered rings are called **furanoses**. Cyclic hemiacetals and hemiketals that contain six-membered rings are called **pyranoses**. We usually represent these structures with planar structures called Haworth projection formulas.

Haworth Projection Formulas

A Haworth projection formula represents a cyclic hemiacetal or hemiketal as a planar structure viewed edge-on. Bond lines representing atoms toward the viewer appear as heavy wedges, bond lines away from the viewer as unaccentuated lines. The carbon atoms are arranged clockwise with the C-1 atom of the aldohexose or aldopentose on the right. For hemiketals the C-2 atom is placed on the right.



Haworth projection of a pyranose



Haworth projection of a furanose

Let's see how the Fischer projection formula of D-glucose can be converted into a hemiacetal written as a Haworth projection formula. The open-chain form of D-glucose looks like a C-shaped structure arranged perpendicular to the page (Figure 20.5). (Recall that the carbon chain in a Fischer projection formula projects away from the reader.) Now, tilt this curved chain to the right so that it is horizontal. Groups on the right in the Fischer projection project downward, whereas groups on the left project upward.

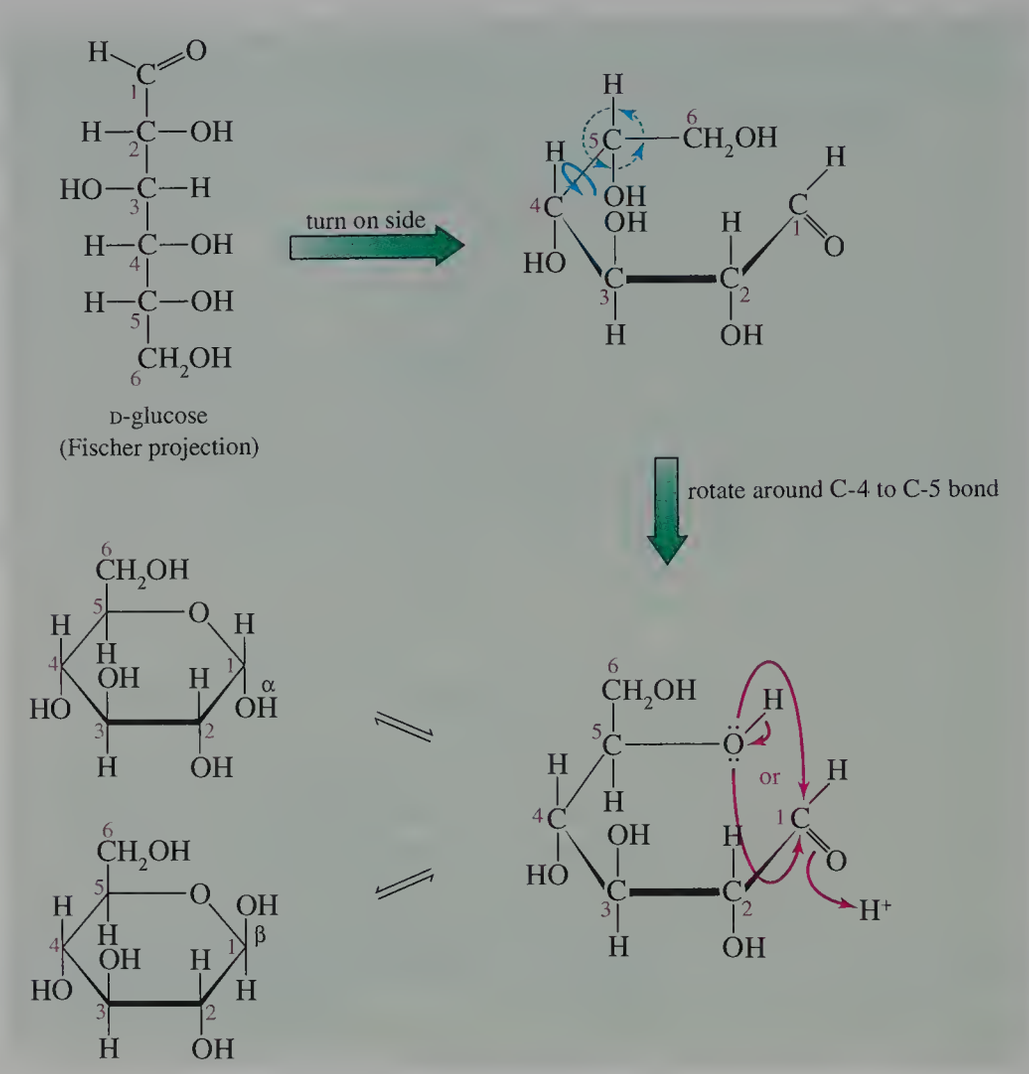
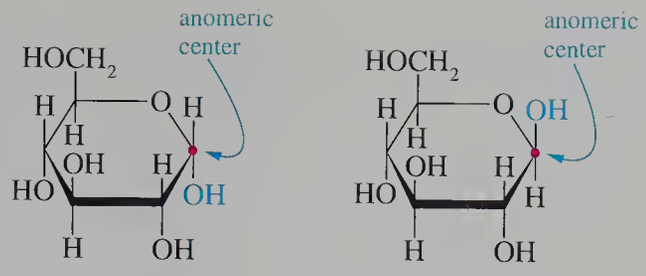


FIGURE 20.5 The Haworth Projection Formula of D-Glucopyranose

In this arrangement, the C-5 OH group is not near enough to the carbonyl carbon atom to form a ring. To bring the C-5 OH group nearer the carbonyl carbon atom, rotate that part of the structure about the bond between the C-4 and C-5 atoms. The CH_2OH group is now above the plane of the curved carbon chain, and the C-5 hydrogen atom is below the plane. The oxygen atom of the C-5 OH group in the plane adds to the carbonyl carbon atom. A six-membered ring containing five carbon atoms and one oxygen atom results. All carbohydrates with a D configuration have the $-CH_2OH$ group located above the ring in a Haworth projection.

When glucose forms a cyclic hemiacetal, four different groups are attached to the C-1 atom. Thus, a new stereogenic center forms at the original carbonyl carbon atom, and two configurations are possible. If the hydroxyl group of the hemiacetal projects below the plane, the compound is α-D-glucopyranose. If it projects above the plane, the compound is β-D-glucopyranose.



α-D-glucopyranose β-D-glucopyranose

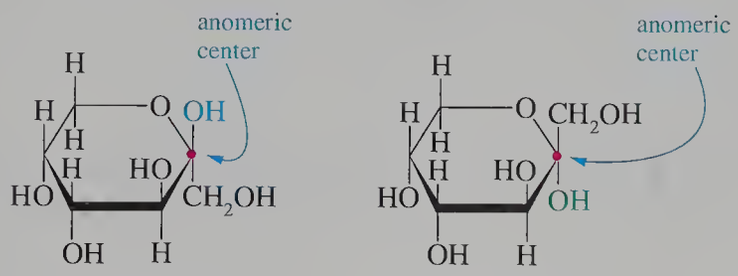
The α and β forms of D-glucose are diastereomers that differ in configuration at one stereogenic center. Hence, they are epimers. Compounds whose configurations differ only at the hemiacetal center are a special type of epimer called **anomers**. The stereogenic carbon atom at the hemiacetal center that forms in the cyclization reaction is called the **anomeric carbon atom**.

Aldohexoses are most stable as pyranoses. The percentages of the anomers of the pyranoses and of the furanoses at equilibrium are given in Table 20.1.

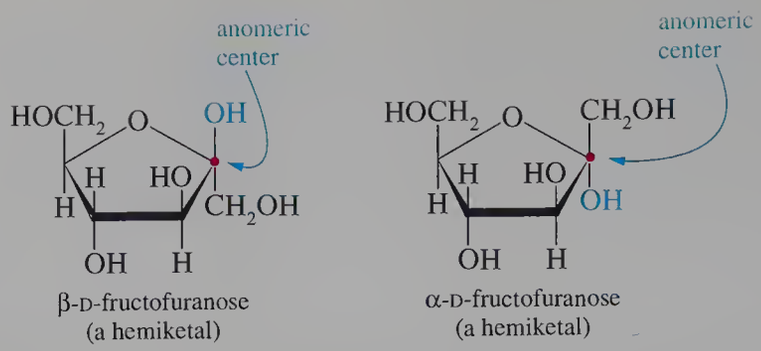
Table 20.1
Composition of Monosaccharides at Equilibrium in Solution (in percent)

	Pyranose		*Furanose*	
Monosaccharide	α	β	α	β
D-glucose	36	64		
D-mannose	67	32	0.8	0.2
D-galactose	31	69		
D-allose	18	70	5	7
D-altrose	27	40	20	13
D-idose	38	38	10	14
D-talose	40	29	20	11
D-arabinose	63	34	2	1
D-ribose	20	56	6	18
D-xylose	37	63		
D-fructose	2	66	7	25

Now let's consider the cyclic forms of the ketohexose D-fructose. D-Fructose cyclizes in aqueous solution to give a mixture containing 32% α- and β-D-fructofuranose and 68% of α- and β-D-fructopyranose. The furanose isomers form when the C-5 OH group adds to the carbonyl carbon atom of the C-2 keto group. A ring of four carbon atoms and one oxygen atom results. The pyranose isomers form when the C-6 hydroxyl group adds to the C-2 carbonyl atom. Again, α and β designate the configuration of the hydroxyl group at the anomeric carbon atom.



β-D-fructopyranose (a hemiketal) α-D-fructopyranose (a hemiketal)



Conformations of Monosaccharides

Haworth projection formulas are easy to draw, but they do not give an accurate three-dimensional representation of carbohydrates. Pyranose rings contain six atoms and exist in chair conformations just like cyclohexane (Section 4.7). Haworth projection formulas are converted into chair representations by "moving" two carbon atoms. The anomeric carbon atom is lowered below the plane of the ring, and the C-4 atom is raised above the plane of the ring. The remaining four atoms, three carbon atoms and the ring oxygen atom, remain unchanged. This process is shown in Figure 20.6 for both α-D-glucopyranose and β-D-glucopyranose. Both the hydrogen atoms and the hydroxyl groups can be shown. However, a more condensed form that omits the C—H bonds is often used.

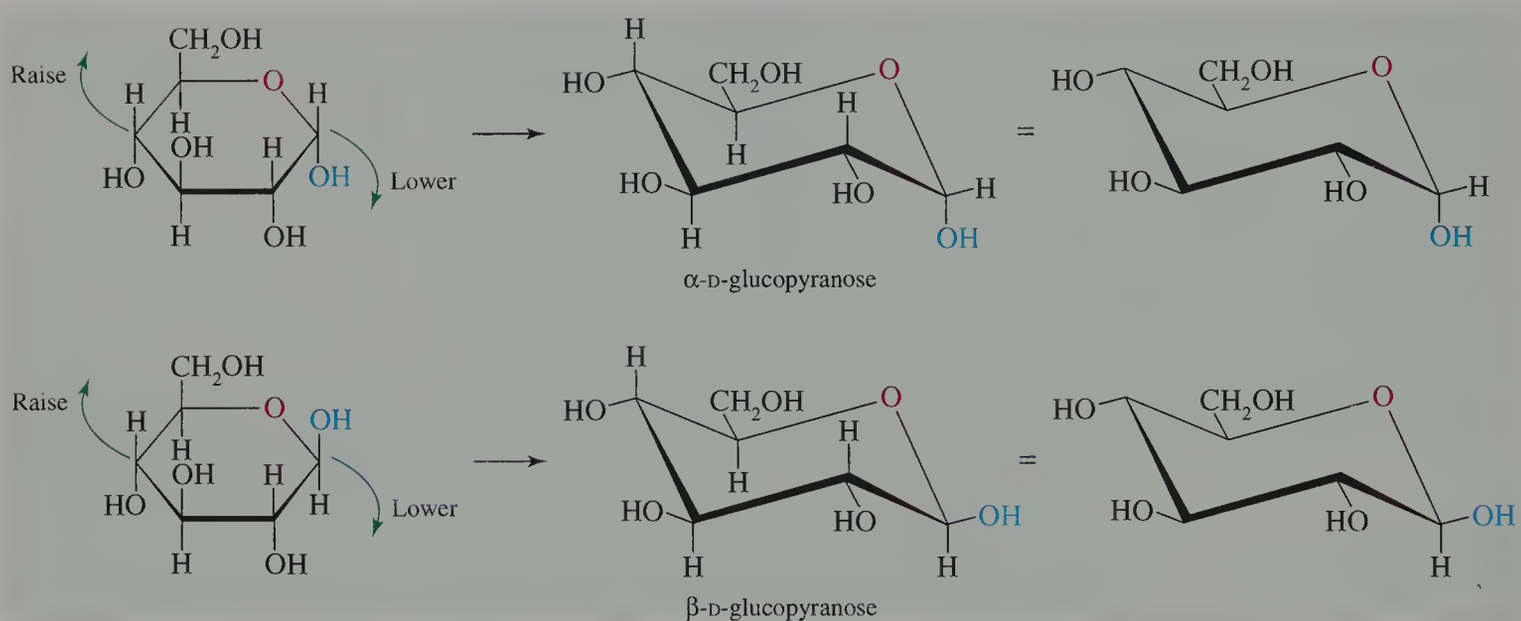
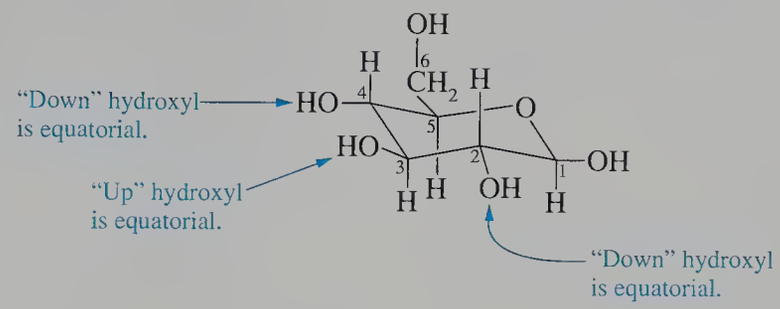


FIGURE 20.6 Conversion of Haworth Projection into Chair Representation

Any hydroxyl group (or other group) that is up in the Haworth projection is also up in the chair conformation. However, we recall that "up" and "down" do not

correspond to axial and equatorial, respectively. Each carbon atom must be individually examined. On one set of alternating carbon atoms, an "up" substituent is axial. On the intervening carbon atoms, an "up" substituent is equatorial.



Note the changes in the locations of the hydroxyl groups in the Haworth projection compared to those in the chair conformation. Although the hydroxyl groups were both up and down in the Haworth projection formula, all hydroxyl groups are equatorial in β-D-glucopyranose. We recall that this anomer is the more stable. That is, it is the major anomer in an equilibrium mixture of glucose. Note also that glucopyranose, the most abundant aldohexose, is the only aldohexose in which all hydroxyl groups are equatorial.

Mutarotation

Now let's consider the experimental consequences of the formation of anomers of monosaccharides. When D-glucose crystallizes from methanol, α-D-glucopyranose, which melts at 146 °C, results. It has α_D = +112.2. On the other hand, when D-glucose crystallizes from acetic acid, the β anomer, which melts at 150 °C, results. It has α_D = +18.7 (Figure 20.7). We recall that diastereomers have different chemical and physical properties, so these data are not surprising.

When α-D-glucopyranose dissolves in water, the optical rotation of the solution slowly changes from the initial value of +112.2 to an equilibrium value of +54. If β-D-glucopyranose dissolves in water, the rotation of the solution slowly changes from the initial value of +18.7 to the same equilibrium value of +54. This gradual change in rotation to an equilibrium point is known as **mutarotation**. Mutarotation results from the interconversion of the cyclic hemiacetals with the open-chain form in solution. Ring opening followed by recyclization can form either the α or β anomer. At equilibrium the solution contains 36% of the α anomer and 64% of the β anomer of glucose, with less than 0.01% of the open-chain form. In cells, an enzyme called mutarotase catalyzes the mutarotation of glucose.

Although the mutarotation of glucose interconverts only anomeric pyranose forms, some aldohexoses form a four-component mixture of anomeric pyranoses and anomeric furanoses. Fructose also forms a four-component mixture of anomeric furanoses and pyranoses (Table 20.1). An analysis of the structural factors contributing to the relative stability of the sizes of the rings and the configuration of the anomers is a complex conformational problem beyond the scope of this text.

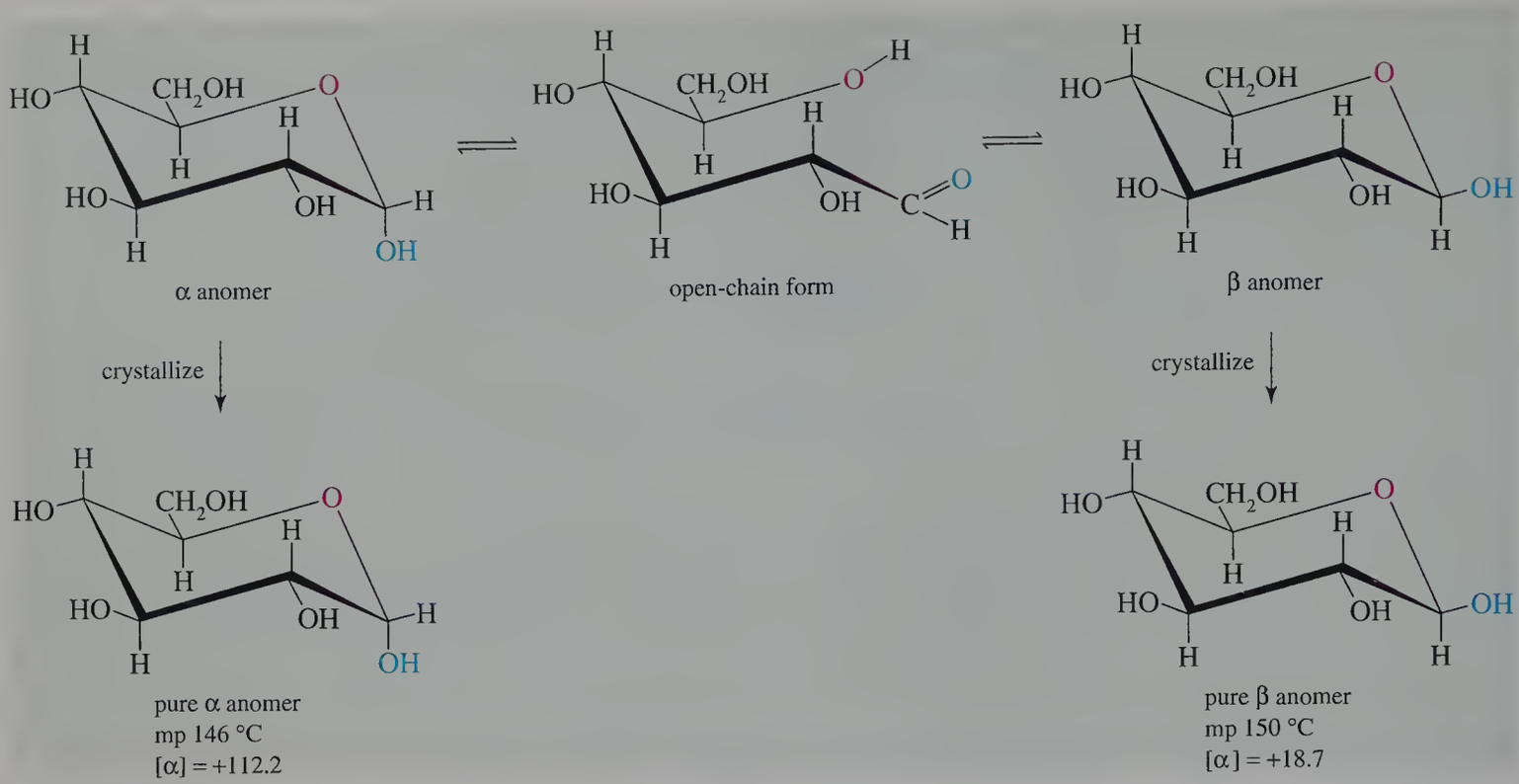


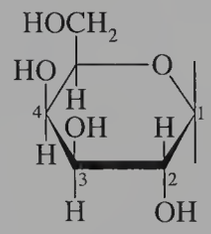
FIGURE 20.7 Interconversion of Anomers and Mutarotation

Problem 20.5

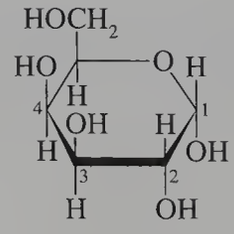
Draw the Haworth projection of the α anomer of the pyranose form of D-galactose, that is, α-D-galactopyranose.

Sample Solution

Draw a pyranose ring containing five carbon atoms and one oxygen atom. For the D configuration, the $-CH_2OH$ group is above the plane of the ring. Enter the hydroxyl groups and hydrogen atoms at the C-2, C-3, and C-4 atoms. They are down, up, and up, respectively, to correspond to right, left, and left, respectively, in the Fischer projection formula.



Finally, the α anomer has a hydroxyl group below the plane of the ring at the anomeric carbon atom, C-1.

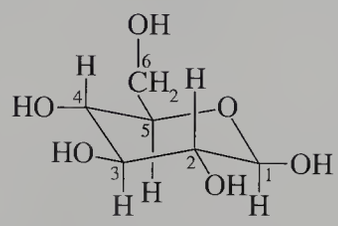


Problem 20.6

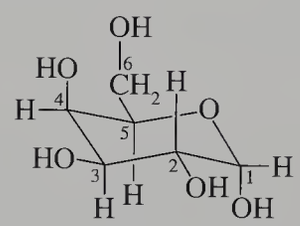
Draw the chair conformation of α-D-galactopyranose using glucose as a reference.

Sample Solution

Recall that the β anomer of glucose has all of its hydroxyl groups in equatorial positions. The α anomer of galactose must have an axial hydroxyl group at the C-1 atom. We also recall that galactose is the C-4 epimer of glucose. Therefore, the hydroxyl group at the C-4 atom must be axial.



β-D-glucopyranose



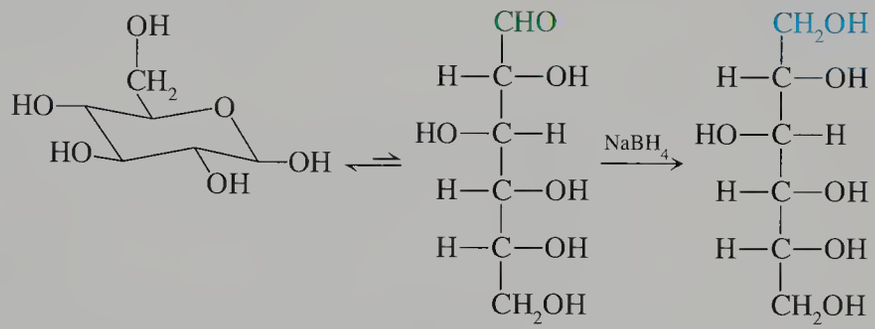
α-D-galactopyranose

20.6 Reduction and Oxidation of Monosaccharides

Although five- and six-carbon monosaccharides exist predominately as hemiacetals and hemiketals, they undergo the characteristic reduction and oxidation reactions of simple aldehydes and ketones. The reduction or oxidation reaction occurs by way of the carbonyl group in the small amount of the open-chain form of the monosaccharide in equilibrium with its cyclic hemiacetal or hemiketal. As the reduction or oxidation occurs, the equilibrium shifts to produce more of the carbonyl form until eventually all the monosaccharide reacts.

Reduction of Monosaccharides

Treating an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an **alditol**. The alditol derived from D-glucose is called D-glucitol. D-Glucitol occurs in some fruits and berries. It is produced and sold commercially as the sugar substitute called sorbitol.



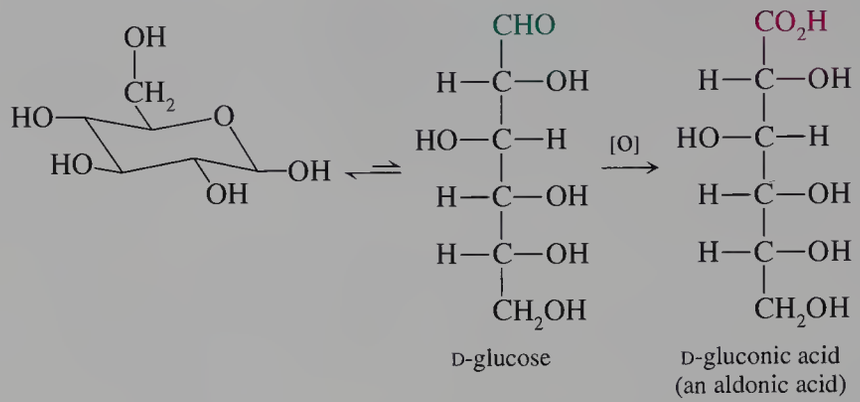
D-glucose

D-glucitol
(an alditol)

Oxidation of Carbohydrates

In Chapter 18 we saw that aldehydes are oxidized by Tollens's reagent, Benedict's solution, and Fehling's solution. These reagents also oxidize open-chain aldoses that exist in equilibrium with the cyclic hemiacetal form. When some of the open-chain

form reacts, the equilibrium shifts to form more compound for subsequent oxidation, and eventually all the aldose is oxidized. Oxidation yields a product with a carboxyl at the original C-1 atom. This product is called an **aldonic acid**.

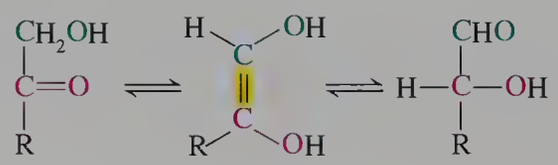


D-glucose

D-gluconic acid
(an aldonic acid)

If Tollens's reagent is used as the oxidizing agent, metallic silver forms a mirror on the walls of the test tube. If Benedict's solution is used, a red precipitate of Cu_2O indicates that a reaction has occurred. We noted earlier that Benedict's solution is used to detect glucose in urine. If no glucose is present in the urine, the Benedict's solution remains blue. But with increasing glucose concentrations, the mixture of precipitate and solution may vary in color from green to yellow to orange to red. Aqueous bromine at approximately pH 6 can also oxidize aldoses to aldonic acids. This reagent is the preferred method for the laboratory synthesis of aldonic acids. It does not oxidize any of the hydroxyl groups in an aldose.

Benedict's solution also oxidizes ketoses. We certainly do not expect this because Benedict's solution does not oxidize ketones. However, α-hydroxy ketones tautomerize in basic solution, and Benedict's solution is basic. The tautomer of a ketose is an enediol that not only reverts to the α-hydroxy ketone, but also forms an isomeric α-hydroxy aldehyde.

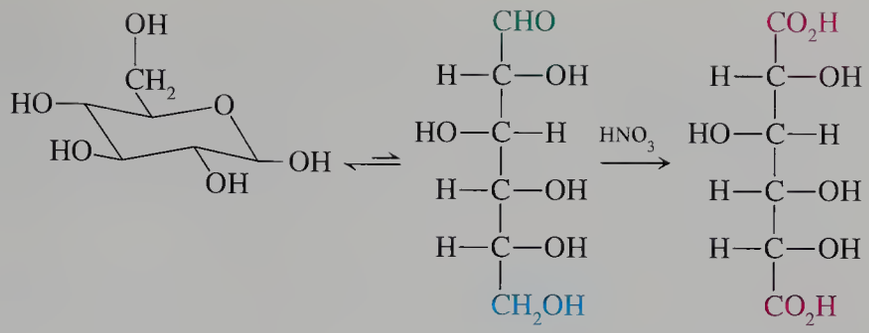


(a ketose) (an enediol) (an aldose)

Shifting a hydrogen atom from the C-2 hydroxyl group to the C-1 atom in the enediol regenerates the original ketose. However, shifting a hydrogen atom from the C-1 hydroxyl group to the C-2 atom forms an aldose. In basic solution, then, a ketose, such as fructose, is in equilibrium with an aldose such as glucose. The aldose reacts with Benedict's solution, and more ketose is converted into aldose. The equilibrium shifts, as predicted by Le Châtelier's principle, and eventually all the ketose is oxidized.

Carbohydrates that react with Benedict's solution are called **reducing sugars**. The term reducing refers to the effect of the carbohydrate on Benedict's solution. Benedict's solution oxidizes the carbohydrate, but the carbohydrate reduces the Benedict's solution. Both aldoses and ketoses are reducing sugars.

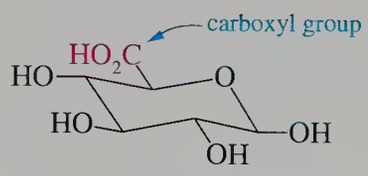
Stronger oxidizing agents can oxidize other hydroxyl groups of aldoses. For example, dilute nitric acid oxidizes both the aldehyde group and the primary alcohol of aldoses to give **aldaric acids**.



D-glucose

D-glucaric acid
(an aldaric acid)

Cells can enzymatically oxidize the terminal $-CH_2OH$ group of an aldose without oxidizing the aldehyde group. The product is a **uronic acid**. The enzyme responsible for this reaction uses $NADP^+$ (nicotinamide adenine dinucleotide phosphate, a close structural relative of NAD^+) as the oxidizing agent. An example of this reaction is the oxidation of D-glucose to give D-glucuronic acid, a component in the polysaccharide hyaluronic acid, found in the vitreous humor of the eye.



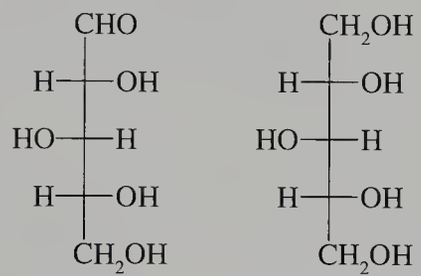
D-glucuronic acid

Problem 20.7

D-Xylitol is used as a sweetener in some chewing gums that are said to have a lower probability of causing caries than those containing glucose and fructose. Deduce the structure of D-xylitol from its name.

Sample Solution

The name resembles D-xylose. Based on the suffix, the compound is the reduced product of xylose. Convert the aldehyde group of xylose to a primary hydroxyl group. The configurations of the chiral centers are the same as in D-xylose.



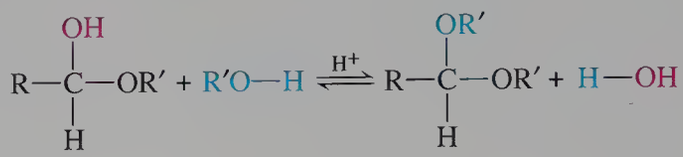
D-xylose D-xylitol

Problem 20.8

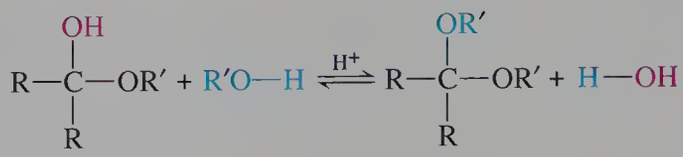
Is ribulose a reducing sugar?

20.7 Glycosides

In Chapter 19 we saw that hemiacetals and hemiketals react with alcohols to yield acetals and ketals, respectively. Acid catalyzes the reaction, shifting the equilibrium to the right if there is excess alcohol or the water that forms is removed. In this substitution reaction, an —OR′ group replaces the —OH group.



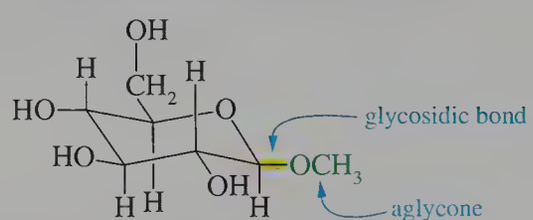
(an acetal)



(a ketal)

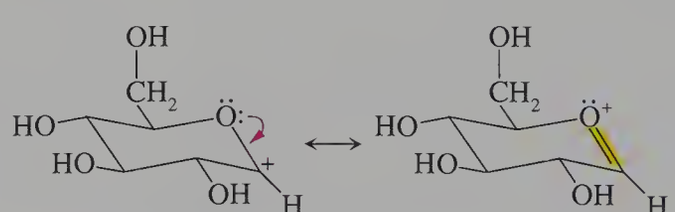
The hemiacetal and hemiketal forms of monosaccharides also react with alcohols to form acetals and ketals. These acetals and ketals are called **glycosides**, and the new carbon–oxygen bond a **glycosidic bond**. The group bonded to the anomeric carbon atom of a glycoside is an **aglycone**. In most aglycones, an oxygen atom from an alcohol or phenol bonds to the anomeric carbon atom. However, nucleosides, nucleotides, nucleic acids, and several coenzymes contain aglycones with a nitrogen atom.

Glycosides are named by citing the aglycone group first and then replacing the *-ose* ending of the carbohydrate with *-oside*. The configuration at the glycosidic carbon atom must be indicated.



methyl β-D-glucopyranoside

Because hemiacetals and hemiketals exist in equilibrium as α or β anomers, two possible glycosides may form. Protonation of the C-1 OH group followed by loss of water yields a carbocation that is resonance stabilized by the oxygen atom in the ring.



resonance-stabilized carbocation in formation of an acetal

This carbocation may be attacked by the nucleophilic oxygen atom of an alcohol from either the top or the bottom of the structure. Subsequent loss of a proton to solvent yields the mixture of α and β anomers (Figure 20.8).

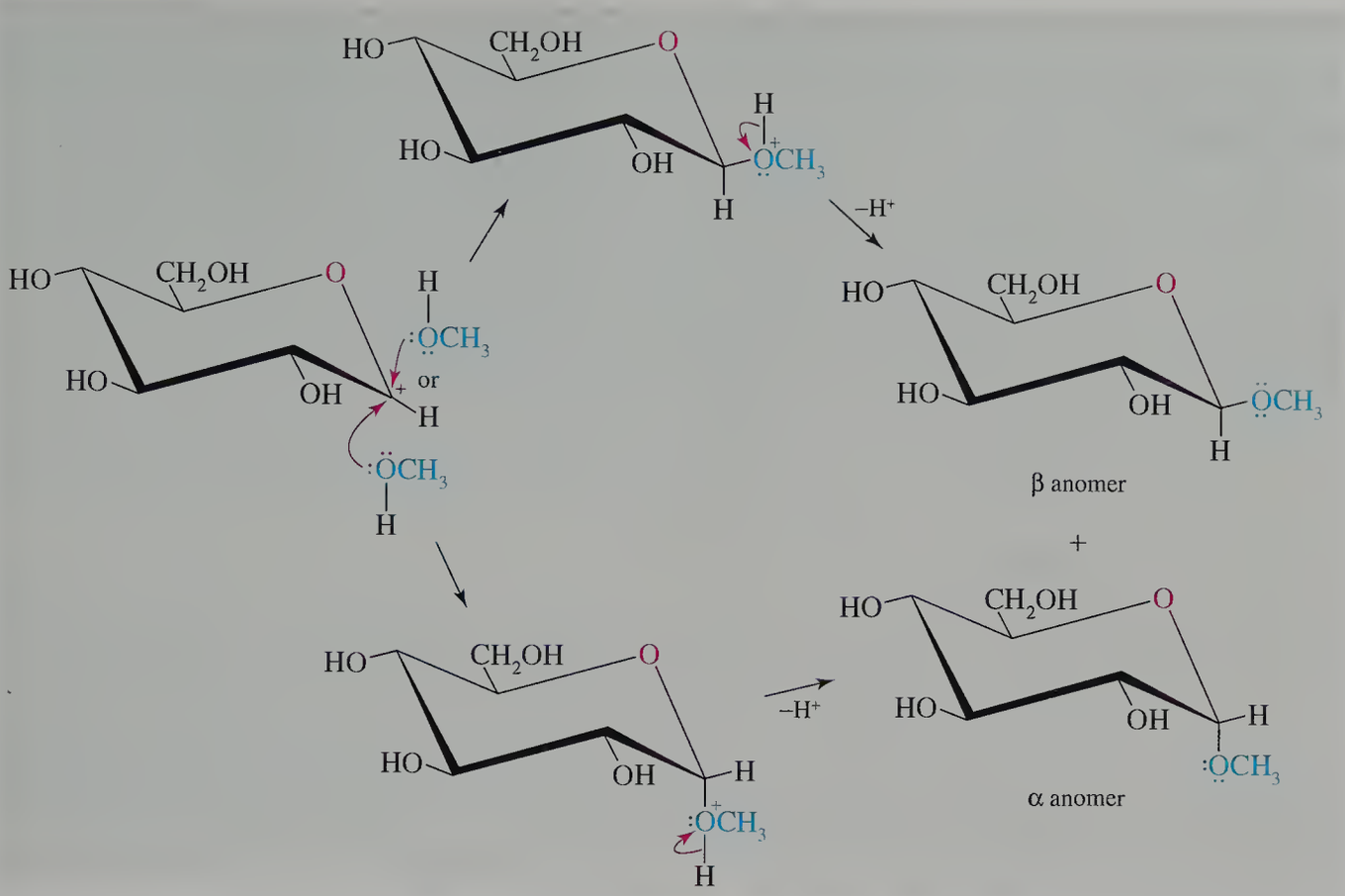
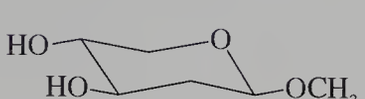


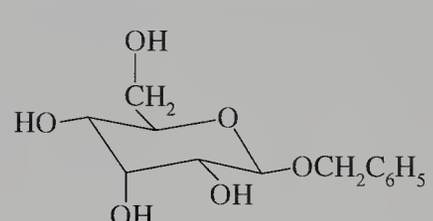
FIGURE 20.8 **Formation of Anomeric Glycosides of an Aldose**

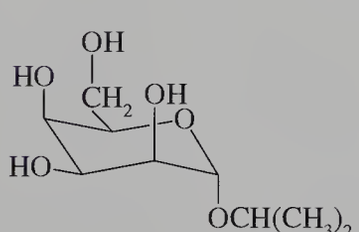
The anomeric glycosides are diastereomers with different physical properties. Like ordinary acetals and ketals, they remain stable in neutral or basic solution. Therefore, they are not reducing sugars because they do not hydrolyze to form a free aldehyde group in Benedict's solution, which is basic. However, glycosides are hydrolyzed in acid solution by the reverse of the reactions shown in Figure 20.8.

Problem 20.9

What compounds are required to form each of the following substances?

(a) 

(b) 

(c) 

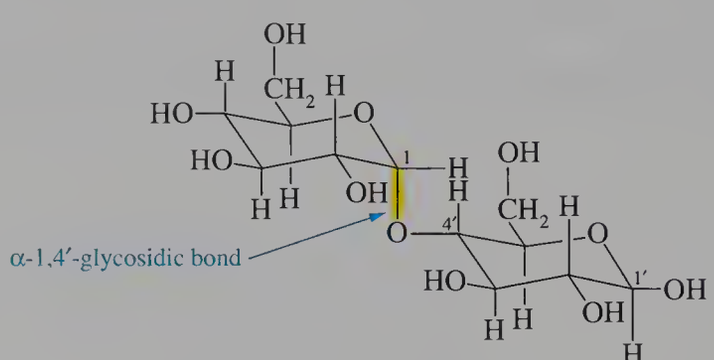
20.8 Disaccharides

Disaccharides are glycosides formed from two monosaccharides. One monosaccharide unit is a hemiacetal or hemiketal linked through its anomeric center to the hydroxyl group of the second monosaccharide unit, which is the aglycone. Disaccharides often are linked by a glycosidic bond between the C-1 atom of the hemiacetal of an aldose and the C-4 atom of the second monosaccharide. Such bonds are designated 1,4′. The prime superscript indicates the carbon atom of the monosaccharide that provides the hydroxyl group. Maltose, cellobiose, and lactose all have 1,4′-glycosidic bonds. The usual α or β designates the configuration of the anomeric carbon atom.

In principle, any of the carbon atoms of a monosaccharide could provide the hydroxyl group of the aglycone. And in fact, 1,1′-, 1,2′-, 1,3′-, 1,4′-, and 1,6′-glycosidic bonds have all been found in naturally occurring disaccharides containing aldohexoses. Note that a 1,1′-glycosidic bond connects both anomeric carbon atoms.

Maltose

Maltose consists of two molecules of D-glucose. The glycosidic oxygen atom of one glucose is α and is bonded to the C-4 atom of another glucose unit, the aglycone. Therefore, maltose is an α-1,4′-glycoside. Maltose results from the enzymatic hydrolysis of starch (a homopolysaccharide) catalyzed by the enzyme **amylase**. The enzyme maltase can further hydrolyze maltose to produce two molecules of D-glucose. Commercial maltose is produced from starch that has been treated with barley malt.



4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranose
(maltose)

Maltose has a more formal name: 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranose. This rather forbidding name is not quite as bad as it looks. The term in parentheses refers to the glucose unit at the left, which contributes the acetal portion of the glycosidic bond. The *-pyrano-* tells us that this part of the structure is a six-membered ring, and the suffix *-syl* tells us that the ring is linked to a partner by a glycosidic bond. The α gives the configuration of the glycosidic bond. The prefix 4-*O*- refers to the position of the oxygen atom of the aglycone, the right-hand ring. The β-D-glucopyranose describes the aglycone. It too is a pyranose. A look at the formal name makes it clear why we use the simpler name maltose.

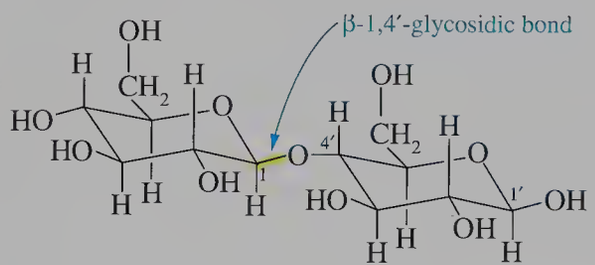
The right-hand glucose ring of maltose is shown as the β anomer, but the hydroxyl group can be either α or β. Because this center is a hemiacetal, both anomeric forms of maltose can exist in equilibrium in solution. This designation for the configuration of the aglycone ring should not be confused with the glycosidic bond at the acetal center, which is always α in maltose.

Because one of the monosaccharide units of maltose is a hemiacetal, maltose undergoes mutarotation. For the same reason, maltose is a reducing sugar. The free aldehyde formed by ring opening can react with Benedict's solution. If we do not

want to specify the configuration of the hemiacetal center of maltose, we use the name 4-*O*-(α-D-glucopyranosyl)-D-glucopyranose.

Cellobiose

Cellobiose is a disaccharide in which two molecules of D-glucose are linked by a β-1,4′-glycosidic bond. Cellobiose thus differs from maltose by the configuration of its glycosidic bond. As in maltose, the aglycone of cellobiose is a hemiacetal, either α or β. Thus, cellobiose undergoes mutarotation and is a reducing sugar. In solution, the two forms of cellobiose exist in equilibrium. Do not confuse the hemiacetal center with that of the glycosidic bond, which is always β in cellobiose.

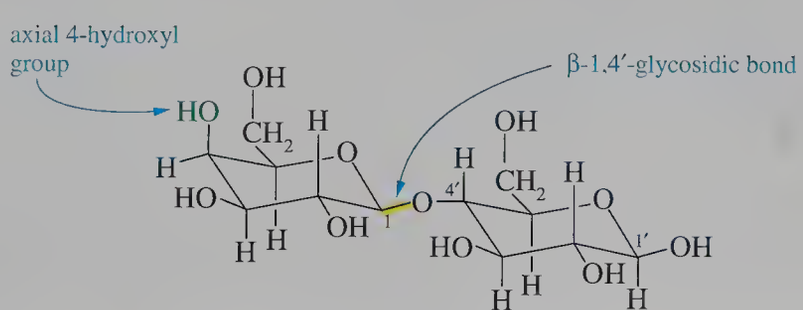


4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose
(cellobiose)

Cellobiose results from the hydrolysis of cellulose, a homopolysaccharide of glucose in which all units are linked by 1,4′-glycosidic bonds. Humans do not have an enzyme to hydrolyze cellobiose. Small differences in configuration at the 1,4′-linkage result in remarkable differences in the chemical reactivity of these biomolecules. Enzymes called glycosidases hydrolyze glycosidic bonds. A glycosidase that hydrolyzes α-1,4′-glycosidic bonds completely ignores the molecules that have β-1,4′-glycosidic bonds (and vice versa).

Lactose

Lactose, often called milk sugar, is a disaccharide found in the milk of many mammals, including both humans and cows. The IUPAC name of lactose is 4-*O*-(β-D-galactopyranosyl)-D-glucopyranose. The configuration at the C-4 atom of galactose is opposite that of glucose (glucose and galactose are C-4 epimers). The hydroxyl group at the C-4 atom of the ring on the left is equatorial in the glucose ring of maltose, but axial in the galactose ring of lactose. The ring on the left in both lactose and cellobiose is linked by a β-glycosidic linkage to the C-4 atom of a D-glucopyranose ring on the right. In both lactose and cellobiose, the glycosidic bond is β-1,4′. Humans have an enzyme called β-galactosidase (also known as lactase) that hydrolyzes the β-1,4′-galactosidic linkage of lactose. However, β-galactosidase does not hydrolyze the β-1,4′-glycosidic linkage of cellobiose.



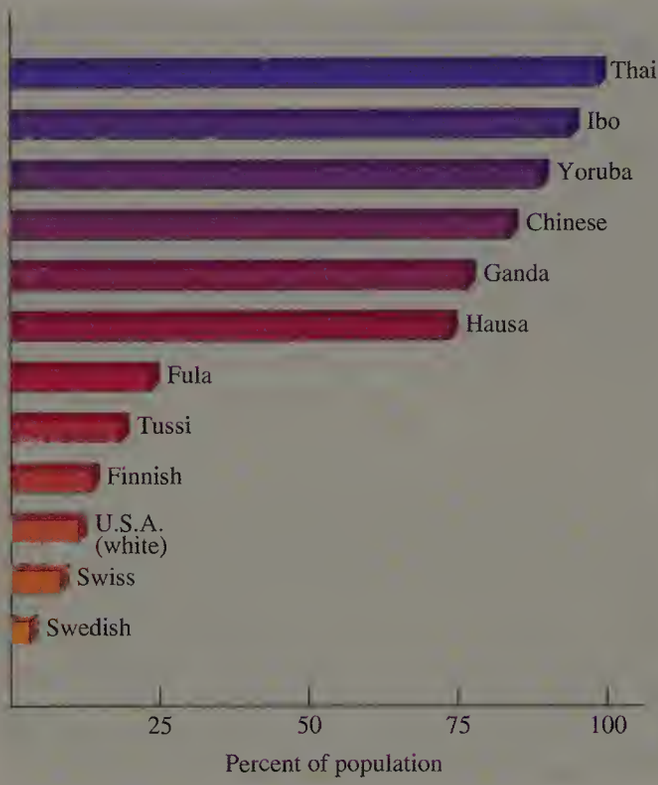
4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose
(lactose)

Lactose Intolerance

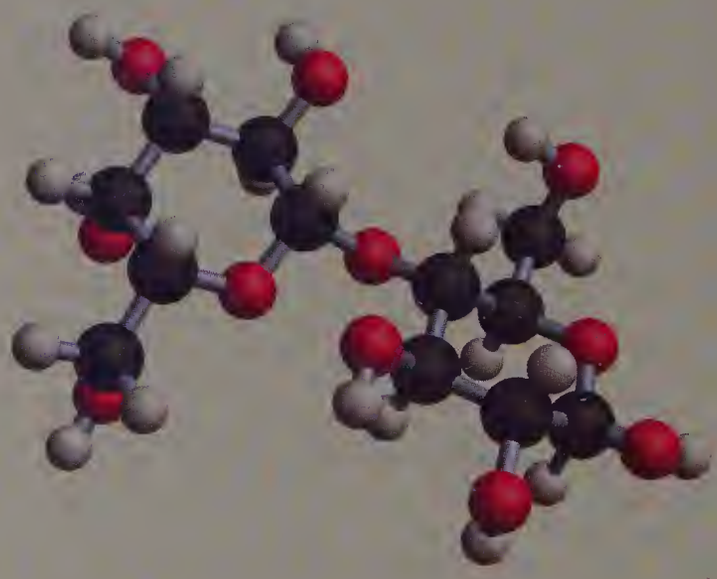
People with lactose intolerance lack the lactase needed to hydrolyze lactose and should not eat food that contains lactose. If they ingest food that contains lactose, the high level of unhydrolyzed lactose in their intestinal fluids draws water from tissues by osmosis. The result is abdominal distention, cramping, and diarrhea. Although lactose intolerance is not life threatening, it is unpleasant.

The level of the enzyme lactase in humans varies with both age and race. Most humans have sufficient lactase for the early years of life, when milk is a major part of their diet. However, in adulthood the lactase level decreases, and lactose intolerance results. This trait shows remarkable genetic variations. For example, most northern Europeans have high lactase levels, as do several nomadic pastoral tribes in Africa (see the figure). The ability to digest milk as adults may be the result of an evolutionary process in societies that consumed large amounts of milk and milk products such as cheese. Those individuals with the enzyme necessary to digest milk may have had a reproductive advantage.

Some peoples, such as the Thai and the Chinese, have a high lactose intolerance. Similarly, the Ibo and Yoruba of Nigeria cannot tolerate lactose as adults. The Fula and Hausa of the Sudan differ greatly in the extent of their lactose intolerance. The Fula raise and milk a breed of cattle called fulani, whereas the Hausa, who show lactose intolerance, do not raise cattle. The Tussi, a cattle-owning class of the Rundi of east Africa, also can digest lactose.



Lactose Intolerance



lactose

As in cellobiose and maltose, the aglycone component of lactose is a hemiacetal, which can be either α or β. Consequently, lactose undergoes mutarotation and is a reducing sugar. The two forms of lactose exist in equilibrium in solution.

The lactose content of milk varies among species; cow's milk contains about 5% lactose, whereas human milk contains about 7%. The enzyme lactase, present in the small intestine, catalyzes hydrolysis of lactose to form glucose and galactose. Galactose is then isomerized into glucose in a reaction catalyzed by the enzyme UDP-galactose-4-epimerase.

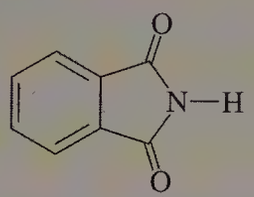
Sweeteners

Although all of us have different sensitivities to various taste sensations, we agree that the monosaccharides and disaccharides taste sweet. The relative degree of sweetness can be determined by comparing different concentrations of sugars or other sweeteners. For example, if a 0.1% solution of a test compound tastes as sweet as a 0.1% solution of sucrose, the two compounds have the same sweetness. If a 0.1% solution of a test compound tastes as sweet as a 10% solution of sucrose, we conclude that the test compound is 100 times as sweet as sucrose. Examples of relative sweetness values are given in the table. Exactly how we sense "sweetness" is not well understood. For example, galactose is not very sweet, but glucose is almost as sweet as sucrose. Even though glucose and fructose have the same configurations at three stereogenic centers, fructose is considerably sweeter than glucose. The disaccharides lactose and maltose are less sweet than sucrose.

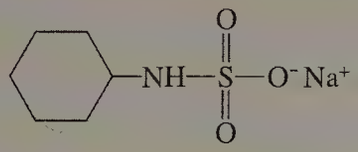
Relative Sweetness of Sugars and Sweeteners

Compound	*Type*	*Relative sweetness*
lactose	disaccharide	0.16
galactose	monosaccharide	0.32
glucose	monosaccharide	0.75
sucrose	disaccharide	1.00
fructose	monosaccharide	1.75
cyclamate	artificial	300
aspartame	artificial	1500
saccharin	artificial	3500

Artificial sweeteners are not carbohydrates. Two artificial sweeteners, cyclamate and saccharin, have few structural features in common and differ distinctly from sugars. Cyclamate was banned in the United States some years ago because experiments with rats showed a link to some cancers. However, Canada still allows its use. On the other hand, the United States currently allows the sale of saccharin, whereas Canada bans it.

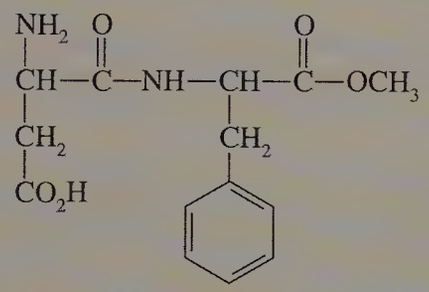


saccharin

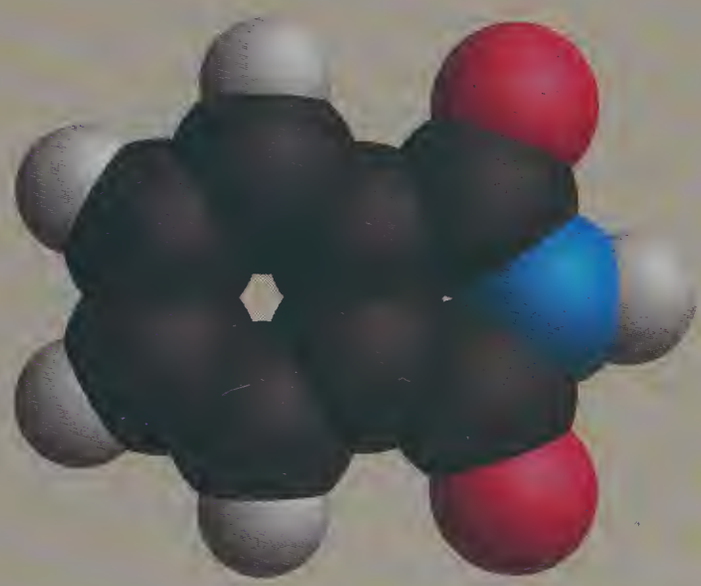


cyclamate

Aspartame is the methyl ester of a dipeptide (two amino acids). It is currently the product of choice among nonnutritive sweeteners because it causes no known health problems. Aspartame is the sweetening ingredient of NutraSweet.



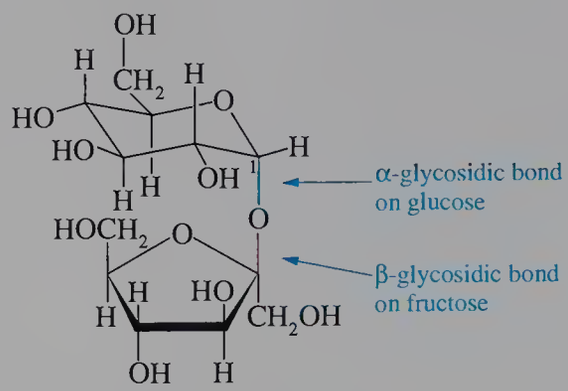
All sweeteners have calories. However, because they are extremely sweet, we use much less of artificial sweeteners than of sucrose. Thus, calorie consumption is reduced. Aspartame has about the same number of calories per gram as sucrose. However, aspartame is about 1500 times as sweet as sucrose. In place of a heaping teaspoon of sucrose—about 10 grams—only 0.006 gram of aspartame produces the same sweetness.



saccharin

Sucrose

We noted at the start of this section that some disaccharides have a glycosidic linkage between both anomeric centers. Sucrose, common table sugar, is a disaccharide of α-glucose and β-fructose in which the anomeric centers are linked 1,2′.

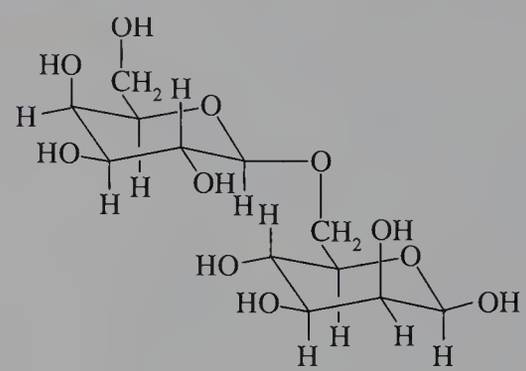


α-D-glucopyranosyl-β-D-fructofuranoside
(sucrose)

Sucrose has both an acetal and a ketal functional group. Neither ring can exist in equilibrium with either an aldehyde or ketone. As a result, sucrose cannot mutarotate and is not a reducing sugar. The systematic name, α-D-glucopyranosyl-β-D-fructofuranoside, ends in the suffix *-oside*, indicating that sucrose is not a reducing sugar.

Problem 20.10

Describe the structure of the following disaccharide.



Sample Solution

The hemiacetal center located on the aglycone ring (at the right) has a hydroxyl group in the β configuration. The glycosidic bond is from the C-1 atom of the acetal ring (on the left) to the C-6 atom of the aglycone ring. Furthermore, the oxygen bridge is formed through the β-glycosidic bond. Thus, the bridge is β-1,6′.

Next examine both rings to determine the identity of the monosaccharides. The ring on the left is galactose: all but the C-4 hydroxyl group are equatorial. The ring on the right is mannose, the C-2 epimer of glucose. Mannose has an axial hydroxyl group at the C-2 position. The compound is 6-*O*-(β-D-galactopyranosyl)-β-D-mannopyranose.

20.9 Polysaccharides

Polysaccharides include homopolysaccharides and heteropolysaccharides, such as hyaluronic acid; heparin, an anticoagulant in blood; and chondroitin, a component of cartilage and tendons. Because the structures of heteropolysaccharides are more complex than those of homopolysaccharides, we will discuss only homopolysaccharides.

The homopolysaccharides starch and cellulose contain only glucose. About 20% of starch is **amylose**, which is soluble in cold water; the remaining 80%, called **amylopectin**, is insoluble in water. Potatoes, rice, wheat, and other cereal grains contain starch. Because starch is a mixture of amylose and amylopectin, it has a variable "molecular weight" that depends on its source.

Starch and cellulose differ by one structural feature, but this difference has great biological importance. Starch, whose glucosyl units are linked α-1,4′, can be digested by most animals. Cellulose, whose glucosyl units are linked β-1,4′, can be digested only by certain microorganisms and animals that harbor those microorganisms in their digestive tracts. These microorganisms produce enzymes that hydrolyze β-glycosides.

Amylose is a linear polymer with 200 to 2000 α-linked glucose units that is a major source of food for some animals. The molecular weight of amylose ranges from

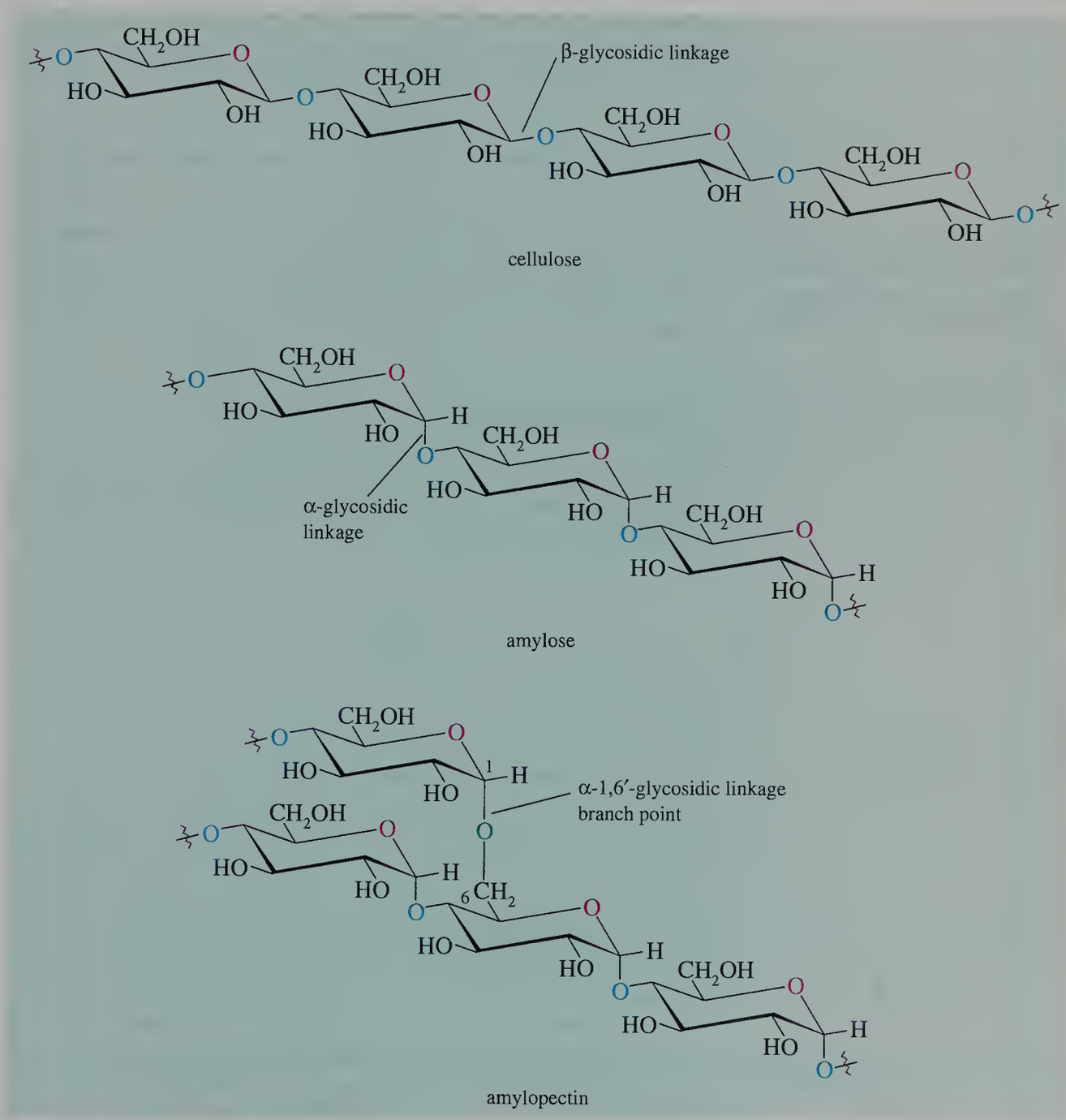


FIGURE 20.9 Structures of Polysaccharides

40,000 to 400,000. Cellulose is a β-linked polymer of glucose (Figure 20.9) that usually contains 5000 to 10,000 glucose units. Certain algae produce cellulose molecules with more than 20,000 glucose units.

Amylopectin contains chains similar to those in amylose, but includes only about 25 glucose units per chain. Amylopectin has branches of glucose-containing chains interconnected by a glycosidic linkage between the C-6 hydroxyl group of one chain and the C-1 atom of another glucose chain (Figure 20.9). The molecular weight of amylopectin can be as high as 1 million. Because each chain has an average molecular weight of 4000, there can be as many as 300 interconnected chains.

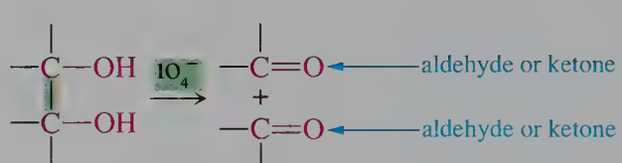
Animals synthesize glycogen as a storage form of glucose. Its structure resembles that of amylopectin, but glycogen has more, and shorter, branches than amylopectin. The average chain length in glycogen is 12 glucose units. Glycogen has a molecular weight greater than 3 million. Glycogen is a source of metabolic energy during periods of diminished food intake. Although cells throughout the body store glycogen, the liver stores the largest amount. An average adult carries enough glycogen for about 15 hours of normal activity.

20.10 Proof of Structure of Monosaccharides

In this section we will learn how to determine the structure of a monosaccharide. Several synthetic reactions can be used to convert one monosaccharide into another. If the structure of a related monosaccharide is known, and the mechanism of the reaction that interconverts them is well understood, then the structure of the "unknown" monosaccharide can be established.

Oxidation by Periodate

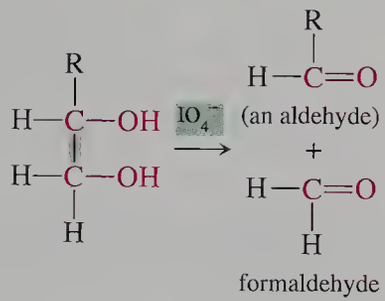
We recall that periodate cleaves vicinal diols to give carbonyl groups at each carbon atom originally bearing a hydroxyl group. One mole of periodate is required for each carbon–carbon bond cleaved.



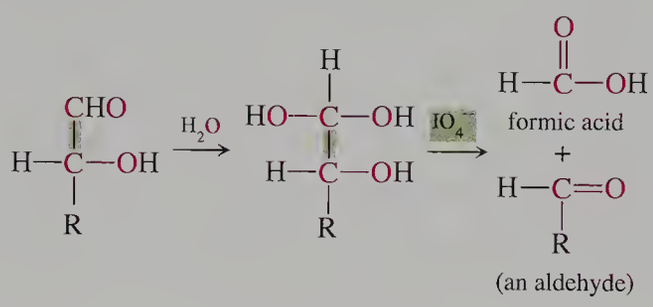
The reaction of monosaccharides with periodate gives a mixture of oxidation products that result from the degradation of the entire molecule. The products include formaldehyde, formic acid, and carbon dioxide. The number of equivalents of each oxidation product indicates whether the monosaccharide is an aldose or ketose and how many adjacent centers have oxygen functionalities. Glucose reacts with five moles of periodate to give one mole of formaldehyde and five moles of formic acid. Fructose also reacts with five moles of periodate, but gives two moles of formaldehyde, three moles of formic acid, and one mole of carbon dioxide.

Let's examine the products that would result from cleaving of all the possible combinations of bonds in a monosaccharide. We will do so by considering various subunits of the structure. However, all the subunits react, so we must analyze all carbon–carbon bonds and the attached functional groups to determine the products that can form. First, consider the subunit that contains a primary hydroxyl group. This

structural feature exists at the highest numbered carbon atom of an aldose. The unit also occurs at C-1 and the highest numbered carbon atom of a ketose.

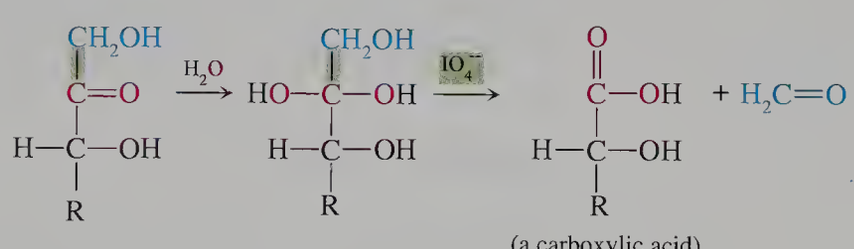


Carbonyl groups also react with periodate by way of their hydrates, which exist in a small quantity at equilibrium. Oxidation of one of the hydroxyl groups of the hydrated aldehyde yields formic acid.

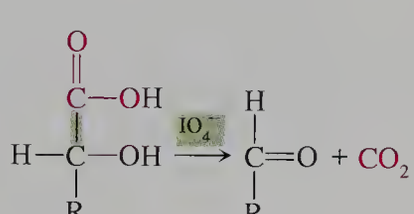


Note that the aldehyde group is oxidized to formic acid, and each secondary alcohol oxidized to an aldehyde by periodate gives a mole of formic acid in subsequent oxidation steps. That's why oxidation of glucose yields five moles of formic acid.

Ketones also form hydrates, but in lesser amounts than aldehydes. Nevertheless, a hydrate forms and then is cleaved to give a carboxylic acid.



In a subsequent step, the hydroxyl group of the carboxylic acid and a hydroxyl group at the α-carbon atom form an iodate ester and the carbon–carbon bond is cleaved. Oxidation of the carboxylic acid group yields carbon dioxide.



Thus, the carbon dioxide from the periodate oxidation of fructose derives from the C-2 atom. The primary alcohols of C-1 and C-6 yield formaldehyde. All the secondary alcohols yield formic acid.

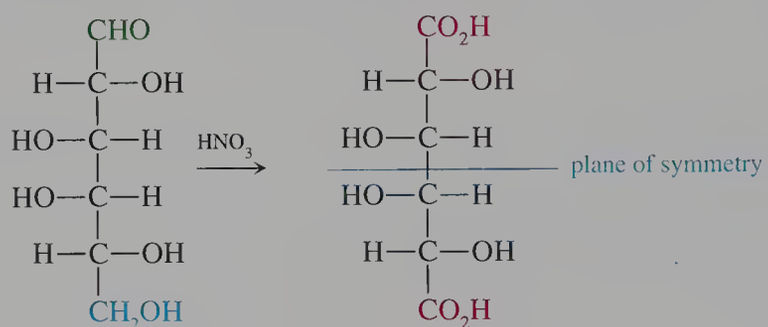
The number of equivalents of periodate consumed indicates the number of

carbon atoms in the monosaccharide that can be oxidized. The following functional groups are identified by the oxidation products.

1. Primary alcohols give formaldehyde.
2. Secondary alcohols give formic acid.
3. Aldehydes give formic acid.
4. Ketones give carbon dioxide.

Oxidation and Optical Activity

The symmetry properties of the aldaric acid obtained by oxidation of an aldose by dilute nitric acid provides information about the possible configurations for the secondary hydroxyl groups. If the aldaric acid formed by oxidation is optically inactive, the hydroxyl groups occur in a symmetrical arrangement. For example, D-galactose gives an optically inactive aldaric acid.



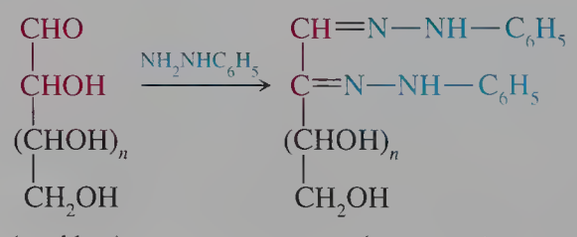
D-galactose optically inactive aldaric acid

This experiment by itself does not establish the identity of D-galactose because D-allose also gives an optically inactive aldaric acid. However, this experiment separates the aldohexoses into two groups of compounds: the six that give optically active aldaric acids and the two that give optically inactive aldaric acids. Additional methods are required in conjunction with this method to determine the structure.

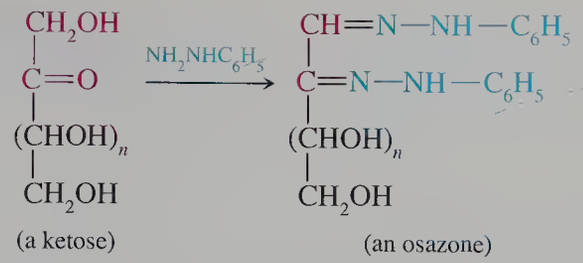
Formation of Osazones

Because they have many hydroxyl groups, the monosaccharides are very soluble in water and they are difficult to crystallize. Emil Fischer found that phenylhydrazine reacts with monosaccharides to give yellow crystalline derivatives called osazones. The identity of an "unknown" monosaccharide can be established by comparing the melting point of its osazone with those of known osazones.

We recall that hydrazine and 2,4-dinitrophenylhydrazine react with carbonyl compounds to give hydrazones. However, monosaccharides do not give simple phenylhydrazone derivatives. After the initial formation of a phenylhydrazone, further reaction occurs to give the osazone, which has two molecules of phenylhydrazine incorporated into it.



(an aldose) (an osazone)



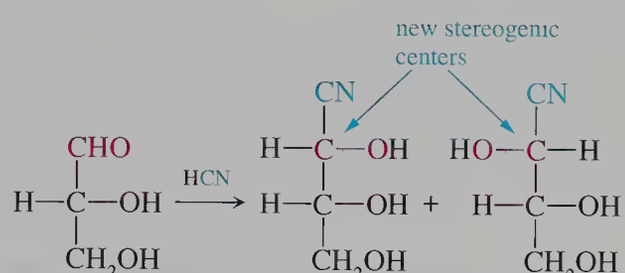
(a ketose) (an osazone)

The formation of an osazone from the initial hydrazone results from oxidation of the adjacent alcohol to a carbonyl by one mole of phenylhydrazine. We will not consider the mechanism of this reaction, but the by-products are aniline, ammonia, and water. The carbonyl group generated then reacts with another molecule of phenylhydrazine to give the second phenylhydrazone unit. The product precipitates at this point and no further reaction occurs.

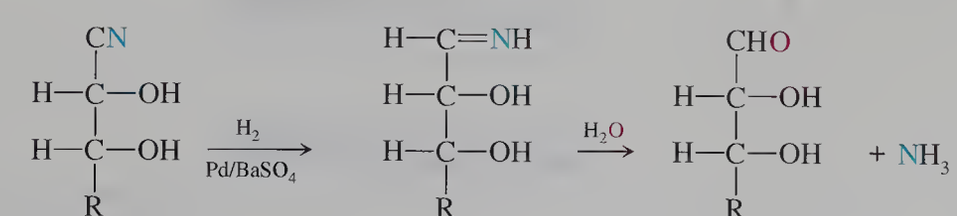
Two aldoses that are C-2 epimers give the same osazone because that stereogenic center is converted to a trigonal center in the osazone. Consequently, both mannose and glucose give the same osazone. The method can be used to establish the configuration of all stereogenic centers in a compound if its osazone is identical to the osazone of another compound whose total configuration is known. Only the configuration of one center is reversed in the "unknown" compound compared to the known compound. However, there is a structurally related ketose that also gives the same osazone. Fructose, glucose, and mannose all give the same osazone because the configurations of C-3, C-4, and C-5 are the same in all three compounds.

Chain Extension of Aldoses

The Kiliani–Fischer synthesis extends chains of monosaccharides using the formation of a cyanohydrin to generate the additional stereogenic center. In the first step, one enantiomeric form of an aldose reacts with HCN to give a mixture of diastereomeric cyanohydrins. We recall that the formation of an additional stereogenic center in a chiral compound results in some stereoselectivity. A mixture results, but because diastereomers have different physical properties, the reaction mixture can be separated to give two cyanohydrins.



In the second step of the Kiliani–Fischer synthesis, the nitrile is partially reduced to an imine using a deactivated palladium catalyst similar to the Lindlar catalyst used to partially reduce alkynes to alkenes. The imine is hydrolyzed to form an aldehyde under the reaction conditions.

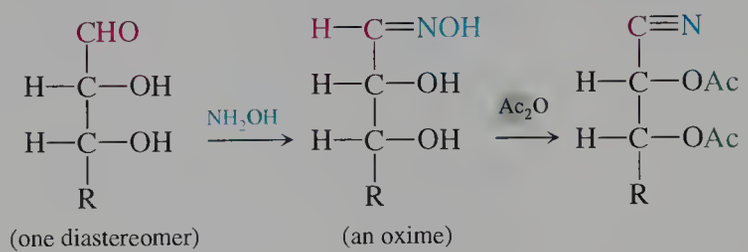


(one diastereomer) (an imine intermediate) (an extended aldose)

Because two products form, we still need information from other reactions to establish the structure of each. For example, ribose gives two structures whose configuration at all centers except C-2 is known. One product is oxidized to give an optically inactive glycaric acid. It must be allose. The other product is then known to be altrose. If altrose is oxidized, the product is an optically active aldaric acid.

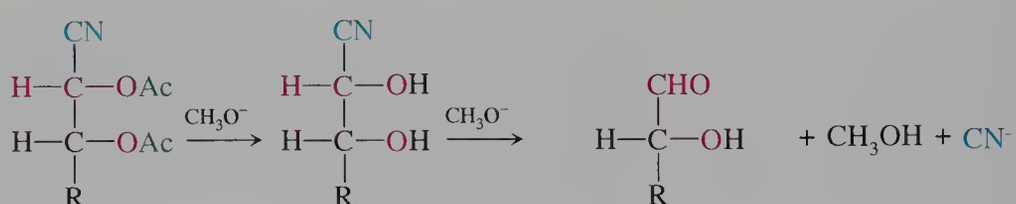
Chain Degradation of Aldoses

The Wohl degradation shortens an aldose chain by one carbon atom in a series of steps, one of which is loss of HCN from a cyanohydrin. In the first step, an oxime forms. Then acetic anhydride is used to dehydrate the oxime and form a nitrile. All hydroxyl groups are converted into acetate esters under the reaction conditions.



(one diastereomer) (an oxime)

In the final step, sodium methoxide is used to remove the acetate groups. The methoxide ion attacks the carbonyl carbon atom to form a tetrahedral intermediate, from which the aldose subsequently leaves. The removal of all acetate groups yields a cyanohydrin. Under basic conditions, it loses HCN to yield a chain-shortened aldose.



(a cyanohydrin) (chain-shortened aldose)

The total transformation converts the original C-2 stereogenic center into an aldehyde carbon atom. The stereochemistry of the remaining stereogenic centers is undisturbed, so a single product results. In the case of glucose, the product is arabinose. Because mannose is the C-2 epimer of glucose, the Wohl degradation of mannose also yields arabinose. The method therefore establishes that the configurations of all other carbon atoms except C-2 are identical in glucose and mannose.

Problem 20.11

What are the products of the periodate oxidation of 2-deoxyribose? How many moles of periodate are required for complete oxidation?

Problem 20.12

Draw the structures of an aldose and a ketose that give the same osazone as xylose.

Problem 20.13

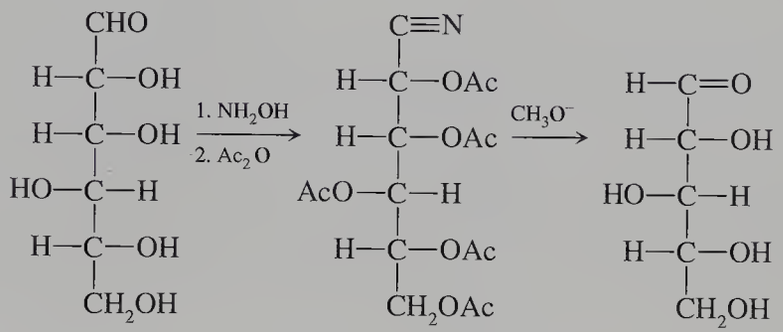
What are the products of the Kiliani–Fischer chain extension of D-ribose? Which products, if any, would give an optically inactive aldaric acid when oxidized by nitric acid?

Problem 20.14

What is the product of the Wohl degradation of gulose? Will the aldaric acid resulting from oxidation by nitric acid be optically active or inactive?

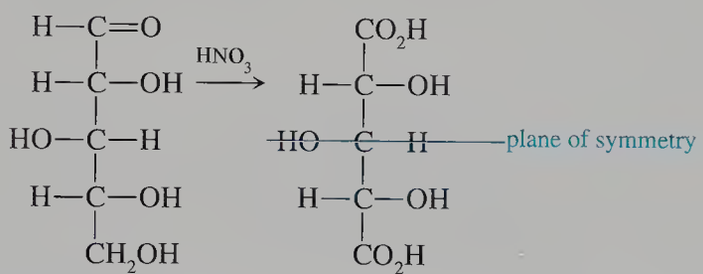
Sample Solution

Formation of an oxime followed by acetylation and subsequent hydrolysis gives a chain-shortened aldose. The configuration of the C-2, C-3, and C-4 chiral centers of the product are the same as the C-3, C-4, and C-5 of gulose.



gulose xylose

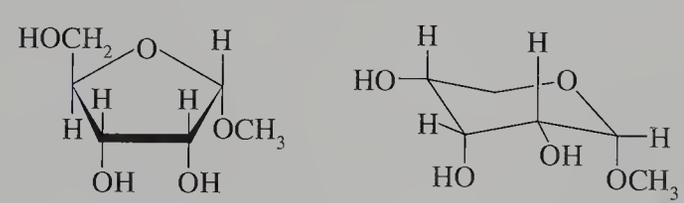
Oxidation of the aldopentose (which is xylose) gives an aldaric acid that has a plane of symmetry and is optically inactive.



20.11 Determination of Ring Size

To determine the ring size of a monosaccharide, it is necessary to maintain the ring and prevent it from equilibrating with other isomeric structures. Because glycosides have "protected" anomeric centers, they do not undergo mutarotation, and they do not react with most reagents under neutral or basic conditions. Hence, chemical reactions can be carried out at other sites in the glycoside to determine the ring size and configuration of the monosaccharide.

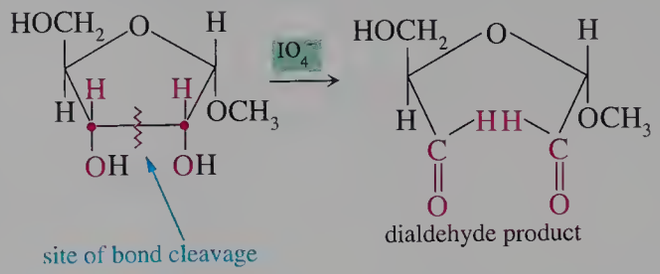
First, the monosaccharide is treated with methanol and HCl to obtain the glycoside. Consider the methyl glycosides of the furanose and pyranose forms of D-ribose.



methyl α-D-ribofuranoside methyl α-D-ribopyranoside

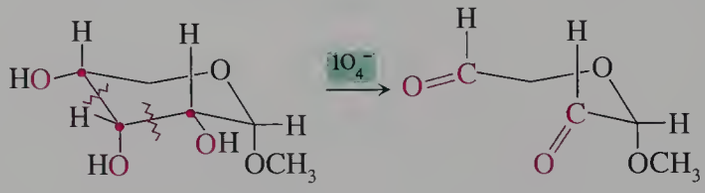
There is only one vicinal arrangement of hydroxyl groups in the furanoside. Only one equivalent of periodate reacts, and a dialdehyde product forms. (In practice, this

product is too sensitive to work with, and it is oxidized using bromine water to give the more stable diacid.)

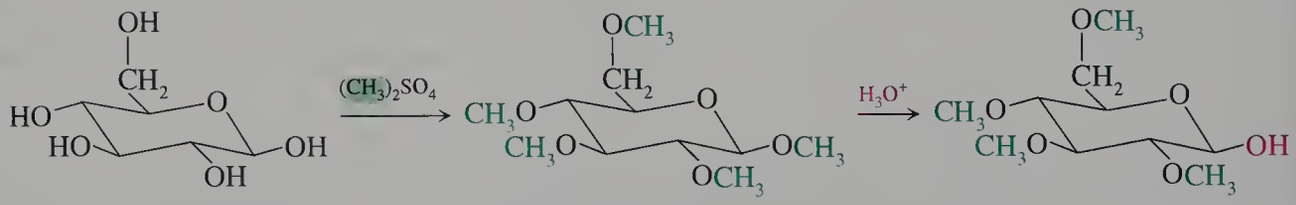


The configuration at the stereogenic center that corresponds to the original C-4 atom in the glycoside indicates whether the monosaccharide is D or L. The product of a D-monosaccharide has the *R* configuration at that center. The configuration at the C-1 atom of the glycoside remains in the dialdehyde product. It is *S* if the glycoside is the α anomer.

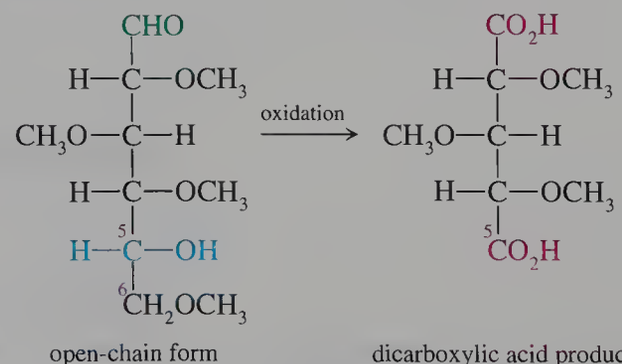
Two bonds are cleaved in the pyranoside, and one mole of formic acid is produced from the C-3 atom. The pyranoside therefore gives different results than the furanoside.



The size of the ring of a monosaccharide can also be determined by methylating all hydroxyl groups and then hydrolyzing the acetal. Because all other oxygen atoms are protected as ethers, they do not hydrolyze under the mild acid conditions that hydrolyze acetals.



Because the original monosaccharide was a pyranose, the only "free" hydroxyl group in the open-chain form is at C-5. Vigorous oxidation breaks the C-5 to C-6 bond and gives a diacid with one less carbon atom than the original monosaccharide. The ether functional groups are unaffected, and the configurations at all centers remain.



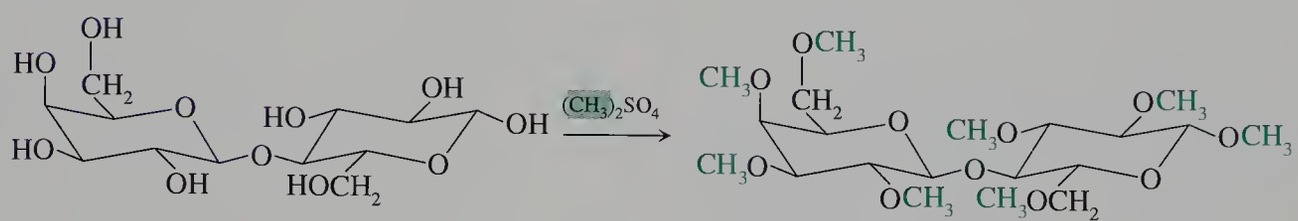
20.12 Structure of Disaccharides

In determining the structure of a disaccharide, hydrolysis data establishes the identity of the component monosaccharides. However, several questions remain.

1. What is the configuration at the acetal or ketal center?
2. What are the sites of the glycosidic linkage?
3. Are the component monosaccharides furanoses or pyranoses?

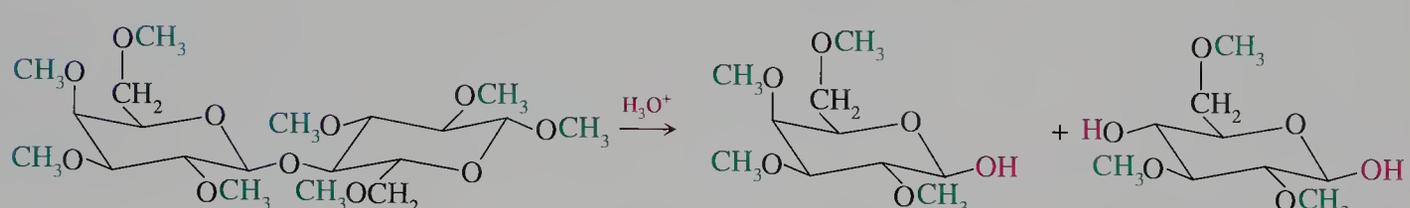
The configuration at the acetal center is often established using enzymes that stereospecifically hydrolyze both the type of monosaccharide and the configuration of the glycosidic center. For example, the enzyme β-galactosidase cleaves only the β-glycosidic linkage of galactose.

The site of a glycosidic linkage is established by complete methylation of the disaccharide followed by hydrolysis. For example, methylation of lactose yields octamethyllactose. Seven of the methyl groups are present as ethers and one as a methyl glycoside.



lactose octamethyllactose

Hydrolysis of the octamethyllactose with dilute acid cleaves the glycosidic linkage joining the two monosaccharides and the methyl glycoside. The products are 2,3,4,6-*O*-tetramethyl-D-galactose and 2,3,6-*O*-trimethyl-D-glucose.



2,3,4,6-*O*-tetramethyl-D-galactose 2,3,6-*O*-trimethyl-D-glucose

The structure of 2,3,4,6-*O*-tetramethyl-D-galactose is established by vigorous oxidation to a five-carbon dicarboxylic acid. Since the hydroxyl group at C-5 was the only one not methylated, galactose must exist as a pyranose.

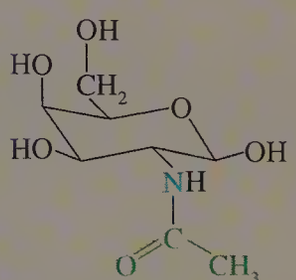
Hydroxyl groups at both C-4 and C-5 are not methylated in the oxidation product derived from glucose. If the glycosidic linkage with galactose was with C-4 of glucose, then glucose would have to exist as a pyranose using the C-5 hydroxyl group. However, if the glycosidic linkage with galactose was with C-5 of glucose, then glucose would have to exist as a furanose formed from the C-4 hydroxyl group. Information from additional reactions is required to make this distinction. However, the specialized reactions required are beyond the scope of an introductory text.

Human Blood Groups

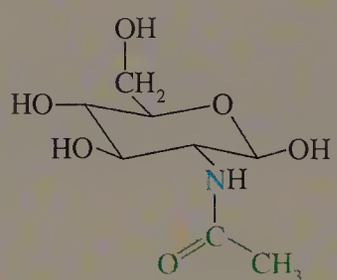
Complex carbohydrates coat the surfaces of nearly all human cells, acting as markers that identify the cell. Some of the markers flag the cell as "self." These molecules enable the immune system to avoid attacking the body's own cells, instead recognizing and destroying foreign cells, whether from a transplant or a parasite.

Human blood cells contain surface markers that divide blood into three major classes, designated A, B, and O. Many minor blood groups are also known, but we will not consider them. The classification of blood groups relies upon differences in the structures of oligosaccharides bonded to a protein called glycophorin that is embedded in the membrane of red blood cells.

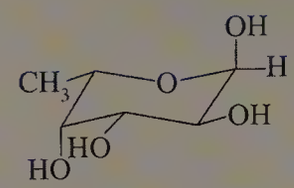
The blood group oligosaccharides contain several different monomers: galactose (Gal), *N*-acetylgalactosamine (GalNAc), and *N*-acetylglucosamine (GlcNAc). They also contain the rather unusual sugar 6-deoxy-α-L-galactose. This sugar has the common name α-L-fucose.



N-acetylgalactosamine
(GalNAc)



N-acetylglucosamine
(GlcNAc)



6-deoxy-α-L-galactose
(α-L-fucose)

The α-L-fucose moiety of each blood group is attached to a trisaccharide in blood groups A and B and to a disaccharide in blood group O. In each oligosaccharide the β-galactose residue is attached to α-L-fucose by an α-1,2′- glycosidic bond. The sugar at the reducing end of these oligosaccharides is linked to glycophorin by an α-glycosidic bond to the hydroxyl group of a serine residue in the protein.

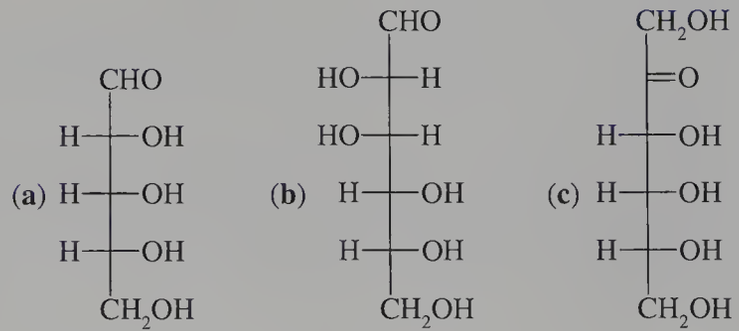
Each blood group is further subdivided into two types of chains that differ in their glycosidic linkages. In a type 1 chain, the β-Gal moiety is linked to β-GlcNAc by a 1,4′-glycosidic bond. In a type 2 chain, the β-Gal moiety is linked to β-GlcNAc by a 1,3′-glycosidic bond.

These carbohydrates are the *antigenic determinants* of their groups. A person with type A blood makes antibodies that "attack" type B blood, forming clumps of type B cells. Similarly, a person with type B blood makes antibodies that "attack" type A blood. However, persons who are type A or type B do not make antibodies against type O blood, so type O persons are called "universal donors." They are not, however, universal acceptors because they produce antibodies against both type A and type B blood.

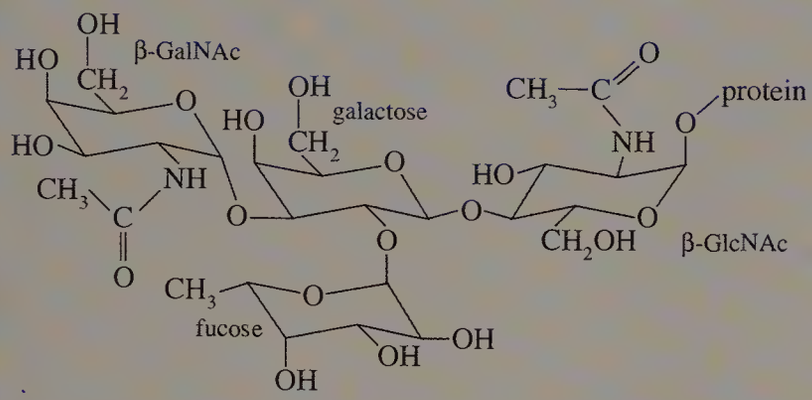
EXERCISES

Classification of Monosaccharides

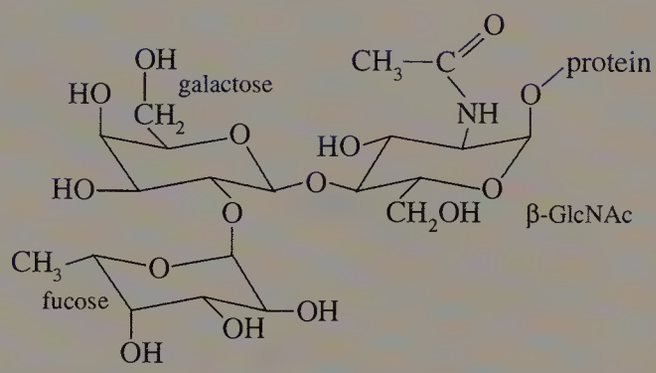
20.1 Classify each of the following monosaccharides.



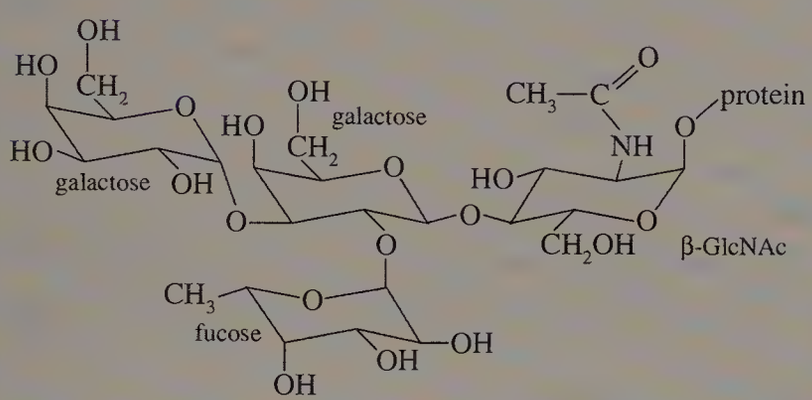
Type A

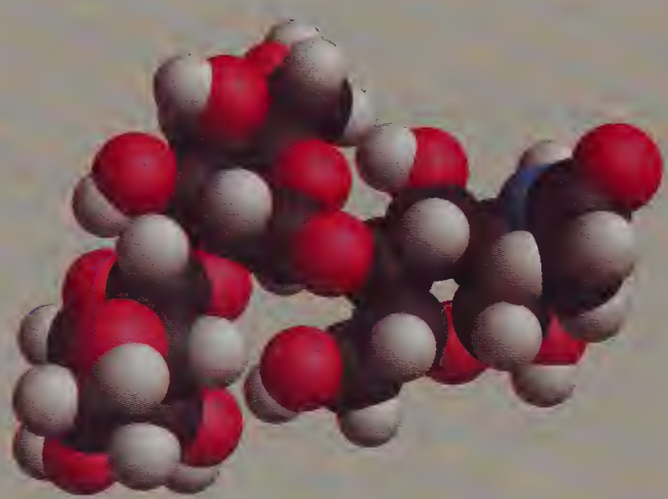


Type O



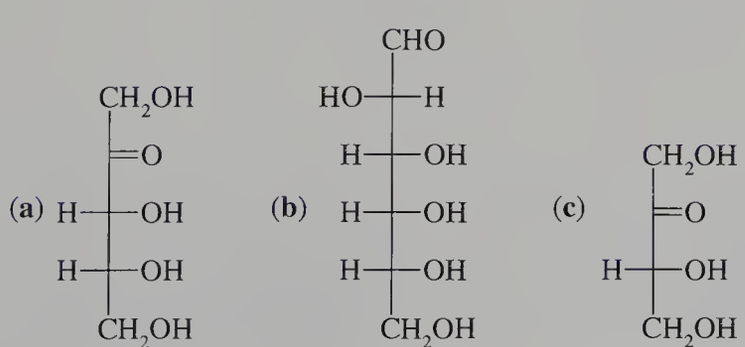
Type B



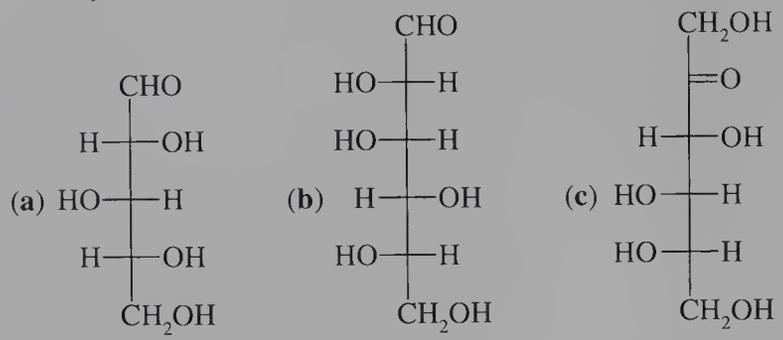


Type O blood group oligosaccharide

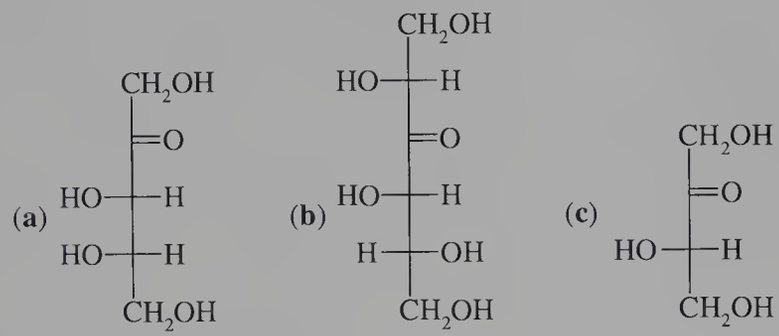
20.2 Classify each of the following monosaccharides.



20.3 Classify each of the following monosaccharides as D or L.



20.4 Classify each of the following monosaccharides as D or L.



Fischer Projection Formulas

20.5 Draw the Fischer projection formulas of the isomeric D-3-ketopentoses.

20.6 Draw the Fischer projection formulas of the isomeric D-3-ketohexoses.

20.7 Draw the Fischer projection formula of each of the following.
(**a**) L-xylose (**b**) L-erythrose (**c**) L-galactose (**d**) L-ribose (**e**) L-fructose

20.8 Draw the Fischer projection formula of each of the following monosaccharides.
(**a**) 6-deoxy-L-galactose (**b**) 3-deoxy-D-ribose (**c**) 2,6-dideoxy-D-allose (**d**) 6-deoxy-L-mannose

Haworth Projection Formulas

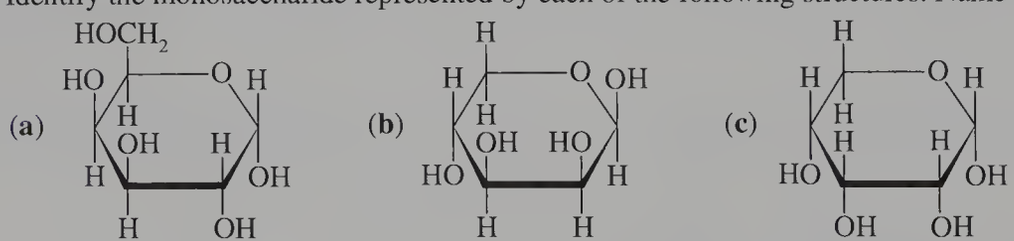
20.9 Draw the Haworth projection formula of the hemiacetal of 5-hydroxyhexanal.

20.10 Draw the Haworth projection formula of the hemiketal of 5-hydroxy-2-hexanone.

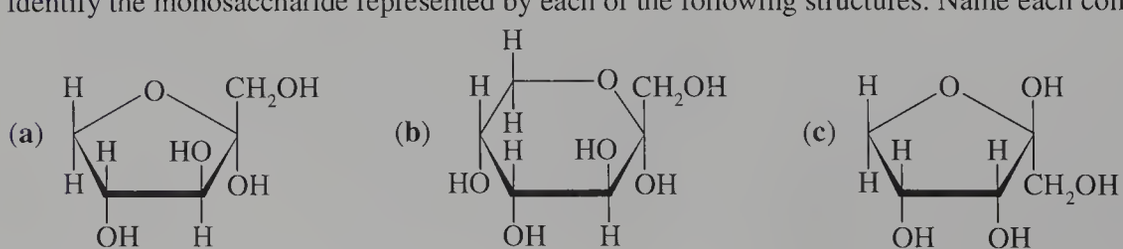
20.11 Draw the Haworth projection formula of the pyranose form of each of the following compounds.
(**a**) α-D-mannose (**b**) β-D-galactose (**c**) α-D-glucose (**d**) α-D-galactose

20.12 Draw the Haworth projection formula of the furanose form of each of the following compounds.
(**a**) α-D-fructose (**b**) β-D-fructose (**c**) α-D-ribulose (**d**) β-L-xylulose

20.13 Identify the monosaccharide represented by each of the following structures. Name each compound.



20.14 Identify the monosaccharide represented by each of the following structures. Name each compound.

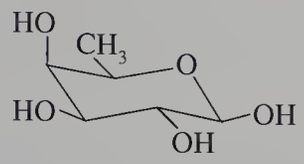


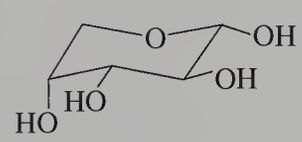
Conformations of Monosaccharides

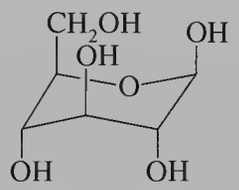
20.15 Draw the standard chair conformation of β-galactopyranose and β-mannopyranose and compare the number of axial hydroxyl groups in each compound.

20.16 Draw the standard chair conformation of β-talopyranose and β-allopyranose and compare the number of axial hydroxyl groups in each compound.

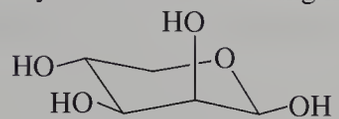
20.17 Identify each of the following monosaccharides.

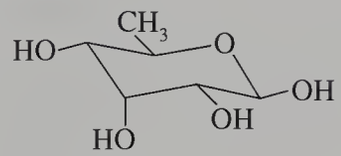
(a) 

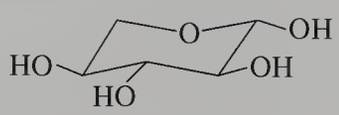
(b) 

(c) 

20.18 Identify each of the following monosaccharides.

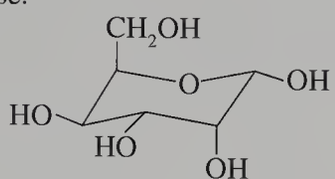
(a) 

(b) 

(c) 

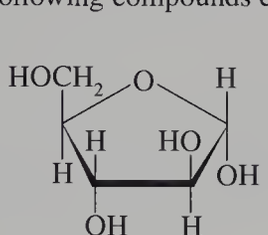
20.19 Write the conventional chair conformation of α-D-idose. Convert it to an alternate conformation by a ring flip. Determine which conformation is the more stable.

20.20 Identify and name the following aldohexose.



Mutarotation

20.21 Which of the following compounds can mutarotate?



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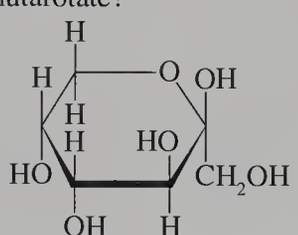

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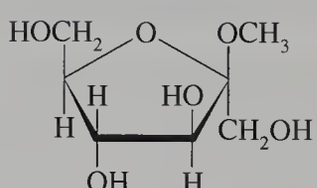
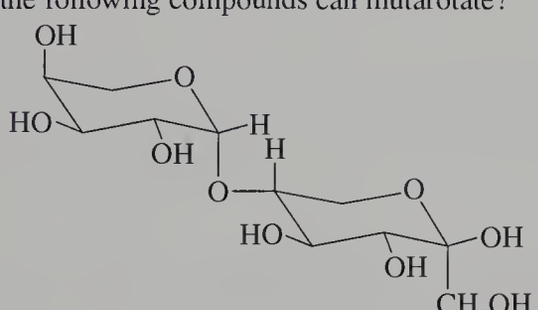


III

20.22 Which of the following compounds can mutarotate?



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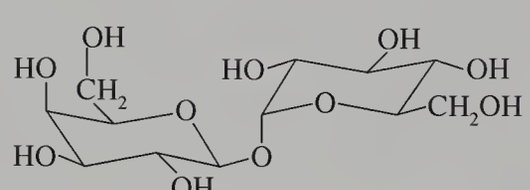


II

20.23 The $[\alpha]_D$ of the α and β anomers of D-galactose are +150.7 and +52.8, respectively. In water, mutarotation of D-galactose results in a specific rotation of +80.2. Which anomer predominates?

20.24 The $[\alpha]_D$ of the α and β anomers of D-mannose are +20.3 and −17.0, respectively. In water, mutarotation of D-mannose results in a specific rotation of +14.2. Disregarding the furanose forms present (less than 1%), calculate the percent of the α anomer.

20.25 In solution, D-ribose forms an equilibrium mixture containing 6% α-furanose, 18% β-furanose, 20% α-pyranose, and 56% β-pyranose. Explain why the β-pyranose form predominates at equilibrium.

20.26 Suggest a reason why D-glucose, D-mannose, D-galactose, and D-allose all have larger percentages of the pyranose form than the other four diastereomeric aldohexoses.

Reduction of Monosaccharides

20.27 Draw the Fischer projections of the alditols of D-erythrose and D-threose. One compound is optically active, and the other is a meso compound. Explain why.

20.28 Which of the alditols of the D-pentoses are optically inactive? Explain why.

20.29 Reduction of D-fructose with sodium borohydride yields a mixture of two alditols. Explain why. Name the two alditols.

20.30 Reduction of D-tagatose with sodium borohydride yields a mixture of galactitol and talitol. What is the structure of D-tagatose?

20.31 What relationship exists between the reduction products of D-galactose and L-galactose?

20.32 Explain why the alditol of D-glucose is identical to the alditol of L-gulose.

Oxidation of Monosaccharides

20.33 Draw the structures of each of the following compounds.
(**a**) D-mannonic acid (**b**) D-galactonic acid (**c**) D-ribonic acid (**d**) D-arabonic acid

20.34 Draw the structures of each of the following compounds.
(**a**) D-allonic acid (**b**) D-talonic acid (**c**) D-xylonic acid (**d**) D-lyxonic acid

20.35 Oxidation of D-erythrose and D-threose with nitric acid yields aldaric acids, one of which is optically inactive. Which one? Explain why.

20.36 Which of the D-aldopentoses will yield optically inactive aldaric acids when oxidized with nitric acid?

Isomerization of Monosaccharides

20.37 Draw the structures of the aldose and ketose that can exist in equilibrium with D-allose in basic solution.

20.38 Draw the structures of the aldose and ketose that can exist in equilibrium with D-galactose in basic solution.

20.39 Draw the structures of one aldose and one ketose that can exist in equilibrium with D-ribose in basic solution.

20.40 Draw the structures of two aldoses that can exist in equilibrium with D-xylulose in basic solution.

20.41 Explain why an equilibrium mixture of dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate contains the two compounds in a 96:4 ratio.

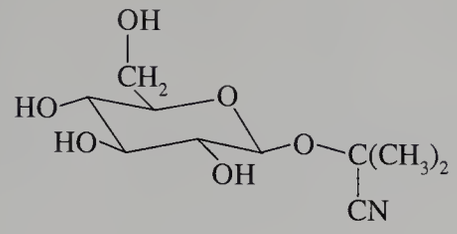
20.42 Although ketones are more stable than isomeric aldehydes by approximately 12 kJ $mole^{-1}$, fructose 6-phosphate is less stable than glucose 6-phosphate by approximately 1.7 kJ $mole^{-1}$. Explain why.

Glycosides

20.43 Draw the Haworth projection formulas of the two glycosides derived from each of the following pairs of components.
(**a**) the pyranose form of D-glucose and ethanol (**b**) the furanose form of D-fructose and phenol
(**c**) the pyranose form of D-ribose and methanol (**d**) the furanose form of D-arabinose and benzyl alcohol

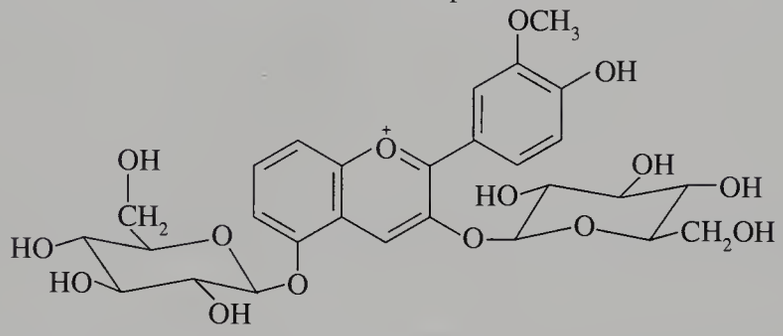
20.44 The individual isomeric methyl acetals of D-glucose can be prepared only by a series of special reactions. Explain why each compound cannot be prepared by direct reaction of D-glucose with methanol.

20.45 Linamarin is found in manioc, a yam found in Brazil. Explain why this compound can be toxic.

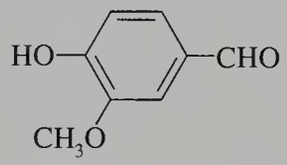


linamarin

20.46 Peonin, a red pigment found in the red peony, has the following structure. What is the monosaccharide product(s) of the hydrolysis of peonin. Draw the structure of the aglycone. Explain why knowing the structure of the aglycone is not sufficient to determine the structure of peonin.



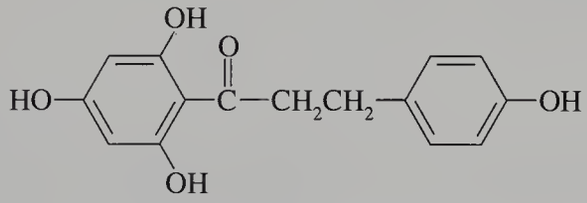
20.47 Vanillin is found as the β-glycoside of D-glucose. Draw the structure of the glycoside.



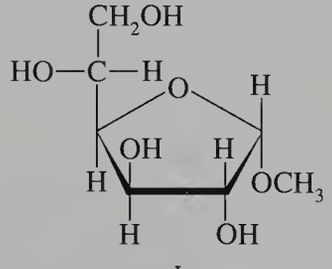
20.48 Arbutin, an antibiotic used for urinary tract infections, is methylated to give a pentamethyl derivative. The derivative is hydrolyzed to give a tetramethylglucose and *p*-methoxyphenol. What is the aglycone of arbutin?

20.49 Salicin is found in the bark of several species of fruit trees. Upon hydrolysis, it yields glucose and 2-(hydroxymethyl)phenol. The mild oxidation of salicin followed by hydrolysis of the oxidation product yields glucuronic acid and salicylic acid (2-hydroxybenzoic acid). What are the possible structures of salicin?

20.50 Phlorizin is a glycoside found in the root bark of a variety of fruit trees. Hydrolysis of phlorizin yields the following phenolic material. How many possible structures are possible for the glycoside? Explain how methylation of the glycoside using dimethyl sulfate followed by hydrolysis of the product with dilute acid can establish the structure of the glycoside.



20.51 Suggest a reason why methyl α-D-glucofuranoside (I) is more slowly hydrolyzed than methyl α-D-fructofuranoside (II) at the same pH.



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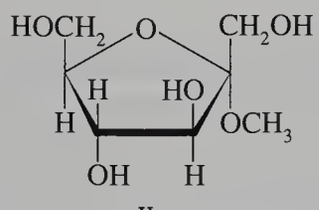
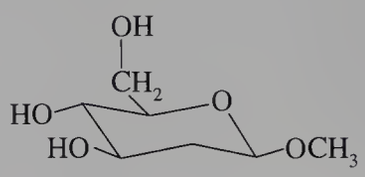


II

20.52 Suggest a reason why methyl β-D-2-deoxyglucopyranoside (I) is hydrolyzed faster than methyl β-D-glucopyranoside (II) at the same pH.



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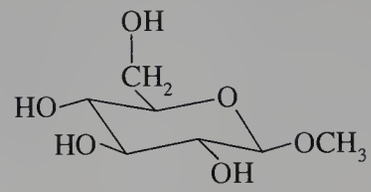
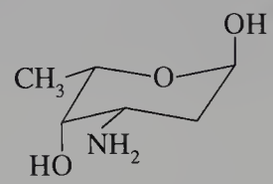


II

20.53 The carbohydrate daunosamine is contained in the antibiotic Adriamycin. Is daunosamine a D or L carbohydrate?



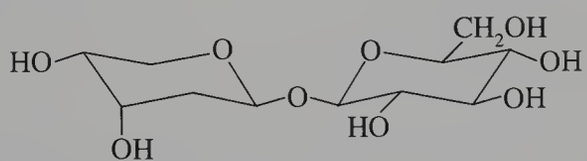
daunosamine

20.54 The melting point of methyl α-D-glucopyranoside is 166 °C. Explain why the melting point of methyl β-D-glucopyranoside, 105 °C, is different. Predict the melting point of methyl β-L-glucopyranoside.

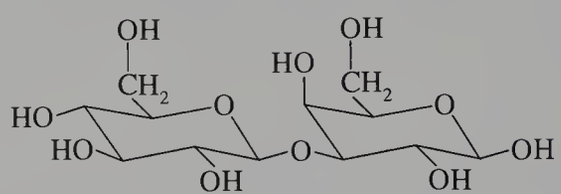
Disaccharides

20.55 Determine the component monosaccharides of each of the following compounds and describe the type of glycosidic linkage in each.

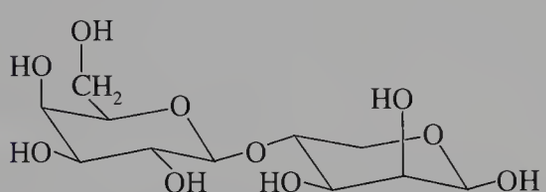
(a)



(b)

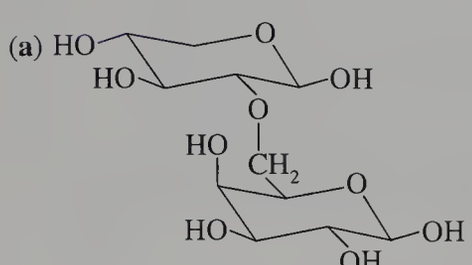


(c)



20.56 Determine the component monosaccharides of each of the following compounds and describe the type of glycosidic linkage in each.

(a)



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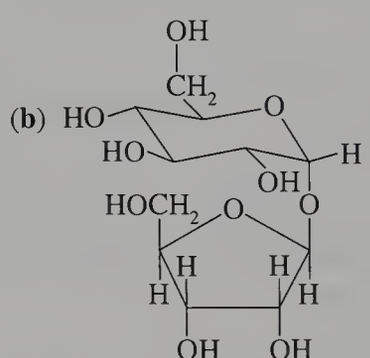

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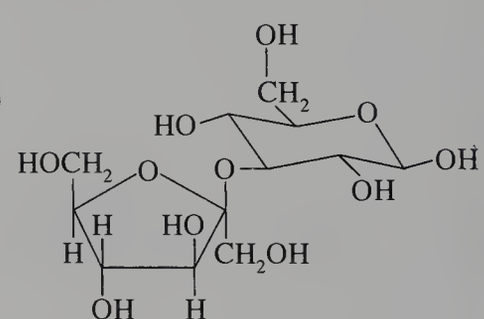
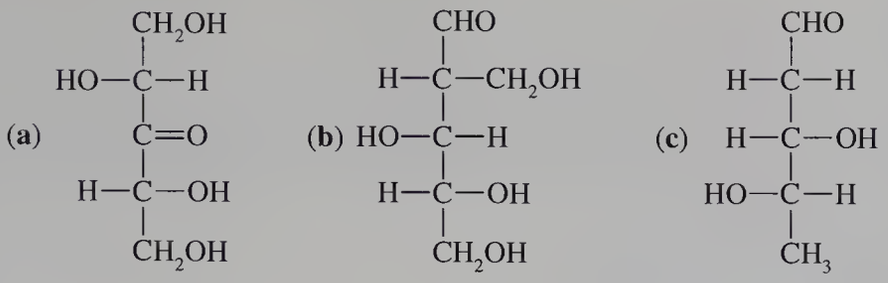


Structure Determination of Monosaccharides

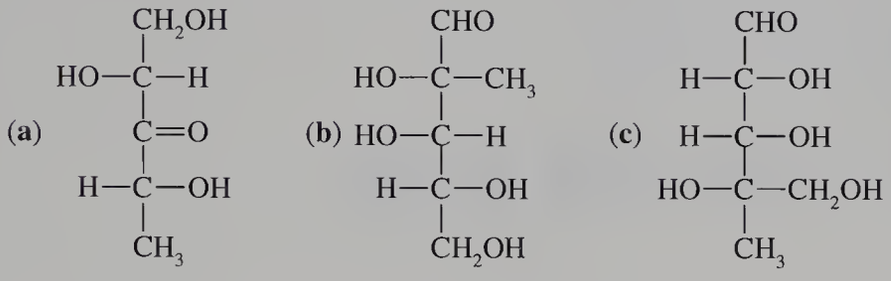
20.57 What are the products of the periodate oxidation of each of the following monosaccharides?
(**a**) ribose (**b**) ribulose (**c**) galactose (**d**) erythrulose

20.58 What are the products of the periodate oxidation of each of the following monosaccharides?
(**a**) xylose (**b**) sorbose (**c**) erythrose (**d**) idose

20.59 What are the products of the periodate oxidation of each of the following monosaccharides?



20.60 What are the products of the periodate oxidation of each of the following monosaccharides?



20.61 There are eight diastereoisomeric D-aldoses, but they yield only four diastereomeric osazones. Explain why.

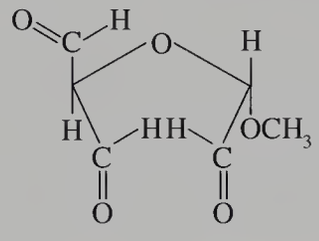
20.62 Draw the structure of the product of the reaction of 2-deoxy-D-ribose with phenylhydrazaine.

20.63 A Wohl degradation is done on a monomethyl ether of D-idose. The product, when oxidized with nitric acid, gives an optically inactive compound. At what position of idose is the methyl ether located?

20.64 A Kiliani–Fischer chain extension is done on a monomethyl ether of D-glucose. One of the products, when oxidized with nitric acid, gives an optically inactive compound. At what position of idose is the methyl ether located?

20.65 An aldohexose is methylated using dimethyl sulfate and then treated with a mild acid. The resulting product, when subjected to a strong oxidizing agent, gives an optically inactive dicarboxylic acid containing five carbon atoms. What are the possible structures of the aldohexose?

20.66 An aldohexose is converted to a methyl glycoside and then is oxidized by periodate to yield the following product. Is the aldohexose a pyranose or a furanose? What is the configuration of the anomeric center of the glycoside? What are the possible structures of the aldohexose?



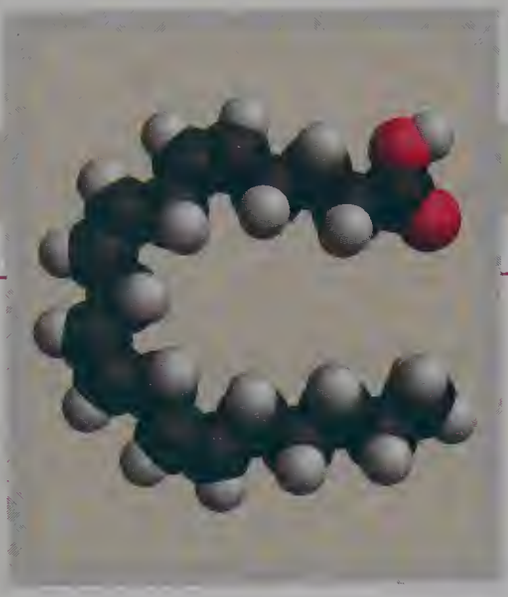
Structure Determination of Disaccharides

20.67 Hydrolysis of the disaccharide primeverose yields D-xylose and D-glucose. Methylation of primeverose using dimethyl sulfate followed by mild acid hydrolysis yields 2,3,4-tri-*O*-methyl-D-xylose and 2,3,4-tri-*O*-methyl-D-glucose. What features of the structure are determined by these data?

20.68 Hydrolysis of the disaccharide trehalose yields only D-glucose. Methylation of trehalose using dimethyl sulfate followed by mild acid hydrolysis yields 2,3,6-tri-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose. What features of the structure are determined by these data?

20.69 Hydrolysis of the disaccharide turanose yields D-fructose and D-glucose. Methylation of turanose using dimethyl sulfate followed by mild acid hydrolysis yields 1,4,5-tri-*O*-methyl-D-fructose and 2,3,4,6-tetra-*O*-methyl-D-glucose. What features of the structure are determined by these data?

20.70 Hydrolysis of a trisaccharide yields two equivalents of glucose and one equivalent of galactose. Methylation, using dimethyl sulfate followed by mild acid hydrolysis, yields 3,6-di-*O*-methyl-D-glucose as one of the products. What features of the structure are determined by these data?

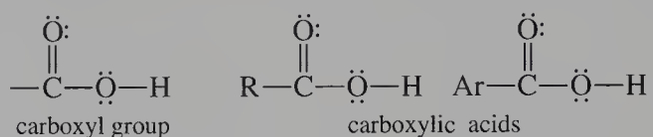


21

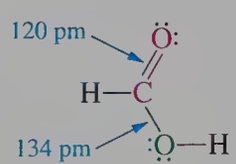
Carboxylic Acids

21.1 The Carboxyl and Acyl Groups

In this chapter we consider the structure, properties, reactions, and synthesis of carboxylic acids. These compounds have a **carboxyl group** bonded to a hydrocarbon unit, which may be saturated, unsaturated, aromatic, or heterocyclic.

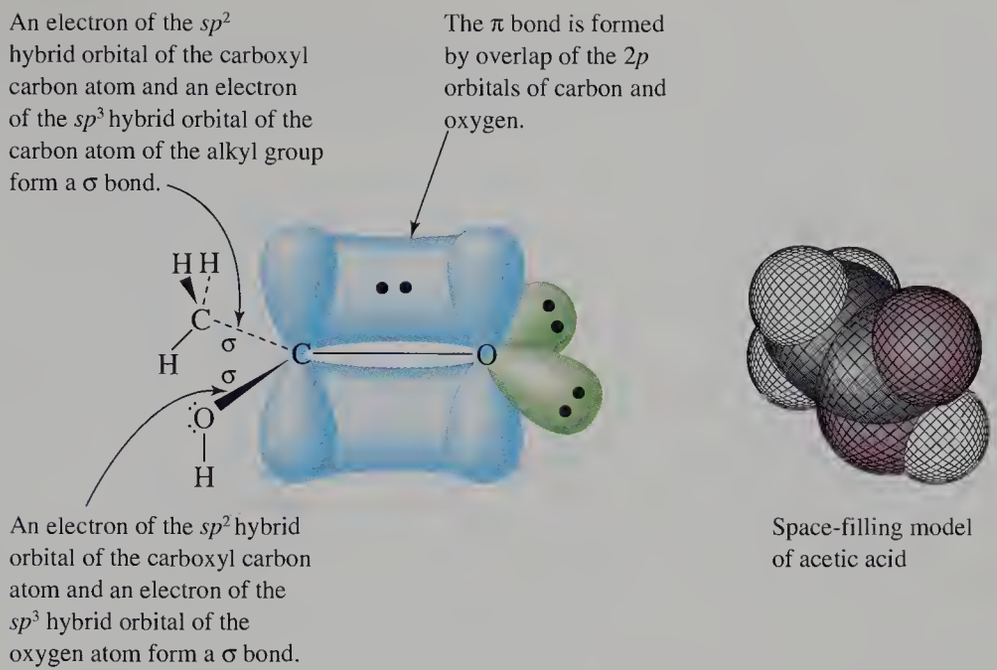


The carboxyl carbon atom is sp^2 hybridized, and three of its valence electrons form three σ bonds at 120° angles to one another (Figure 21.1). One of the σ bonds is to a hydrogen atom or a carbon atom of an alkyl, aromatic, or heterocyclic group. The other two σ bonds are to oxygen atoms: one to the hydroxyl oxygen atom and the other to the carbonyl oxygen atom. The carbonyl carbon atom also has one electron in a 2*p* orbital forming a π bond with an electron in a 2*p* orbital of the carbonyl oxygen atom. The carbon–oxygen double bond of a carboxylic acid such as formic acid is shorter than the carbon–oxygen single bond because of σ + π bonding of the multiple bond.

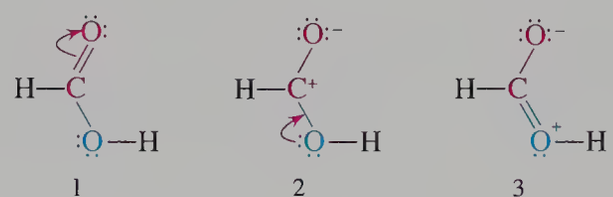


We can write the structure of formic acid as a structure with a C—O single bond and a C=O double bond. Although this is the most stable resonance form, other structures contribute. We recall that the chemical properties of the carbonyl groups of aldehydes and ketones are interpreted using both dipolar resonance forms and the more stable, uncharged Lewis structure. A carboxylic acid also has dipolar resonance structures. The dipolar resonance structure 2, which has an electron-deficient carbon atom, is less important for a carboxylic acid than for an aldehyde or ketone. The hydroxyl oxygen atom can donate an electron pair to carbon to give resonance

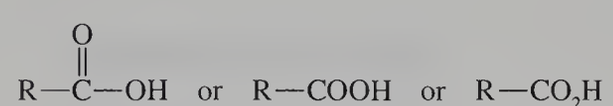
FIGURE 21.1 Bonding in Carboxylic Acids
The atoms bonded to the carboxyl carbon atom of a carboxylic acid all lie in a plane with the carboxyl carbon atom. The carboxyl carbon atom is sp^2 hybridized, and there is a π bond between the carbonyl oxygen atom and the carbon atom.



structure 3 in which every atom has a Lewis octet. This stabilizes the C=O group, and the carbonyl carbon atom is less electrophilic than that of aldehydes or ketones.



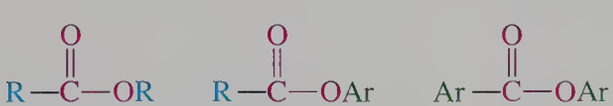
Although the bond angles at the carbonyl carbon atom are all approximately 120°, the carboxyl group may be represented with vertical and horizontal lines. To save space, two condensed representations of the carboxyl group are in common use. Unless required to account for the mechanism of a reaction, the nonbonded electrons are not shown.



equivalent representations of a carboxylic acid

Acyl Group and Acid Derivatives

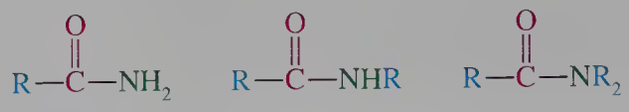
The "RCO" unit contained in a carboxylic acid is called an **acyl group**. Replacing the OH group from a carboxylic acid by other oxygen groups or electronegative atoms gives families of acid derivatives. If an alkoxy (—OR) or phenoxy (—OAr) group is bonded to the acyl group, the derivative is an **ester**.



examples of esters

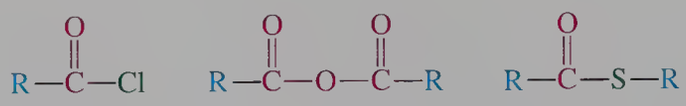
If the substituent is linked to the acyl group through a nitrogen atom, the compound is called an **amide**. The classification of amides depends on the number of

carbon groups, including the acyl group, bonded to the nitrogen atom. These compounds are much less reactive than esters. The amide functional group is responsible for the structural stability of proteins.



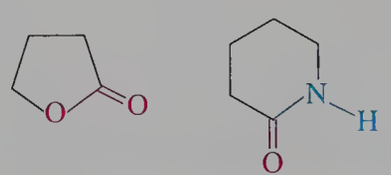
primary amide secondary amide tertiary amide

When the substituent attached to an acyl group is a chlorine atom, the derivative is called an **acid chloride**. These compounds, which are highly reactive, do not occur in nature, but they are valuable reagents for the laboratory synthesis of esters and amides. When two acyl groups are bonded to a common oxygen atom, the compound is an **acid anhydride**. These compounds are also employed for laboratory synthesis of esters and amides. When a substituent is linked to an acyl group through a sulfur atom, the derivative is called a **thioester**. Thioesters are less reactive than acid chlorides and acid anhydrides, but sufficiently reactive to participate in many biochemical acyl transfer reactions.



acid chloride acid anhydride thioester

Esters, amides, anhydrides, and thioesters may make up part of a cyclic structure. Cyclic esters are called **lactones**. Cyclic amides are called **lactams**. Cyclic acyl derivatives behave chemically like acyclic compounds.



a lactone (a cyclic ester) a lactam (a cyclic amide)

Problem 21.1

Propose two reasons why the C—O single bond of carboxylic acids (136 pm) is shorter than that of an alcohol (142 pm). Which of the two factors is the more important?

21.2 Nomenclature of Carboxylic Acids

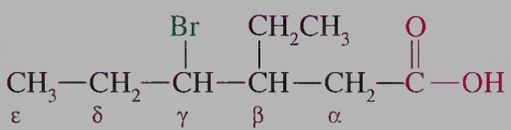
The carboxylic acids are abundant in nature and were among the first organic substances isolated. Because they have been known for so long, many have common names. Both the common and the IUPAC names of several carboxylic acids are given in Table 21.1.

Common Names

In the common names, the positions of groups attached to the parent chain are designated alpha (α), beta (β), gamma (γ), delta (δ), and so forth. The —COOH group itself is not designated by a Greek letter.

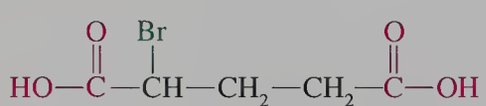
Table 21.1
Nomenclature of Carboxylic Acids

Formula	*Common name*	*IUPAC name*
HCO_2H	formic acid	methanoic acid
CH_3CO_2H	acetic acid	ethanoic acid
$CH_3CH_2CO_2H$	propionic acid	propanoic acid
$CH_3(CH_2)_2CO_2H$	butyric acid	butanoic acid
$CH_3(CH_2)_3CO_2H$	valeric acid	pentanoic acid
$CH_3(CH_2)_4CO_2H$	caproic acid	hexanoic acid
$CH_3(CH_2)_6CO_2H$	caprylic acid	octanoic acid
$CH_3(CH_2)_8CO_2H$	capric acid	decanoic acid
$CH_3(CH_2)_{10}CO_2H$	lauric acid	dodecanoic acid
$CH_3(CH_2)_{12}CO_2H$	myristic acid	tetradecanoic acid
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	hexadecanoic acid
$CH_3(CH_2)_{16}CO_2H$	stearic acid	octadecanoic acid

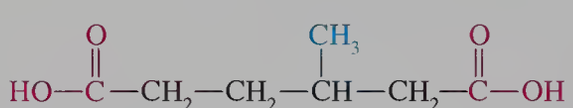


γ-bromo-β-ethylcaproic acid

Some unbranched carboxylic acids contain a —COOH group at each end of the chain. The common names of some of these **dicarboxylic acids** use Greek letters starting with the carbon atom adjacent to the carboxyl group closest to the substituent.

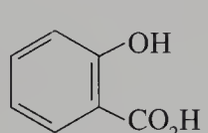


α-bromoglutaric acid

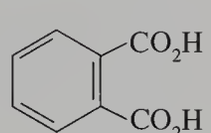


β-methyladipic acid

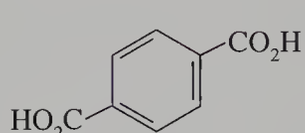
Aromatic acids containing one or more carboxyl groups are often referred to by their common names.



salicylic acid



phthalic acid



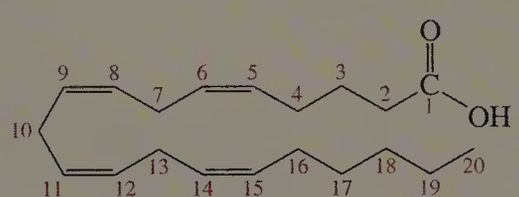
terephthalic acid

IUPAC Names

Carboxylic acids are named by rules similar to those outlined for aldehydes.

1. Name the longest continuous carbon chain containing the carboxyl carbon atom as the parent chain. Replace the final *-e* of the parent hydrocarbon by the ending *-oic acid*.

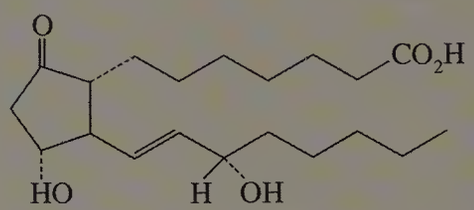
Carboxylic acids are widely distributed in natural products. Some have profound effects on biological processes even at extremely low concentrations. Prostaglandins, leukotrienes, and thromboxanes make up a class of hormones called eicosanoids, all of which derive from arachidonic acid, a 20-carbon unsaturated acid (see the figure). However, unlike many hormones, the eicosanoids are not produced by glands and secreted into the blood to affect cells throughout the body. Instead eicosanoids act locally, in the cells that produce them or on neighboring cells. They regulate normal processes, such as smooth muscle contraction, and affect cellular processes that result from diseases. For example, prostaglandins contribute to the symptoms of an illness such as swelling, nausea, vomiting, and pain.



arachidonic acid

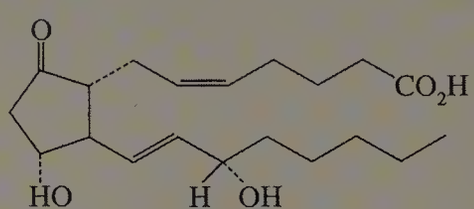
Prostaglandins are 20-carbon fatty acids that contain a trans-substituted, five-membered ring. They are classified as PGA through PGI based on the number and type of their functional groups, such as hydroxyl groups and ketone groups. A subscript on the letter indicates the number of double bonds.

The prostaglandins were originally isolated from the prostate gland. But all nucleated cells produce them, and they can affect any cell type, even at very low concentrations. They can also alter the effects of many hormones. For example, hormone-sensitive enzymes that hydrolyze lipids respond to insulin and to other hormones that regulate the concentration of blood glucose. PGE_1 inhibits these enzymes at a concentration of 10 nM (10^{-8} M).



prostaglandin E_1

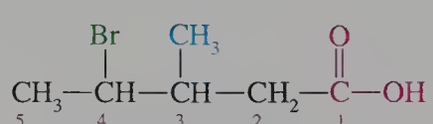
Prostaglandins affect virtually every aspect of reproduction. They regulate menstruation and control fertility and contraception. PGE_2 stimulates smooth muscle contraction in the uterus. It has been used clinically to induce labor and to abort pregnancies prematurely.



prostaglandin E_2

PGG_2 causes inflammation, an effect inhibited by aspirin. Aspirin prevents the first step in prostaglandin synthesis, in which the five-membered ring forms.

2. Number the parent chain by assigning the number 1 to the carboxyl carbon atom. Do not add the number 1 to the name to indicate the position of the carboxyl carbon atom because it is understood to be located at the end of the chain. Add the names and locations of any substituents as prefixes to the parent name.



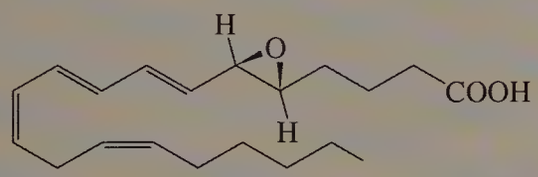
4-bromo-3-methylpentanoic acid

3. The carboxylic acid group has a higher priority than double or triple bonds. To name a carboxylic acid that contains a double or triple bond, replace the final *-e* of the name of the parent alkene or alkyne name with the suffix *-oic acid*. Indicate the position of the multiple bond with a prefix.

A class of steroid hormones called corticosteroids also inhibits prostaglandin biosynthesis. These steroids act in the following way. Arachidonic acid does not occur free in cells, but is esterified to a phospholipid and incorporated in this form into cell membranes. Arachidonic acid is released by enzymes called phospholipases, and corticosteroids inhibit these enzymes. Corticosteroids such as cortisone are used to reduce inflammation.

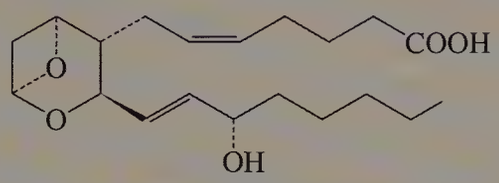
Much research aims to develop synthetic prostaglandins for use as therapeutic drugs. Natural prostaglandins cannot be taken orally because they are rapidly degraded and do not survive long enough for effective action. Thus, one research goal is to develop modified prostaglandins that can be administered orally.

Leukotrienes act as mediators in inflammatory disorders such as asthma, ulcerative colitis, rheumatoid arthritis, and psoriasis. Leukotriene A_4 is a long-acting bronchoconstrictor released in the lungs during severe asthmatic reactions. Drugs that can modulate the effects of leukotrienes could prevent or moderate such hypersensitivity. Researchers are studying ways to intervene at the site of the biosynthesis of the leukotrienes or at the receptor sites for them.

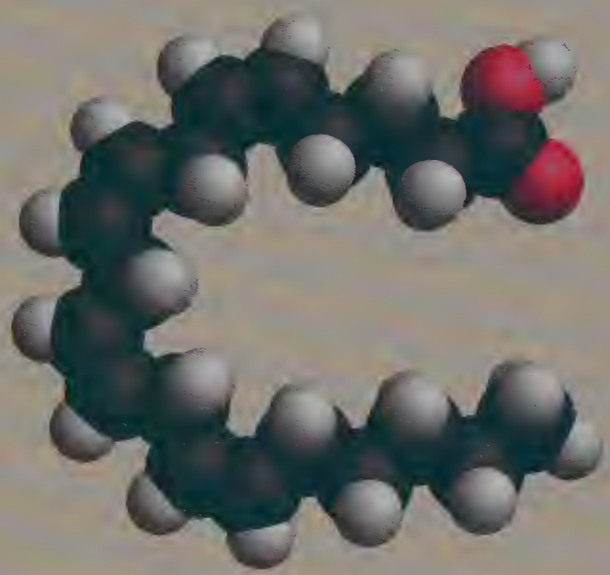


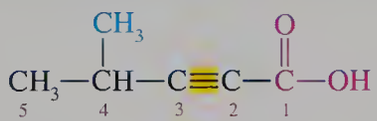
leukotriene A_4

Thromboxane A_2 is produced in blood platelets. It causes constriction of smooth muscle of arterial walls, reducing blood flow.



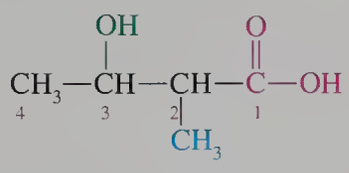
thromboxane A_2


arachidonic acid



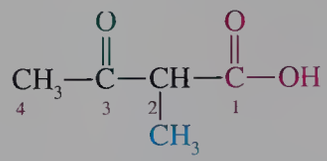
4-methyl-2-pentynoic acid

4. The carboxylic acid functional group has a higher priority than aldehyde, ketone, halogen, hydroxyl, and alkoxy groups. Indicate the names and locations of these substituents with prefixes to the name of the parent carboxylic acid.



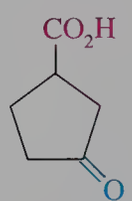
3-hydroxy-2-methylbutanoic acid

5. If a carboxylic acid contains an aldehyde or ketone, indicate the carbonyl group with the prefix *oxo-*. The priority order is carboxylic acid > aldehyde > ketone.

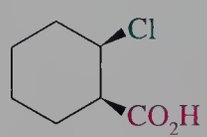


2-methyl-3-oxobutanoic acid

6. Name compounds that have a $—CO_2H$ group bonded to a cycloalkane ring as derivatives of the cycloalkane, and add the suffix *carboxylic acid*. Assign the carbon atom to which the carboxyl carbon atom is bonded the number 1, but do not include this number in the name.

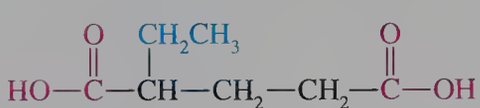


3-oxocyclopentanecarboxylic acid

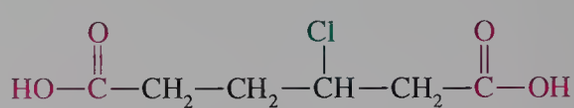


cis-2-chlorocyclohexanecarboxylic acid

7. Name dicarboxylic acids by adding the suffix *-dioic acid* to the name of the parent alkane that includes the carbon atoms of both carboxyl groups. Number the chain starting with the carboxyl carbon atom closest to the first substituent.



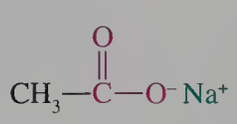
2-ethylpentanedioic acid



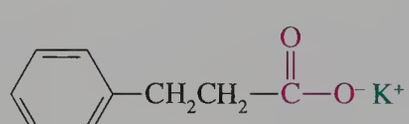
3-chlorohexanedioic acid

Names of Carboxylates

The conjugate base of a carboxylic acid is a **carboxylate** anion. The common name of the conjugate base is obtained by changing the *-ic acid* ending to *-ate*. The IUPAC name of the conjugate base is obtained by changing the *-oic acid* ending to *-oate*. In the salt of a carboxylic acid, the name of the carboxylate anion is preceded by the name of the metal ion.



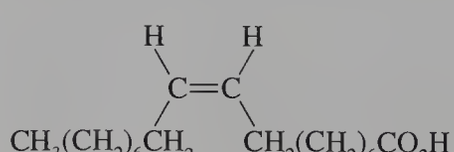
sodium ethanoate
(sodium acetate)



potassium 3-phenylpropanoate
(potassium β-phenylpropionate)

Problem 21.2

The structure of oleic acid, an unsaturated carboxylic acid present as an ester in vegetable oils, is shown below. What is the IUPAC name of oleic acid?

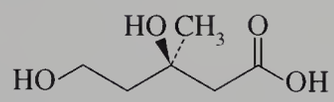


Sample Solution

First determine the length of the continuous chain that contains the $—CO_2H$ group; it contains 18 carbon atoms. The double bond is located at the C-9 atom in the chain, numbering from the carboxyl group on the right. Thus the compound is a 9-octadecenoic acid. The configuration about the double bond is *Z*, and thus the complete name is (*Z*)-9-octadecenoic acid.

Problem 21.3

Mevalonic acid is required to form isopentenyl pyrophosphate, an intermediate in terpene synthesis. It has the following structure. Assign its IUPAC name.

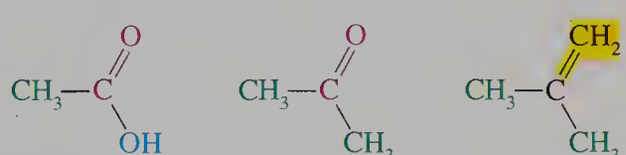


21.3 Physical Properties of Carboxylic Acids

The first physical property usually associated with liquid carboxylic acids is their sharp, unpleasant odor. For example, butanoic acid occurs in rancid butter and aged cheese. Caproic, caprylic, and capric acids have the smell of goats. (The Latin word for goat, *caper*, is the source of the common names of these acids.) Differences in biological effects of these compounds, such as odor, depend on poorly understood physiological responses. However, physical properties such as boiling points, melting points, and solubility directly relate to structure. We can understand these properties by considering the types of intermolecular interactions in these compounds.

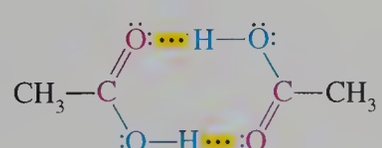
Boiling Point

Low molecular weight carboxylic acids are liquids at room temperature. Those with higher molecular weights are wax-like solids. The boiling points of carboxylic acids are much higher than compounds with the same molecular weight and similar structures.



bp 118 °C bp 56.5 °C bp –7 °C

Carboxylic acids have high boiling points because they form hydrogen-bonded dimers. The hydroxyl group of one molecule acts as a proton donor to the carbonyl oxygen atom of the second molecule. The hydroxyl group of the second molecule acts as a proton donor to the carbonyl oxygen atom of the first molecule.



hydrogen-bonded dimer of a carboxylic acid

The two hydrogen bonds stabilize the dimer so much that its structure remains stable even in the gas phase. As a result, the boiling points of carboxylic acids are higher

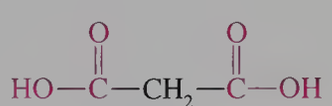
than those of substances of comparable molecular weights because hydrogen bond dimerization doubles their "effective" molecular weight. The boiling points of some representative carboxylic acids are given in Table 21.2.

Table 21.2
Boiling Points of Carboxylic Acids

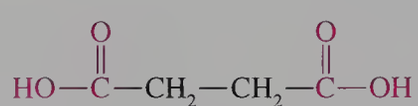
IUPAC name	*Common name*	*Boiling point (°C)*
methanoic acid	formic acid	101
ethanoic acid	acetic acid	118
propanoic acid	propionic acid	141
butanoic acid	butyric acid	164
2-methylpropanoic acid	isobutyric acid	155
pentanoic acid	valeric acid	186
3-methylbutanoic acid	isovaleric acid	177
2,2-dimethylpropanoic acid	pivalic acid	164
hexanoic acid	caproic acid	205
octanoic acid	caprylic acid	239
decanoic acid	capric acid	270
dodecanoic acid	lauric acid	299

Melting Point

Saturated carboxylic acids with more than eight carbon atoms are solids at room temperature (Table 21.3). Their melting points increase with increasing chain length, as expected, because London forces increase with increasing chain length. The hydrocarbon chains of saturated acids pack tightly in the solid. The melting points of dicarboxylic acids are very high because they can form twice as many hydrogen bonds as carboxylic acids.



malonic acid
mp 136 °C



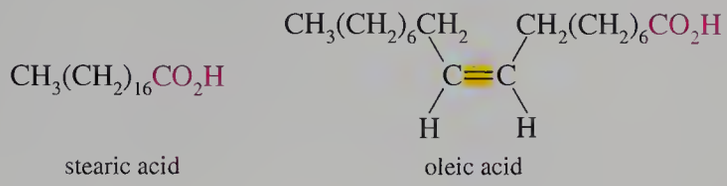
succinic acid
mp 185 °C

Unsaturation lowers the melting points of carboxylic acids, especially if the configuration around the double bond is cis. These unsaturated acids are called "bent" molecules because of the geometry around the double bonds. The "bends" hinder efficient molecular packing, making London forces weaker than those in saturated

Table 21.3
Melting Points of Carboxylic Acids

Number of carbon atoms	*IUPAC name*	*Common name*	*Melting point (°C)*
10	decanoic acid	capric acid	31.3
12	dodecanoic acid	lauric acid	43.2
14	tetradecanoic acid	myristic acid	54.4
16	hexadecanoic acid	palmitic acid	62.8
18	octadecanoic acid	stearic acid	69.6
20	eicosanoic acid	arachidic acid	75.4
22	docosanoic acid	behenic acid	79.9
24	tetracosanoic acid	lignoceric acid	84.2
26	hexacosanoic acid	ceratoic acid	87.7

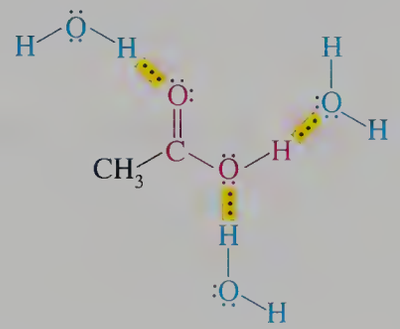
fatty acids. For example, the melting point of stearic acid is 69.6 °C. The single cis double bond of oleic acid decreases the melting point to 33.4 °C.



stearic acid oleic acid

Solubilities

Carboxylic acids with low molecular weights dissolve in water because the carboxyl group forms several hydrogen bonds with water. A carboxylic acid serves both as a hydrogen bond donor through its hydroxyl hydrogen atom and as a hydrogen bond acceptor through the lone pair electrons of both oxygen atoms. The solubility of carboxylic acids, like that of alcohols, decreases with increasing chain length because long nonpolar hydrocarbon chains dominate the physical properties of the acid.



hydrogen bonds between acetic acid and water in aqueous solution

Carboxylic acids dissolve in common alcohol solvents such as ethanol. This solubility results from intermolecular hydrogen bonds between solute and solvent and from van der Waals attractions between the ethyl group of ethanol and the nonpolar "tail" of the carboxylic acid. Nonpolar solvents, such as chloroform, are also excellent solvents for carboxylic acids. In these solvents, the carboxylic acids exist as relatively nonpolar hydrogen-bonded dimers that are compatible with the solvent.

Problem 21.4

Rank toluene, benzyl alcohol, benzaldehyde, and benzoic acid in order of increasing boiling point. Rank them in increasing order of solubility in water.

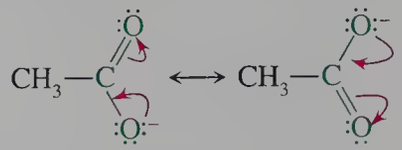
21.4 Acidity of Carboxylic Acids

The ionization of an acid, HA, is reflected in the acid dissociation constant, K_a. It depends on both the strength of the H—A bond and the stability of the conjugate base, A^-, in the solvent. Although acetic acid and other carboxylic acids are weak acids, they are far more acidic than alcohols or phenols. For example, the K_a of acetic acid is about 10^{11} times that of ethanol.

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \qquad K_a = 1 \times 10^{-16}$$
$$CH_3CO_2H + H_2O \rightleftharpoons CH_3CO_2^- + H_3O^+ \qquad K_a = 1.8 \times 10^{-5}$$

Resonance Stabilization of the Carboxylate Ion

Carboxylic acids are much more acidic than alcohols because the ionization reaction yields a resonance-stabilized carboxylate anion. Stabilization of the conjugate base increases the equilibrium constant for ionization of the acid. Dispersal of charge in the acetate ion between the two oxygen atoms makes acetic acid far more acidic than ethanol. In the ethoxide ion ($CH_3CH_2O^-$), a single oxygen atom carries the negative charge.



resonance contributors of acetate ion

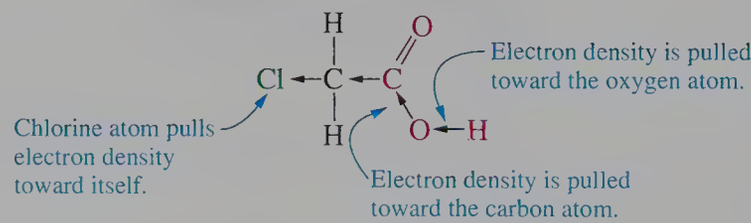
Electron delocalization in the acetate ion results in a difference between the carbon–oxygen bond lengths of the acetate ion and those of acetic acid. The lengths of both bonds in the acetate ion are 125 pm. Because both oxygen atoms are equivalent, each one bears one-half the negative charge. Acetic acid has two different carbon–oxygen bond lengths: the C—O single bond length is 136 pm and the C=O double bond length is 121 pm.

Inductive Effect on Acidity

The acidity of carboxylic acids is also partly the result of an inductive effect. That is, the carbonyl group polarizes the H—O bond by attracting electrons through the σ-bonding network. The withdrawal of electron density from the H—O bond weakens it, increasing the acidity of the ionizable hydrogen atom.

An inductive effect caused by the alkyl or aryl group attached to the carbonyl carbon atom also affects the acidity of carboxylic acids. An alkyl group is electron releasing with respect to hydrogen. This release of electron density to the carboxyl group stabilizes the acid and slightly destabilizes the conjugate base. Thus, acetic acid (pK_a 4.72) is weaker than formic acid (pK_a 3.75). Beyond the α carbon atom, additional carbon atoms do not significantly affect the pK_a (Table 21.4).

An electronegative group attached to the α carbon atom of a carboxylic acid also increases acidity. For example, halogen atoms pull electron density away from the carbon skeleton, as well as indirectly from the O—H bond. As a consequence, the proton is more easily removed and the K_a value increases (Table 21.4).



As the distance between the halogen atom and the carboxyl group increases, the inductive effect falls off dramatically. For β- and γ-substituted acids, the pK_a values approach that of an unsubstituted carboxylic acid.

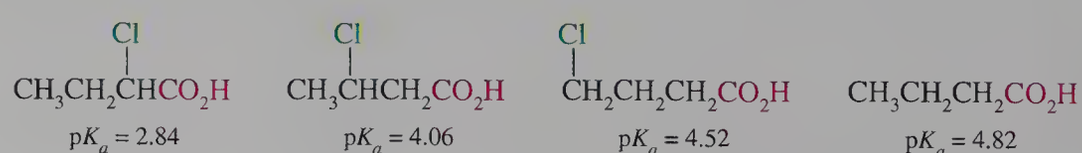


Table 21.4
pK_a Values of Carboxylic Acids

Name	*Formula*	pK_a
methanoic acid	HCO_2H	3.75
ethanoic acid	CH_3CO_2H	4.72
propanoic acid	$CH_3CH_2CO_2H$	4.87
butanoic acid	$CH_3(CH_2)_2CO_2H$	4.82
2-methylpropanoic acid	$(CH_3)_2CHCO_2H$	4.84
pentanoic acid	$CH_3(CH_2)_3CO_2H$	4.81
2,2-dimethylpropanoic acid	$(CH_3)_3CCO_2H$	5.03
fluoroethanoic acid	FCH_2CO_2H	2.59
chloroethanoic acid	$ClCH_2CO_2H$	2.86
bromoethanoic acid	$BrCH_2CO_2H$	2.90
iodoethanoic acid	ICH_2CO_2H	3.18
dichloroethanoic acid	Cl_2CHCO_2H	1.26
trichloroethanoic acid	Cl_3CCO_2H	0.64
trifluoroethanoic acid	F_3CCO_2H	0.23
methoxyethanoic acid	$CH_3OCH_2CO_2H$	3.55
cyanoethanoic acid	$NCCH_2CO_2H$	2.46
nitroethanoic acid	$NO_2CH_2CO_2H$	1.70

Table 21.5 lists the pK_a values for the first and second ionization constants of dicarboxylic acids. The effect of one electron-withdrawing carboxyl group on the acidity of the other carboxyl group decreases with distance between the two groups. Note that the pK_a for the second ionization is larger than for the first ionization because the charged carboxylate group withdraws electrons more strongly than a carboxyl group.

Table 21.5
pK_a Values of Dicarboxylic Acids

Name	*Formula*	pK_{a1}	pK_{a2}
oxalic acid	HO_2CCO_2H	1.27	4.27
malonic acid	$HO_2CCH_2CO_2H$	2.85	5.70
succinic acid	$HO_2C(CH_2)_2CO_2H$	4.20	5.64
glutaric acid	$HO_2C(CH_2)_3CO_2H$	4.35	5.42
adipic acid	$HO_2C(CH_2)_4CO_2H$	4.41	5.41
pimelic acid	$HO_2C(CH_2)_5CO_2H$	4.51	5.42
suberic acid	$HO_2C(CH_2)_6CO_2H$	4.52	5.41
azeleic acid	$HO_2C(CH_2)_7CO_2H$	4.54	5.41
sebacic acid	$HO_2C(CH_2)_8CO_2H$	4.55	5.40

Table 21.6
pK_a Values of Substituted Benzoic Acids

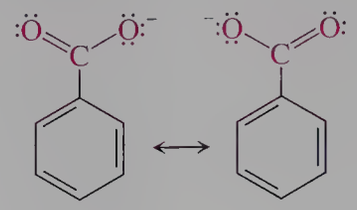
Substituent	*Ortho*	*Meta*	*Para*
CH_3O	4.09	4.10	4.47
CH_3	3.91	4.27	4.37
H	4.20	4.20	4.20
Cl	2.92	3.82	3.98
NO_2	2.17	3.49	3.42

Acidity of Aromatic Carboxylic Acids

An aryl group is electron withdrawing relative to an alkyl group because the sp^2 hybrid orbital of the aromatic Ar—CO_2H bond draws the bonding electrons toward the aryl group. Thus, benzoic acid (pK_a 4.19) is a stronger acid than acetic acid. Table 21.6 lists the pK_a values of some aromatic carboxylic acids.

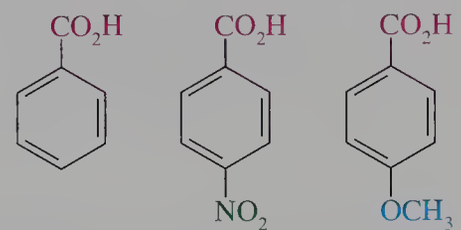
Substituents on an aromatic ring affect the reactivity of the ring toward electrophilic substitution by a combination of inductive and resonance effects (Section 14.5). Electron-withdrawing groups decrease the electron density of the ring. Electron-donating groups increase the electron density of the ring. However, the

principal resonance forms of the benzoate ion have the negative charge on the oxygen atoms. This negative charge cannot be delocalized into the aromatic ring.



resonance contributors of the benzoate ion

Nevertheless, substituents bonded to an aromatic ring affect the acidity of benzoic acids. An electron-withdrawing group, such as $-NO_2$, decreases the electron density at the carbon atom to which the carboxylate group is bonded. As a result, the O—H bond is polarized, and its acidity is increased. The decrease in electron density also stabilizes the resulting carboxylate ion. Electron-donating groups, such as $-OCH_3$, have the opposite effect.



$pK_a = 4.20$ $pK_a = 3.42$ $pK_a = 4.47$

The effect of a para substituent reflects both inductive and resonance contributions to the carbon atom bearing the carboxyl group. The effect of a meta substituent results only from inductive effects. The contribution of groups ortho to the carboxyl group is not easily interpreted because of steric effects on the conformation of the carboxyl group as well as solvation effects.

Problem 21.5

Explain why the pK_a value of $CH_2{=}CHCH_2CO_2H$ (4.3) is smaller than the pK_a of butanoic acid (4.8).

Sample Solution

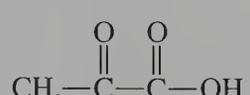
The vinyl group bonded to the α carbon atom is electron withdrawing relative to the ethyl group bonded to the α carbon atom of butanoic acid. The sp^2-hybridized carbon atom of the vinyl group draws electron density of the carbon–carbon bond away from the α carbon atom. Thus, the acidity of the unsaturated acid is greater and the pK_a is smaller.

Problem 21.6

Explain why *p*-nitrobenzoic acid is a stronger acid than *m*-nitrobenzoic acid even though its nitro group is farther from the carboxyl group.

Problem 21.7

Pyruvic acid is a key metabolic intermediate in oxidative processes that provide energy for the growth and maintenance of cells. Its pK_a is 2.5, indicating that it is about 100 times more acidic than propanoic acid (pK_a 4.7). Explain why.



pyruvic acid

21.5 Carboxylate Ions

What is the ratio of the concentrations of the carboxylate ion to nonionized carboxylic acid, RCO_2^-/RCO_2H, in aqueous solution? The answer depends on the pK_a of the carboxylic acid and the pH of the solution. In this section we consider three cases: water, solutions buffered at pH = 7, and strongly basic solutions.

Carboxylic Acids in Water

The ionization of a weak acid, such as acetic acid, produces a very low concentration of acetate ion. (You may recall making such calculations in your general chemistry course.) The ionization reaction is

$$CH_3CO_2H \rightleftharpoons H^+ + CH_3CO_2^- \qquad K_a = 1.8 \times 10^{-5}$$

The concentration of H^+ and $CH_3CO_2^-$ in a 0.10 M solution is related to K_a by the following equation.

$$K_a = \frac{[H^+]\,[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{x^2}{0.10 - x} \approx \frac{x^2}{0.10} = 1.8 \times 10^{-5}$$

Since $K_a \ll 1$, we can make the approximation that $0.10 - x \approx 0.10$. When we solve for x, we find that the acetate ion concentration is 1.3×10^{-3} M. Thus, for acetic acid in water the ratio of the acetate ion to acetic acid is approximately 0.013.

$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{1.3 \times 10^{-3}}{0.10} = 0.013$$

Carboxylic Acids at pH 7

When a weak acid, such as acetic acid, is added to a solution buffered at pH = 7, the ratio of the conjugate base and carboxylic acid differs from that in water. Rearranging the equation for the dissociation of a weak acid, and substituting 1×10^{-7} for the concentration of hydrogen ion in the buffered solution, gives the following ratio of conjugate base to carboxylic acid.

$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{K_a}{[H^+]} = \frac{1.8 \times 10^{-5}}{1.0 \times 10^{-7}} = 1.8 \times 10^2$$

In the buffered solution, which is more basic than the solution of a carboxylic acid in water, the carboxylate ion predominates. For this reason, biochemists prefer to name carboxylic acids, not as the acids, but as carboxylates because this is the form that exists at **biological pH**. In many biological fluids, a complex buffer system maintains the pH near neutrality. For example, the pH of blood normally remains at 7.4.

Carboxylic Acids in Basic Solution

The pH of a 5% solution of sodium bicarbonate is about 8.5. What happens when a carboxylic acid dissolves in this basic solution? The bicarbonate ion controls the hydrogen ion concentration as long as the amount of dissolved carboxylic acid is

Soaps and Detergents

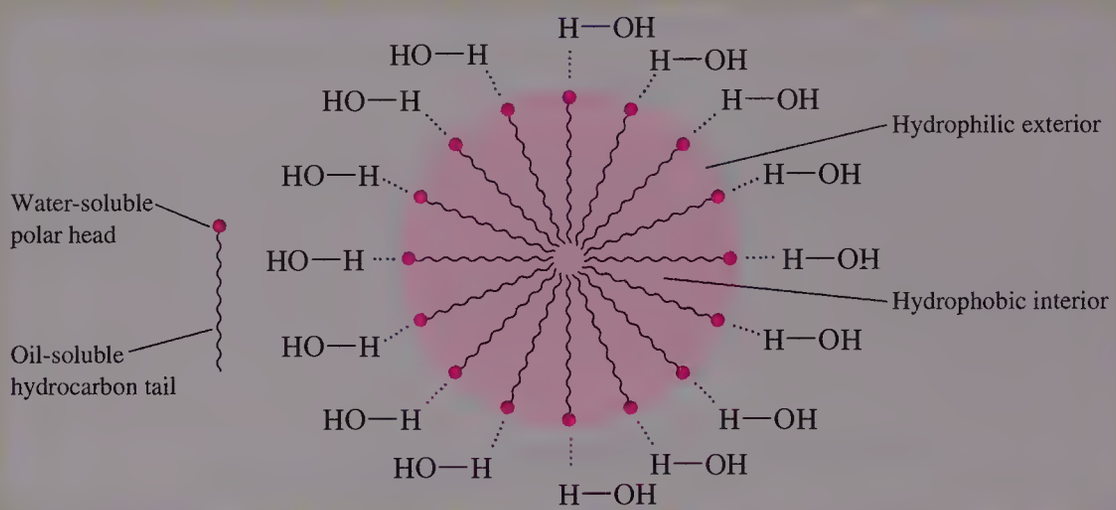
Soaps are salts of long-chain acids called fatty acids. The best soaps are carboxylate salts made from saturated acids with 14 to 18 carbon atoms. Soaps fabricated as bars are usually sodium salts, whereas the potassium salts, which are softer, are used in shaving creams.

$$CH_3(CH_2)_{16}CO_2^- \; Na^+$$

sodium stearate
(a soap)

Soaps were originally produced from animal fats, triesters of glycerol and carboxylic acids containing 12 to 18 carbon atoms.

The carboxylate salts of fatty acids have long nonpolar hydrocarbon chains. Therefore, they do not form solutions of individual ions, but are dispersed as associated structures called **micelles**, spherical aggregations of molecules or ions. In a micelle of carboxylate salts, the nonpolar hydrocarbon chains point toward the interior of the sphere and the polar carboxylate "heads" lie on the surface of the sphere (see the figure). This spherical arrangement encloses the maximum amount of "hydrocarbon" material for the smallest surface area. As a consequence, the hydrogen-bonded structure of water is disrupted to the smallest extent possible.



Micelle of a Soap or Detergent

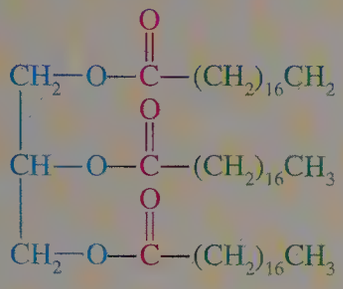
less than the bicarbonate. At pH 8.5, the hydrogen ion concentration is 3×10^{-9}. The ratio of carboxylate ion to carboxylic acid is larger than in the buffered solution at pH 7.

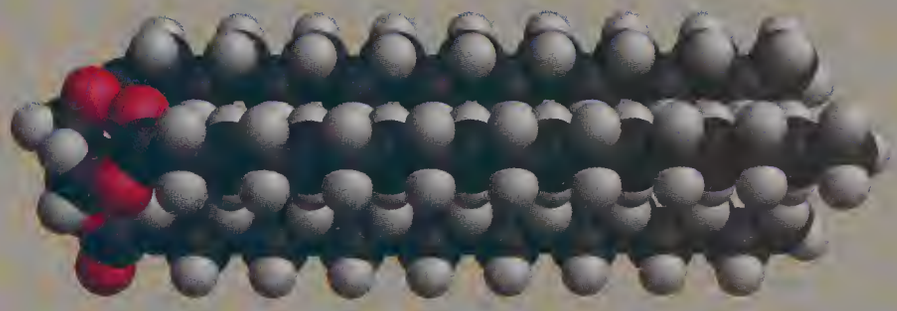
$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{K_a}{[H^+]} = \frac{1.8 \times 10^{-5}}{3 \times 10^{-9}} = 6 \times 10^3$$

Less than 0.02% of the carboxylic acid remains. Because carboxylate ions carry a charge, they are more soluble than carboxylic acids. Thus, carboxylic acids readily dissolve in sodium bicarbonate solution. Weaker acids such as phenols ($pK_a \sim 10$) are not converted to their conjugate bases at pH = 8, so phenols are less soluble than carboxylic acids in sodium bicarbonate.

Separation and Purification of Carboxylic Acids

Because carboxylic acids are weak acids, carboxylates are relatively strong bases. Carboxylate salts react with hydronium ion to form the carboxylic acid.



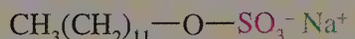


tristearin (a fat)

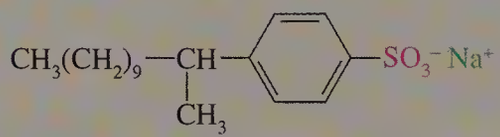
The nonpolar hydrocarbon chain of a fatty acid repels water and is called **hydrophobic**. In contrast, the polar "head" of the carboxylate group forms hydrogen bonds to water and is called **hydrophilic**. London forces between hydrocarbon chains hold the micelle together. The tendency of nonpolar solutes to aggregate in aqueous solution is called the **hydrophobic effect**. The micelle surface, which may contain as many as a 100 carboxylate groups, has a large number of negative charges. As a result, individual micelles repel each other and remain suspended in water.

An example of a hydrophobic substance is grease, which does not dissolve in water because it is nonpolar. However, grease will dissolve in the hydrocarbon region of the micelle. This process accounts for the cleansing action of a soap.

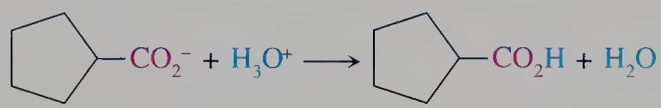
Micelles also interact with the ions in hard water, which contains relatively high concentrations of Ca^{2+} and Mg^{2+} ions. These ions react with the carboxylate ions of soaps and form precipitates that reduce the cleansing power of the soap. For this reason, detergents—salts of organic sulfate esters—work better than soaps in hard water. Like soaps, detergents have long hydrophobic tails and hydrophilic heads and form micelles. However, they do not form precipitates with Ca^{2+} and Mg^{2+} ions.



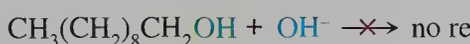
sodium dodecyl sulfate



sodium *p*-(2-dodecyl)benzenesulfonate



The reaction of carboxylic acids with hydroxide ions and the reaction of carboxylate salts with hydronium ions have some practical applications in separating acids from mixtures. Because they are ionic, carboxylate salts are more soluble in water than their corresponding carboxylic acids. Carboxylic acids are often separated from other, nonpolar organic compounds in the laboratory by adding a solution of sodium hydroxide to form the more soluble carboxylate salt. Consider, for example, a mixture of 1-decanol and decanoic acid. 1-Decanol is not soluble in water and does not react with sodium hydroxide. However, decanoic acid reacts with sodium hydroxide and thus dissolves in the basic solution. The 1-decanol remains undissolved.



(insoluble in water)

(insoluble in water) (soluble in water)

Undissolved 1-decanol is physically separated from the basic solution. Then, HCl is added to neutralize the basic solution, and insoluble decanoic acid separates from the aqueous solution.

$$\underset{\text{(soluble in water)}}{CH_3(CH_2)_8CO_2^-} + H_3O^+ \longrightarrow \underset{\text{(insoluble in water)}}{CH_3(CH_2)_8CO_2H} + H_2O$$

This procedure is very useful in isolating acids from complex mixtures. It is also used to purify acids produced by chemical synthesis in the laboratory.

Problem 21.8

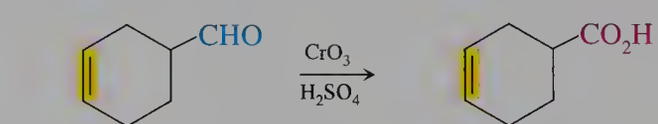
Ibuprofen, the active ingredient in Motrin, Advil, and Nuprin, is a carboxylic acid with $pK_a = 5.2$. Determine the ratio of the conjugate base to acid in stomach acid at pH = 2 and blood at pH = 7.4.

21.6 Synthesis of Carboxylic Acids

In this section we first consider oxidative methods of preparing carboxylic acids. Then we discuss two general methods that are useful in preparing carboxylic acids from starting materials containing one less carbon atom than the product. These methods, the carboxylation of a Grignard reagent and the hydrolysis of a nitrile, are based in part on reactions we have studied in earlier chapters.

Oxidative Methods

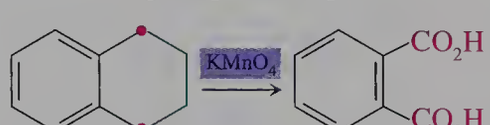
We recall that aldehydes and primary alcohols are oxidized by Jones reagent (Sections 16.4 and 18.5) to produce carboxylic acids. The oxidation of alcohols proceeds by way of aldehydes, which are in turn more readily oxidized to carboxylic acids.



3-cyclohexenecarbaldehyde → 3-cyclohexenecarboxylic acid

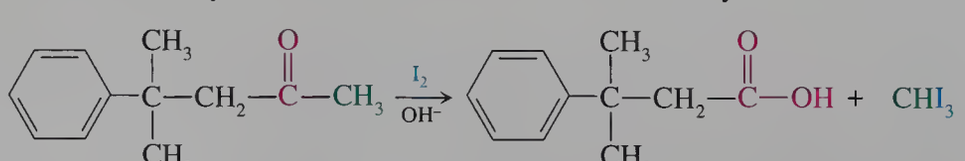
$$\underset{\text{1-decanol}}{CH_3(CH_2)_8CH_2OH} \xrightarrow[H_2SO_4]{CrO_3} \underset{\text{decanoic acid}}{CH_3(CH_2)_8CO_2H}$$

Alkylbenzenes are oxidized by potassium permanganate to give benzoic acids. We recall that the entire side chain is oxidized in this reaction. The oxidation of tetralin, which has a saturated ring, to produce phthalic acid is a related example.



tetralin → phthalic acid

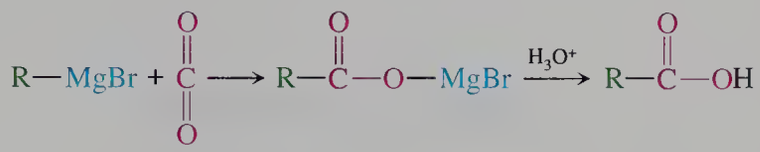
The haloform reaction (Section 23.5) may also be considered an oxidative method. In this reaction, the methyl group of a methyl ketone is converted to a haloform and the carbonyl carbon atom is oxidized to a carboxylic acid.



4-methyl-4-phenyl-2-pentanone → 3-methyl-3-phenylbutanoic acid + iodoform

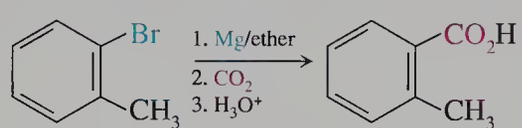
Carboxylation of Grignard Reagents

In Chapter 16 we learned that the Grignard reagent acts as a nucleophile and that it reacts with the electrophilic carbonyl group of aldehydes or ketones. A similar reaction occurs between a Grignard reagent and the carbon–oxygen double bond of carbon dioxide to yield the magnesium salt of a carboxylic acid. Acidification gives the carboxylic acid.



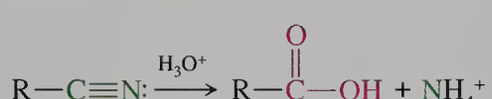
Starting from the haloalkane, the reaction sequence requires three steps. First, the haloalkane is converted to a Grignard reagent. Second, the ether solution is poured over solid carbon dioxide (dry ice). Finally, the reaction mixture is acidified.

The reaction sequence can be shown using a single arrow with the three steps listed.

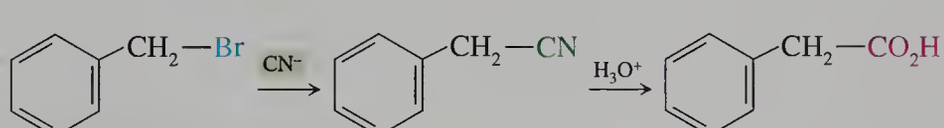


Hydrolysis of Nitriles

The second synthesis that adds one carbon atom to the parent chain of the reacting haloalkane involves an S_N2 displacement of halide by cyanide ion (Section 8.10). The resulting product, called a nitrile (RCN), can be hydrolyzed to produce a carboxylic acid. (We will present the chemistry of nitriles in Chapter 22.)



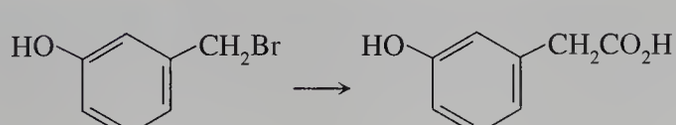
We recall that substitution reactions of the S_N2 type are most effective with primary haloalkanes. Elimination reactions decrease the yield for secondary haloalkanes.



benzyl bromide phenylacetic acid

Problem 21.9

Suggest a synthesis that accomplishes the following transformation.



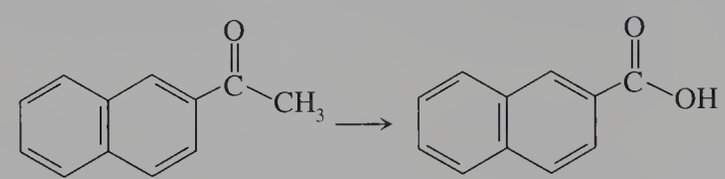
Sample Solution

One carbon atom in the form of a carboxyl group must be added to the side chain of the aromatic compound. Two general methods are available starting from a halogen-substituted compound. The method using a Grignard reaction followed by carbonation cannot be used in this case. The phenolic hydroxyl group is sufficiently acidic to destroy the Grignard reagent. The second method, involving displacement of a halide ion by the cyanide ion followed by hydrolysis, can be used. The substituted benzyl bromide is a primary haloalkane that readily reacts in an S_N2 reaction. Subsequent hydrolysis of the nitrile under acidic conditions gives the desired compound.

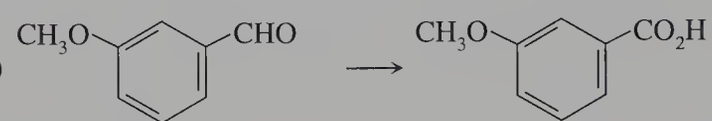
Problem 21.10

What reaction conditions are required for each of the following transformations?

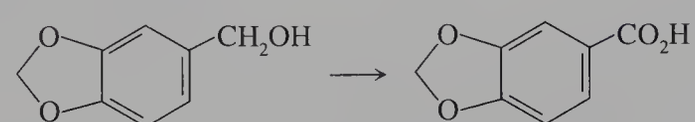
(a)



(b)



(c)



21.7 Reduction of Carboxylic Acids

We recall that $LiAlH_4$ reduces esters of carboxylic acids, yielding primary alcohols (Section 16.9). An aldehyde occurs as an intermediate in the reaction, but cannot be isolated because lithium aluminum hydride reduces it more readily than the ester. Sodium borohydride is a less effective hydride source that does not reduce esters.

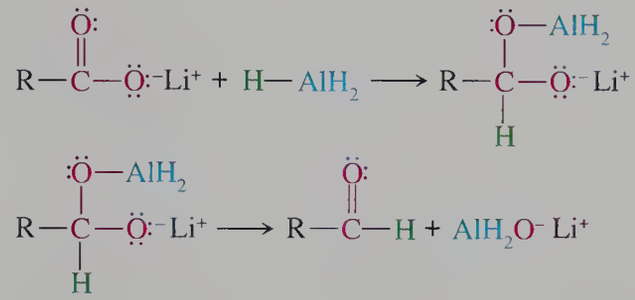
Carboxylic acids are also reduced by lithium aluminum hydride but not by sodium borohydride. However, the reduction of carboxylic acids requires important differences in the reaction conditions compared to those for esters. First, the acidic proton of the carboxylic acid reacts with an equivalent of hydride ion to generate hydrogen gas and a lithium salt of the carboxylic acid. Thus, the reaction destroys part of the hydride reagent.

$$R{-}CO_2H + LiAlH_4 \longrightarrow RCO_2^- Li^+ + H_2 + AlH_3$$

Second, the continued reaction of the remaining aluminum hydride or excess lithium aluminum hydride with the carboxylate salt is more difficult than for an ester. The reaction requires higher temperatures and longer reaction times because the hydride ion must react with a carbonyl carbon atom of the carboxylate, which is less electrophilic than the carbonyl carbon atom of an ester.

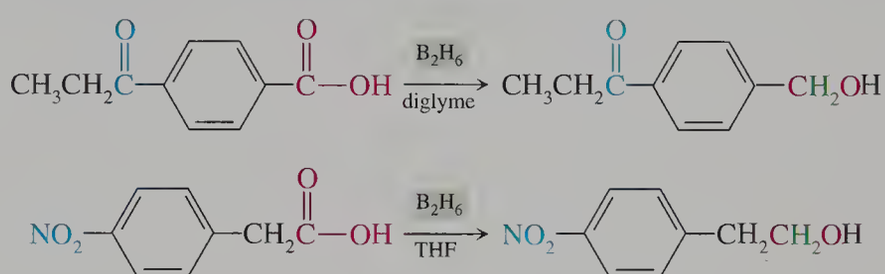
The first step in the mechanism of the reduction of carboxylate is an addition reaction to the carbonyl group. This reaction is similar to the addition reaction of alde-

hydes and ketones. A subsequent elimination reaction forms an aldehyde. This reaction is reminiscent of the reverse of the formation of a hemiacetal, which also has two oxygen atoms bonded to the same carbon atom, to give the more stable carbonyl compound.



However, the aldehyde does not survive under these reaction conditions because it is reduced by $LiAlH_4$, or by remaining hydride in species such as AlH_3 or AlH_2O^-.

Carboxylic acids are more easily reduced to primary alcohols using diborane in an ether solvent such as diglyme or THF. The reaction occurs very rapidly even at room temperature. The principal advantage of this reagent is its selectivity. For example, it reduces a carboxylic acid at a faster rate than a ketone or ester. It will very slowly reduce a nitrile, but does not reduce a nitro group.



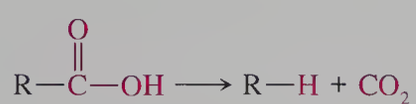
Lithium aluminum hydride would reduce both the carboxylic acid and the keto group. In the case of the nitro-substituted carboxylic acid, the nitro group would be simultaneously reduced to an amine.

Problem 21.11

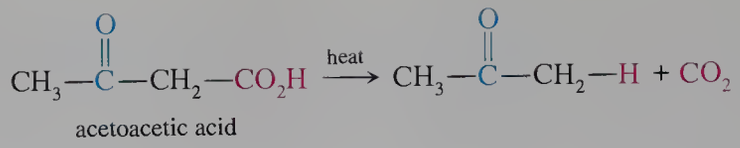
What is the product of the reaction of 3-(*p*-cyanophenyl)propanoic acid with $LiAlH_4$? What is the product using B_2H_6?

21.8 Decarboxylation of Carboxylic Acids

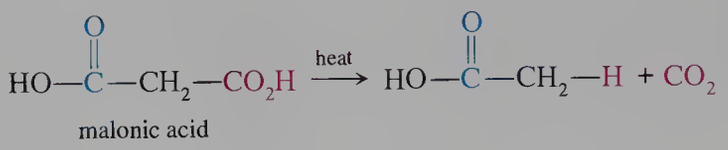
Decarboxylation is the loss of a carboxyl group and its replacement by a hydrogen atom.



Decarboxylation does not occur readily for simple carboxylic acids. However, carboxylic acids containing a β carbonyl group decarboxylate at relatively low temperatures. Two compounds of this type are acetoacetic acid and malonic acid.

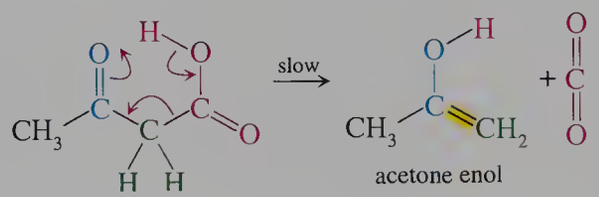


acetoacetic acid



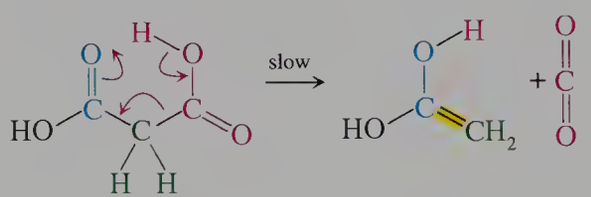
malonic acid

The decarboxylation of acetoacetic acid, a β-keto acid, occurs by way of a cyclic transition state in which a proton is transferred from the carboxyl group to the carbonyl oxygen atom. Subsequent rapid conversion of the enol product gives acetone.



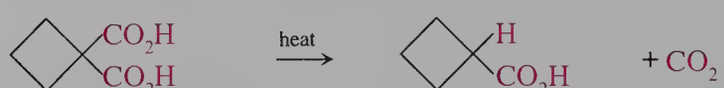
acetone enol

Malonic acid decarboxylates by way of a similar transition state to give an enol of acetic acid that tautomerizes to acetic acid.

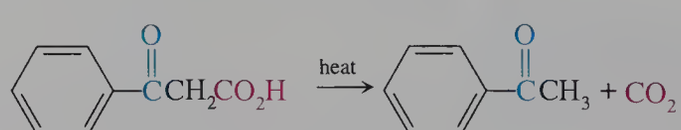


Neither reaction occurs for the conjugate base of these acids because a proton is required for transfer between oxygen atoms. If the conjugate base is carefully neutralized, the carboxylic acid can be isolated at room temperature without decarboxylation.

Groups bonded to the C-2 atom of either acetoacetic acids or malonic acids, or to the C-4 of acetoacetic acids, do not participate in the mechanism of the process. Both types of compounds are produced in condensation reactions of the related esters (Chapter 23). Hydrolysis of these esters yields carboxylic acids that are then heated to decarboxylate them.



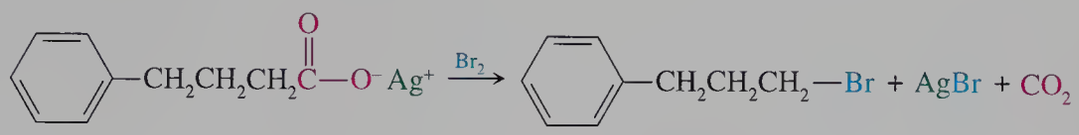
1,1-cyclobutanedicarboxylic acid cyclobutanecarboxylic acid



3-phenyl-3-oxopropanoic acid 1-phenylethanone

The Hunsdiecker Reaction

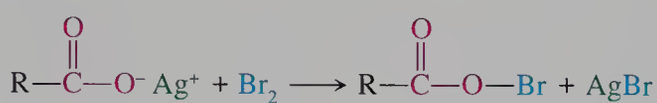
If the silver salt of a carboxylic acid is treated with bromine, the salt decarboxylates and a bromoalkane forms. This process is called the **Hunsdiecker reaction**.



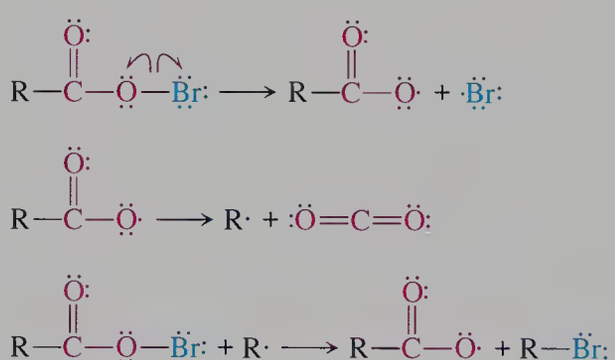
silver 4-phenylbutanoate

1-bromo-3-phenylpropane

The silver salt forms from reaction of a carboxylic acid with silver oxide (Ag_2O). Then bromine is added and the reaction mixture is heated. The silver salt reacts with bromine to give an acyl hypobromite. Mercury and lead salts can also be used in the Hunsdiecker reaction.



The acyl hypobromite has a very weak O—Br bond. It undergoes homolytic cleavage, which initiates a series of two free radical propagation steps.



Problem 21.12

Heating 4-methyl-1,1-cyclohexanedicarboxylic acid yields a mixture of two isomeric compounds. Draw their structures and explain their origin.

Problem 21.13

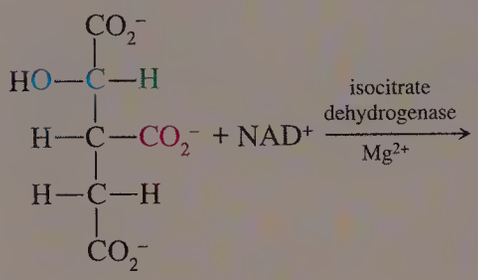
Explain why the Hunsdiecker reaction of *cis*-4-methylcyclohexanecarboxylic acid gives a mixture of two isomeric compounds.

Sample Solution

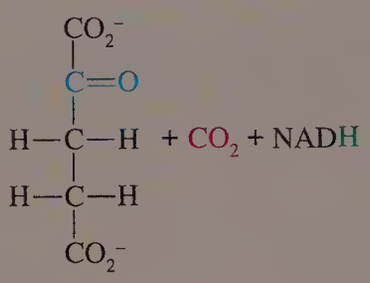
The intermediate secondary cycloalkyl radical is either planar or rapidly inverting, so the configuration of the C-1 atom is not maintained. Transfer of a bromine atom to the C-1 atom can occur from either an equatorial or an axial direction. Thus, both *cis*- and *trans*-1-bromo-4-methylcyclohexanes are produced.

Biological Decarboxylation Reactions

The decarboxylation of β-keto acids is an important biological process. The conversion of isocitrate to α-ketoglutarate in the citric acid cycle provides one example. This reaction is catalyzed by isocitrate dehydrogenase, an NAD^+-dependent dehydrogenase.

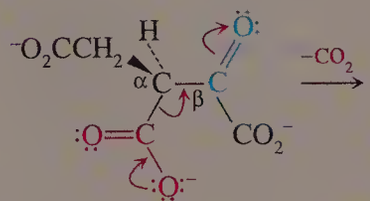


isocitrate

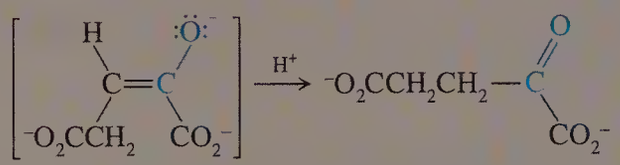


α-ketoglutarate

The first step is oxidation of the hydroxyl group of isocitrate to a carbonyl group. The oxalosuccinate product, a β-keto acid, subsequently loses carbon dioxide.

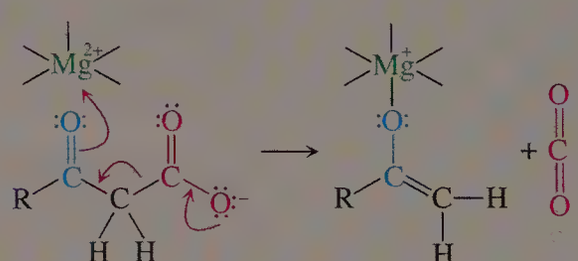


(*S*)-3-oxalosuccinate



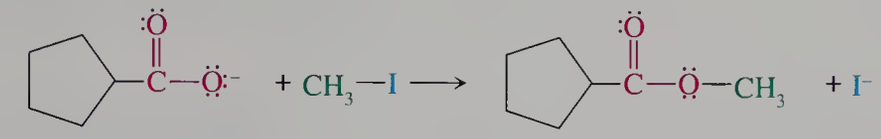
α-ketoglutarate

The biological decarboxylation of a β-keto acid presents a slight difficulty. We recall that carboxylic acids exist predominantly as anions at pH 7 and that the decarboxylation of β-keto acids occurs from the carboxylic acid, not from the carboxylate. Why is this decarboxylation of an anion a favorable process? Decarboxylation of the anion of a β-keto acid produces an enolate anion. An enolate anion has a $pK_a \approx 20$. Hence, an enolate anion remains very unstable at pH 7. ($\Delta G°$ for formation of an enolate is about 80 kJ $mole^{-1}$.) A reaction that produces an unstable intermediate has a high activation energy and is slow. Thus, the enzyme-catalyzed decarboxylation of the anionic form of a β-keto acid has to stabilize the enolate intermediate. The biological decarboxylation requires Mg^{2+} ions. A Mg^{2+} ion forms a complex with the carbonyl group of the β-keto acid, a process with two effects. First, it polarizes the carbonyl group, making it more electron withdrawing. That is, the metal ion acts as an "electron sink" that withdraws electron density away from the carboxylate group. This facilitates loss of CO_2. Second, the Mg^{2+} ion stabilizes the enolate intermediate by coordination with the negatively charged oxygen atom. Stabilization of the enolate lowers the energy of the transition state, increasing the rate of the reaction. The mechanism of the enzymatic decarboxylation reaction is shown below. The enolate picks up a proton from water and tautomerizes to the keto form.



21.9 Reactions of Carboxylic Acids and Derivatives—A Preview

Carboxylic acids share some of the structural features of alcohols and ketones. For example, we learned that the hydroxyl group of a carboxylic acid or alcohol is acidic. Like the alkoxide ion, the carboxylate ion is a nucleophile.

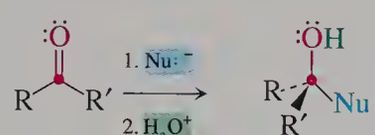


cyclopentanecarboxylate — methyl cyclopentanecarboxylate

One of the characteristic reactions of carbonyl groups is addition, in which the oxygen atom reacts with an electrophile such as a proton and the carbon atom reacts with a nucleophile. A second characteristic reaction results from the acidity of the α hydrogen atoms. The carbanion formed from the α carbon atom undergoes condensation reactions with the carbonyl group of a second molecule (Chapter 23). Both types of reactions also occur with carboxylic acids or their derivatives. However, the electron pairs of the hydroxyl group bonded to the carbonyl carbon atom contribute to the resonance forms of the carboxylic acid, making the carbonyl carbon atom less electrophilic and the α hydrogen atom less acidic. The chemistry of the carbonyl group itself is previewed below and discussed in detail in Chapter 22. The chemistry of the α carbon atom is presented in Chapter 23.

Nucleophilic Acyl Substitution

In the addition reactions of aldehydes and ketones, a tetrahedral product forms because of attack of a nucleophile at the carbonyl carbon atom. Examples include the formation of hemiacetals with alcohols and the synthesis of alcohols using the Grignard reagent.



tetrahedral product

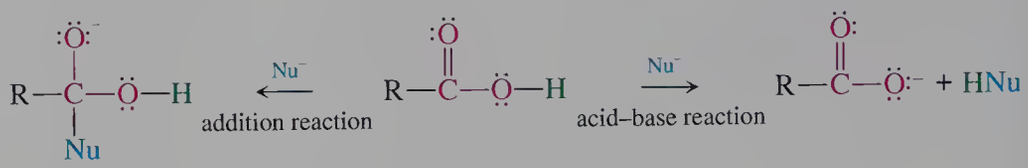
Carboxylic acids and acyl derivatives also react with nucleophiles. In these reactions, the nucleophile attacks the carbonyl carbon atom to generate an unstable tetrahedral intermediate that allows a leaving group to depart to form a different acyl derivative. The overall process is called **nucleophilic acyl substitution**, or an **acyl transfer reaction**, because it transfers an acyl group from one group (the leaving group) to another (the nucleophile).

tetrahedral intermediate

The net reaction is a substitution whose stoichiometry resembles that of an S_N2 substitution reaction of haloalkanes. However, the resemblance is only superficial. An S_N2 reaction occurs in a single step in which the nucleophile bonds to the carbon atom as the leaving group leaves. Nucleophilic acyl substitution occurs in two steps. The

rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. The loss of the leaving group occurs in a second, faster step. The overall process is called an addition–elimination reaction.

Only certain types of nucleophiles attack carboxylic acids. Most are bases that can either react with the acidic hydrogen atom of the carboxylic acid or attack the carbonyl carbon atom.

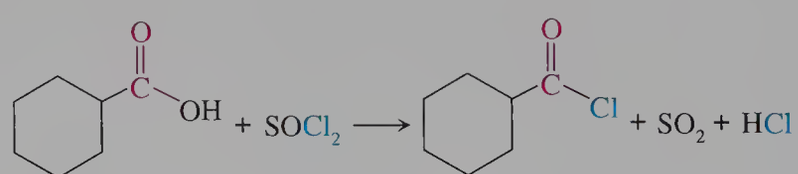


Because carboxylic acids are acidic, the acid–base reaction with the nucleophile often predominates. However, the addition–elimination reaction is common for acyl derivatives because they do not have an acidic hydroxyl hydrogen atom.

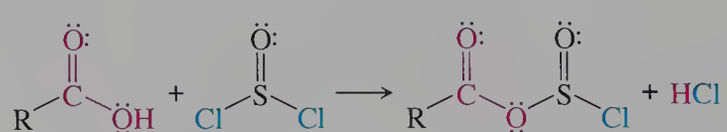
21.10 Conversion of Carboxylic Acids into Acyl Halides

Carboxylic acids are converted into acyl halides for use in nucleophilic acyl substitution reactions for two reasons. First, the competing reaction of nucleophiles with the acidic proton of carboxylic acids is eliminated. Second, a chloride ion is a better leaving group than a hydroxide ion.

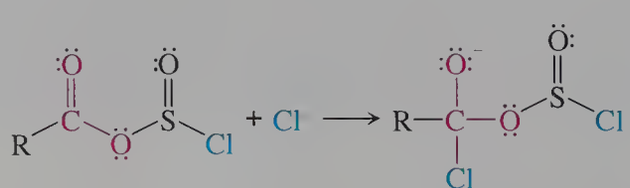
We recall that the replacement of a hydroxyl group of an alcohol by chlorine is accomplished by converting the hydroxyl group into a better leaving group. Thionyl chloride can be used in such a reaction. It reacts with an alcohol to give a chlorosulfite ester (Section 16.3). Under similar reaction conditions, a carboxylic acid is converted into an acyl chloride.



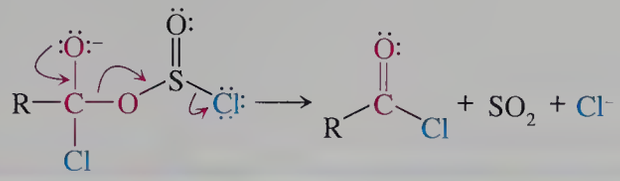
The mechanism for the reaction of $SOCl_2$ with carboxylic acids, which occurs in three steps, resembles the mechanism for the reaction of $SOCl_2$ with alcohols. In the first step, a chlorosulfite derivative forms as a result of nucleophilic displacement of a chloride ion from sulfur by the lone pair electrons of the hydroxyl group of the carboxylic acid.



The chlorosulfite group withdraws electrons readily, making the carbonyl carbon atom susceptible to attack by the chloride ion formed in the first step. A tetrahedral intermediate forms. It can exist either as an anion, as shown, or it can be protonated by the acid formed in the first step of the mechanism.



The third step is a concerted process in which the chlorosulfite group decomposes into an acyl chloride, sulfur dioxide, and chloride ion.

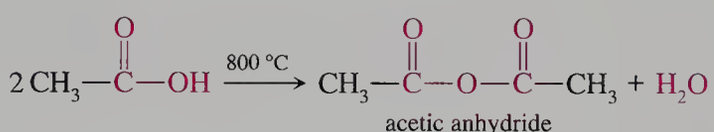


Problem 21.14

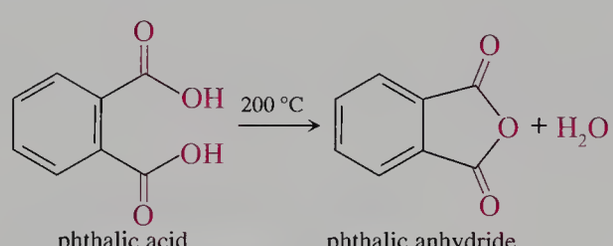
Carboxylic acids can be converted into acyl bromides by reaction with PBr_3. Review the mechanism for the conversion of alcohols into alkyl bromides by this reagent and write a plausible mechanism for the reaction of this reagent with carboxylic acids.

21.11 Conversion of Carboxylic Acids into Anhydrides

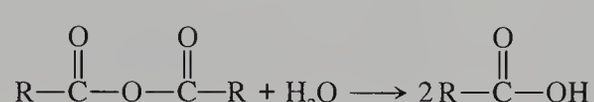
The term anhydride means "without water". Acid anhydrides can be prepared by heating carboxylic acids. For example, heating acetic acid to 800 °C in a commercial process causes the direct loss of water. Industry produces large quantities of the resulting acetic anhydride by this method. Acetic anhydride is an important commercial reagent for the acylation of organic compounds.



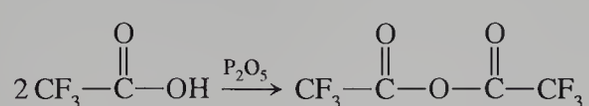
Dicarboxylic acids that can form five- or six-membered cyclic anhydrides dehydrate at substantially lower temperatures.



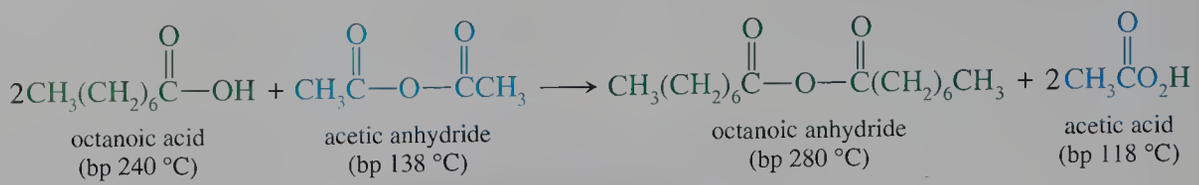
Both of these reactions, which form anhydrides directly from the carboxylic acids, are endothermic. However, the reaction goes to completion because the high temperature drives water off as a gas. Acid anhydrides react spontaneously at room temperature with water to form two equivalents of a carboxylic acid.



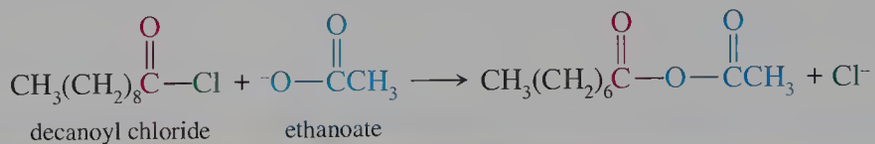
Anhydrides can be used as dehydrating agents to react with the water produced in the formation of another anhydride. For example, phosphorus pentoxide reacts with water to form phosphoric acid and complex phosphoric acid derivatives. The anhydride of a carboxylic acid can often be distilled from the reaction mixture because the phosphoric acid by-products are nonvolatile.



Acetic anhydride can also be used as a dehydrating agent for the preparation of anhydrides that have higher boiling points than acetic acid. Distilling the acetic acid out of the reaction mixture leaves the desired anhydride of the carboxylic acid.



The displacement of a halide from an acyl halide by a carboxylate ion is a common laboratory method of synthesizing anhydrides. This method has the advantage of making the preparation of mixed anhydrides possible.



Problem 21.15

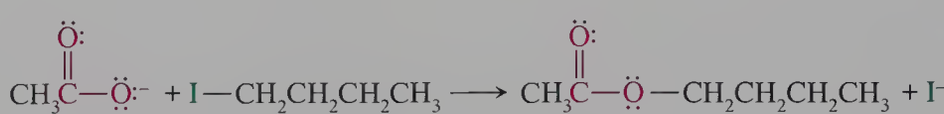
Maleic acid and fumaric acid are isomeric 2-butenedioic acids. Maleic acid easily loses water when heated to form a compound with molecular formula $C_4H_2O_3$. Fumaric acid loses water, but only at a higher temperature, and yields a polymeric product. Assign the structures of the two acids based on this information.

21.12 Synthesis of Esters

The formation of an ester can be pictured as the joining of an acyl carbon atom and an alkyl (or aryl) carbon atom by way of an oxygen atom. The oxygen atom of the OR group can be supplied from the acyl component or the alkyl component. In the syntheses described in this section, we will show examples of both methods.

Alkylation of Carboxylates

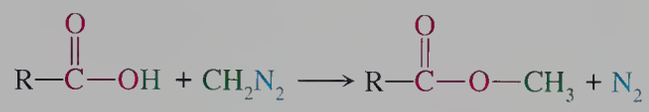
We recall that a carbon–oxygen bond of an ether can be formed by nucleophilic displacement of a halide from an alkyl halide by an alkoxide. For example, the Williamson ether synthesis (Section 17.6) can be classified as an alkylation of oxygen. A similar alkylation reaction occurs with a carboxylate acting as a nucleophile. However, because carboxylate ions are resonance stabilized, they are weaker nucleophiles than alkoxides. On the other hand, they are also less basic, and the competing elimination reaction is less likely to occur.



Because the reaction occurs by an S_N2 mechanism and the carboxylate ion is a poor nucleophile, the reaction works best for primary alkyl halides. Note that the bridging oxygen atom of the ester derives from the acyl fragment.

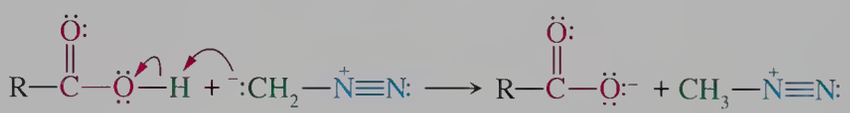
Esterification Using Diazomethane

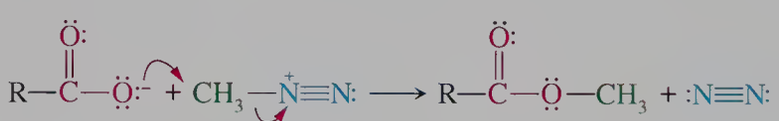
Carboxylic acids are converted to their methyl esters by simply adding an ether solution of the acid to an ether solution of diazomethane. In this reaction, the oxygen atom linking the acyl and alkyl carbon atoms is provided by the acyl group.



The method is limited to the preparation of esters in small quantities because diazomethane is a toxic, explosive gas prepared only in solution. The ester is isolated as a pure compound by evaporating the solvent. The nitrogen by-product is released during the reaction. Under these workup conditions, the excess diazomethane is also released.

The mechanism of the reaction of diazomethane with a carboxylic acid illustrates why diazomethane must be handled carefully. Diazomethane is easily protonated at the carbon atom to give a methyldiazonium ion. This ion is very susceptible to attack by a nucleophile because nitrogen gas is very stable and thus is an especially good neutral leaving group.

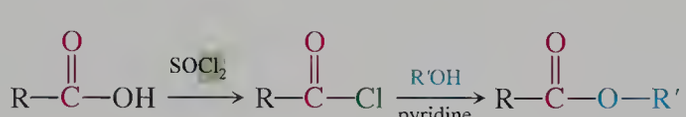




Many biological molecules can also react with diazomethane. The alkylation of sites responsible for catalytic activity has serious consequences for the reactivity of the enzymes and other biomolecules required to maintain cellular function.

Reaction of Acyl Chlorides with Alcohols

Carboxylic acids are efficiently converted to esters by way of an acid halide intermediate. First, the acid is converted to an acid chloride by treating it with $SOCl_2$. Then the resulting acid chloride reacts with an alcohol.



In the second reaction, pyridine neutralizes HCl so that it won't react with the alcohol to yield an alkyl halide or with some other functional group in the reactants.

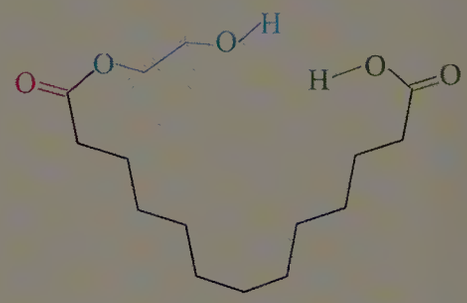
The mechanism of the reaction of an acid halide with an alcohol, excluding proton transfers, consists of two steps. In the first step, the alcohol acts as a nucleophile that attacks the electrophilic carbon atom of the acyl halide. Subsequent

Synthesis of a Macrocyclic Lactone

Large ring compounds containing one or more functional groups such as ketones or esters have odors that are desirable for the formulation of perfumes. For many years such compounds were obtained from natural sources such as the civet cat. However, to increase the range of available odors and to produce such materials in larger amounts, chemists have developed methods to form large ring compounds (macrocycles) from acyclic starting materials. In general, these methods must take into account the unfavorable ΔS_{rxn} associated with the probability of the ends of a long-chain compound coming together in a cyclization reaction. We recall that five- and six-membered rings form easily but the probability of ring formation falls off with chain length (Section 17.6).

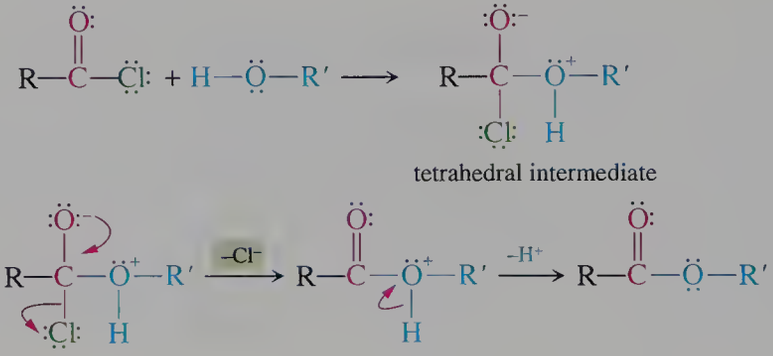
The cyclization of a hydroxy acid to give a lactone is a reaction that can provide macrocyclic molecules of possible use for the development of commercial products. However, because diacids and dialcohols are more common, a cyclization reaction to give a dilactone is more advantageous for a commercial process. Consider the reaction of tridecanedioic acid (brasslic acid) with ethylene glycol. The initial intermolecular reaction to give a monoester occurs readily under acidic conditions.

$$HO_2C{-}(CH_2)_{11}{-}CO_2H + HOCH_2CH_2{-}OH \xrightarrow[-H_2O]{H^+}$$

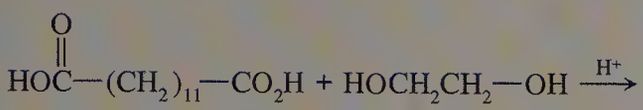


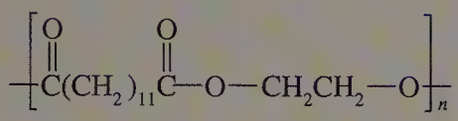
An intramolecular cyclization of the terminal alcohol and carboxyl group to give a second ester group is a unimolecular process that can occur in competition with an intermolecular process giving a polymer. The intermolecular process is bimolecular, and its rate decreases more rapidly at lower concentration than the intramolecular cyclization reaction. However, even at high dilution, the polymerization reaction is still favored.

loss of chloride ion from the tetrahedral intermediate and deprotonation gives the ester.

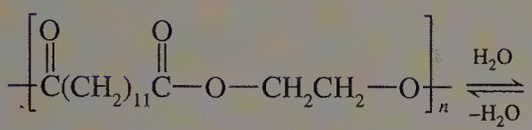


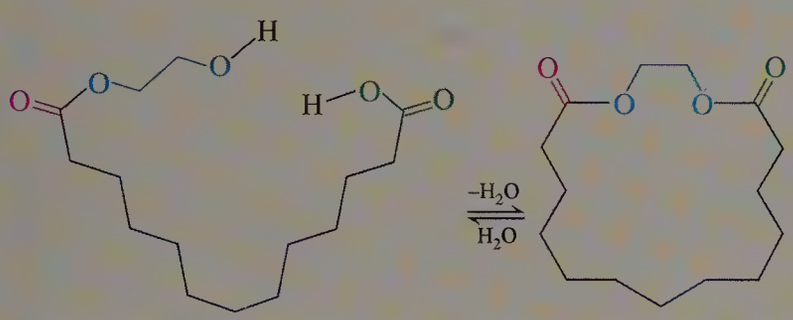
The bridging oxygen atom of the ester is provided by the alcohol. We recall that nucleophilicity of alkoxides depends on the steric environment near the oxygen atom. A similar effect is noted for the nucleophilic attack of an alcohol at the acyl carbon atom. The rate of reaction is primary > secondary > tertiary. The difference in rate often allows the selective formation of an ester of an unhindered alcohol in the presence of a hindered alcohol. For example, reaction of the following diol with one

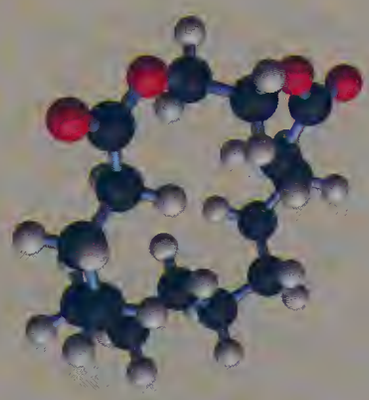




Because esterification reactions are easily reversed, heating the reaction mixture sets up an equilibrium that gives some of the 17-membered dilactone. The dilactone has a much lower boiling point than the polymer. Thus, the dilactone can be distilled out of the reaction mixture and more of the polymer generates the monoester to form more of the dilactone. This commercial method takes advantage of Le Châtelier's principle. Continued heating produces more dilactone that is continuously removed from the equilibrium mixture.

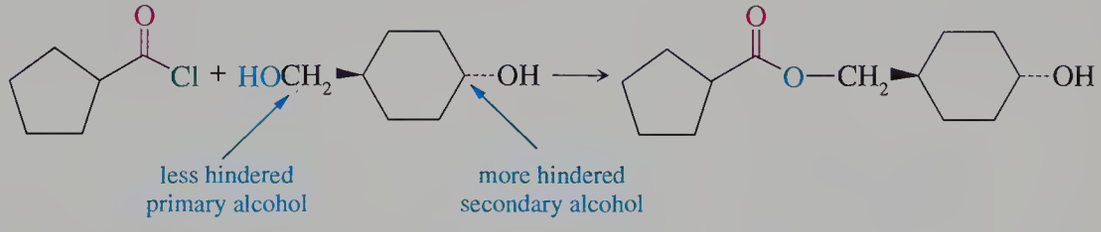






dilactone

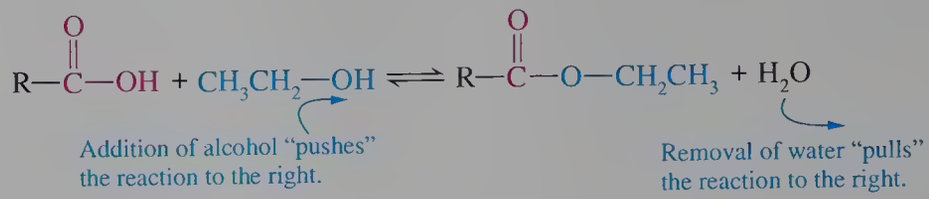
equivalent of an acid chloride gives an ester of the primary alcohol rather than the secondary alcohol.



Fischer Esterification

Carboxylic acids can react directly with alcohols to give esters in a process called the **Fischer esterification** reaction. The reaction is catalyzed by inorganic acids such as hydrogen chloride or sulfuric acid. Both the carboxylic acid and its ester exist in substantial amounts at equilibrium. The equilibrium constants for esters of primary alcohols are approximately 1.0. However, distilling the water out of the reaction mixture or adding excess alcohol increases the yield of ester. Removing water or adding alcohol shifts the equilibrium toward the product, as predicted by Le Châtelier's principle.

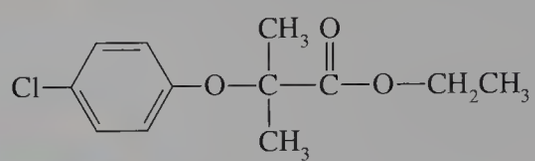
Ethyl esters of acids are obtained by using ethanol as a solvent. Under such conditions, the high concentration of ethanol favors a high conversion of the acid to the ester.



Esters cannot be prepared from tertiary alcohols using the Fischer esterification method because these alcohols tend to dehydrate under acid conditions. Esters of phenols also cannot be prepared by Fischer esterification because the equilibrium constant for the reaction is about 10^{-4}. Even by "pushing" the reaction, the yield is too low to be practical.

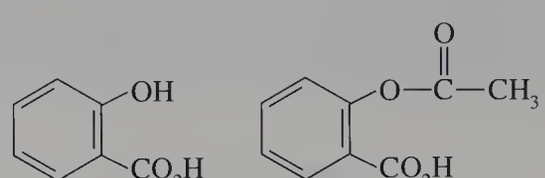
Problem 21.16

Clofibrate is a drug that can lower the concentration of blood triglycerides and cholesterol. How could this compound be commercially synthesized?



Problem 21.17

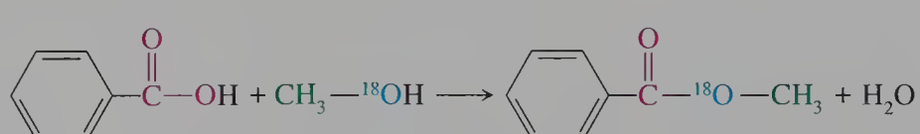
Acetylsalicylic acid is commonly known as aspirin. It is commercially synthesized from salicylic acid but not by using acetic acid as the acylating agent. Why not?



salicylic acid acetylsalicylic acid

21.13 Mechanism of Esterification

Does the oxygen atom linking the acyl and alkyl carbon atoms of an ester come from the oxygen of the acid or the alcohol? From a different perspective, does the water come from the hydroxyl group of the alcohol and the hydrogen of the acid or from the hydrogen atom of the alcohol and the hydroxyl group of the acid? Studies on the mechanism of the acid-catalyzed esterification reaction using ^{18}O-labeled methanol answer these related questions. When methanol reacts with benzoic acid, the oxygen-18 is contained in the ester, not in the water. Therefore, the CO—OH bond of the acid, rather than the COO—H bond, is cleaved. Also, the O—H bond of the alcohol is cleaved rather than the C—O bond.

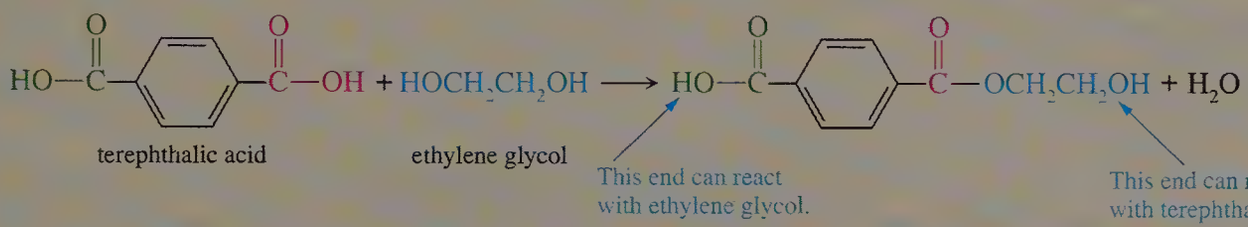


The data obtained from isotopic labeling studies and several other observations have clearly established the mechanism of the acid-catalyzed esterification of carboxylic acids. In the first step, protonation occurs at the lone pair of electrons of the

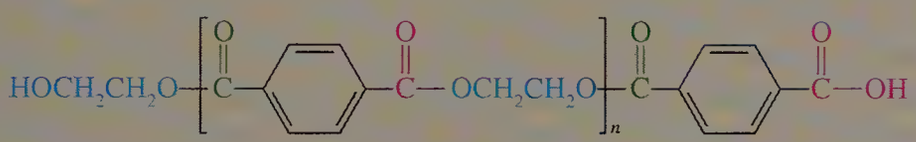
Polyesters

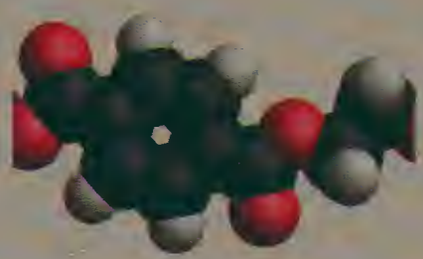
Many commercial products, called **condensation polymers**, are made by reacting monomers to give large molecules and some small molecule, such as water, as a by-product. This polymerization process differs from addition polymerization, in which the entire monomer remains in the polymer.

In condensation polymerization reactions, each monomer has two functional groups. An example of condensation polymerization is the reaction of terephthalic acid and ethylene glycol. One step in the reaction sequence is shown.



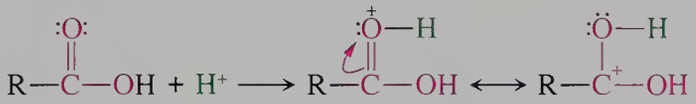
Although the product looks like a simple ester, it is also both an acid and an alcohol. Its acid end can react with more ethylene glycol, and its alcohol end can react with more terephthalic acid. Each reaction produces a larger molecule that continues to react to form a high molecular weight polyester. The polymer is industrially processed into a fiber called Dacron. Dacron is used in woven and knitted fabrics in combination with cotton or wool. Dacron fabric is physiologically inert, so it can be used in the form of a mesh to replace diseased sections of blood vessels.



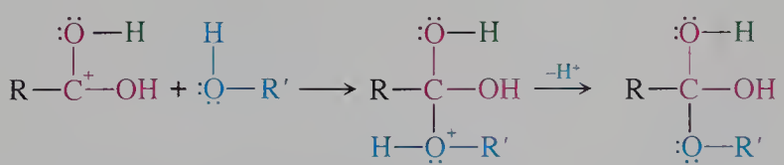


repeating unit of polyester

carbonyl oxygen atom. This reaction increases the electrophilicity of the carbonyl carbon atom, which otherwise is less reactive than the carbonyl carbon atom of an acyl chloride.



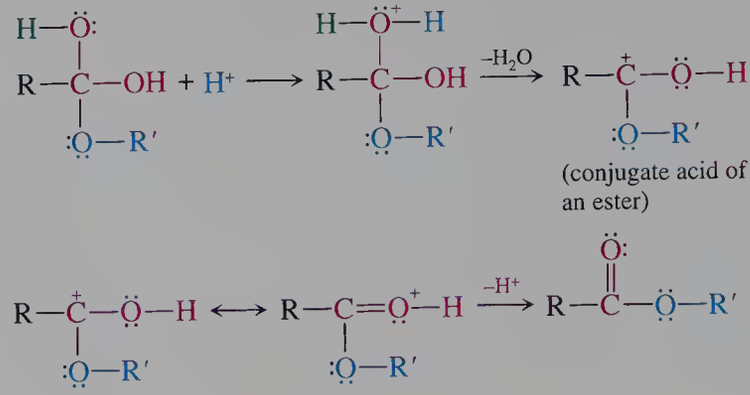
Nucleophilic attack by the alcohol gives a tetrahedral intermediate, the conjugate acid of a hydrate of an ester. This step is analogous to the acid-catalyzed nucleophilic addition of an alcohol to an aldehyde to give a hemiacetal or addition of water to give a hydrate. Deprotonation of the addition product in a solvent-mediated step gives the hydrate.



(hydrate of an ester)

The loss of water from the hydrate of the ester occurs in acid-catalyzed steps similar to those for loss of water from the hydrate of an aldehyde or ketone. Protonation

of one of the two hydroxyl groups prepares it to leave as water. Loss of a proton from the remaining hydroxyl group in a solvent-mediated reaction gives the ester.



21.14 Spectroscopy of Carboxylic Acids

Infrared Spectroscopy

For either a pure liquid or in solution, the C=O stretching absorption of carboxylic acids occurs near 1710 cm^{-1}. Under these conditions, a carboxylic acid exists as a hydrogen-bonded dimer. (At high temperature in the gas phase the monomer has a C=O stretching absorption at 1760 cm^{-1}.) Thus the position of the C=O stretching absorption is close to that of aldehydes and ketones. However, the absorption of carboxylic acids is much broader than those of aldehydes and ketones, and this characteristic is one of the hallmarks of the infrared spectra of carboxylic acids.

The O—H stretching absorption of carboxylic acids is also a highly characteristic feature. It occurs in the same region of the spectrum as that of alcohols. However, as in the case of the C=O absorption, the O—H absorption is very broad (2400–3600 cm^{-1}). As a consequence, this absorption strongly overlaps the region of C—H stretching absorption, which is often largely obscured. The presence of broad absorptions in both the 3000 cm^{-1} and the 1700 cm^{-1} regions clearly identifies carboxylic acids.

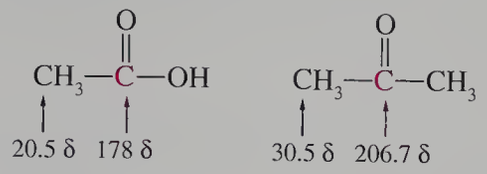
Proton NMR Spectroscopy

Like aldehydes and ketones, the α protons of carboxylic acids have NMR absorptions in the 2.0–2.5 δ region, depending on the degree of substitution of the α carbon atom. Therefore, an absorption in this region is not a characteristic that can be used to identify a carboxylic acid. The absorption of the O—H hydrogen atom depends on the acidity of the individual carboxylic acid as well as its concentration in the solvent used to determine the spectrum. In most cases the hydroxyl proton resonance occurs in the 9–12 δ region. This strong deshielding effect is a consequence of the strong hydrogen bonding in the dimer. Although this resonance is in the same region as the aldehydic hydrogen atom of aldehydes, the two are easily distinguished. Like the hydroxyl hydrogen atom of alcohol, the hydrogen atom of carboxylic acids is rapidly exchanged by deuterium using D_2O. If the resonance in the 9–12 δ region disappears after adding some D_2O to the NMR sample, we know that the compound is a carboxylic acid and not an aldehyde. The display of the O—H resonance of carboxylic acids is often offset by a specified amount to superimpose on the remainder of the spectrum, which is usually an 8- or 10-ppm range.

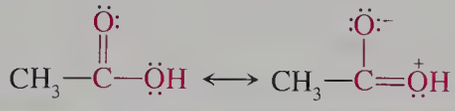
Carbon NMR Spectroscopy

As in the case of aldehydes and ketones, the carbon NMR spectra of carboxylic acids has a low field absorption due to the carbonyl carbon atom and a slightly deshielded

α carbon atom. Both absorptions resemble those of aldehydes and ketones, but those of carboxylic acids are at somewhat higher field.

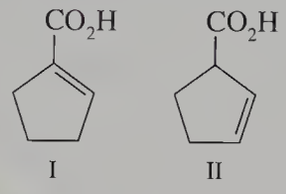


Based on the electronegativity of the oxygen atom, the hydroxyl group of a carboxylic acid might be expected to inductively withdraw electrons from the carbonyl carbon atom and cause deshielding of both that atom and the α carbon atom. However, the unshared pairs of electrons of the oxygen atom can be donated by resonance. Apparently, the decrease of the positive charge of the carbonyl carbon atom and the changes in the π system as a result of donation of electrons by oxygen are sufficient to shield both the carbonyl carbon atom and the α carbon atom of carboxylic acids relative to the carbonyl carbon atom of aldehydes and ketones.



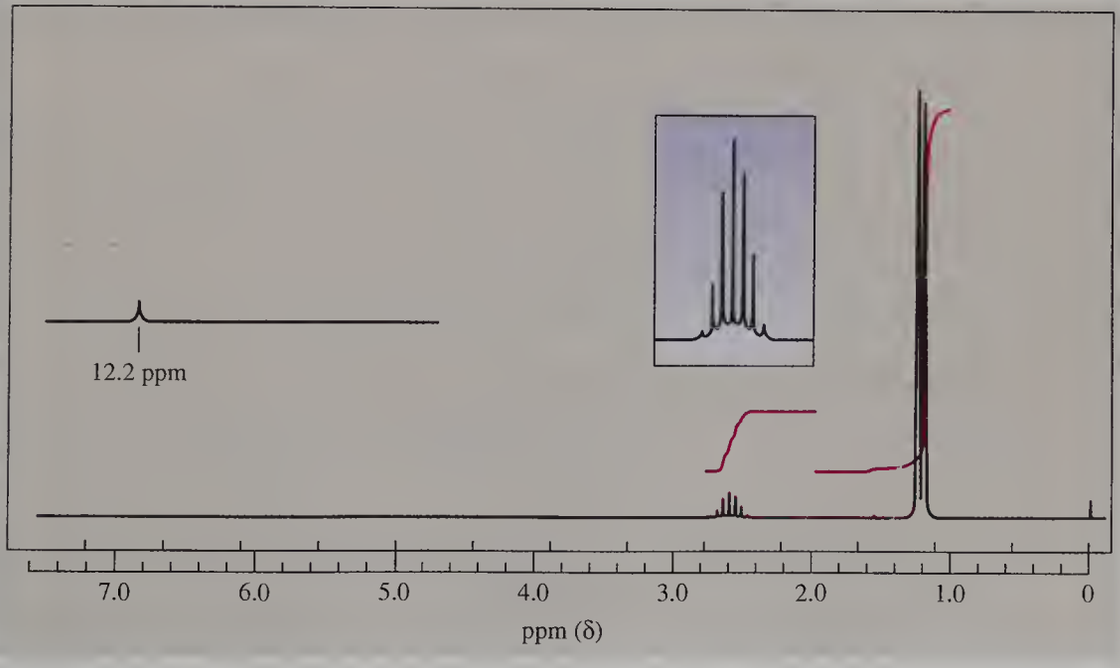
Problem 21.18

How can the two following isomeric carboxylic acids be distinguished using infrared spectroscopy?



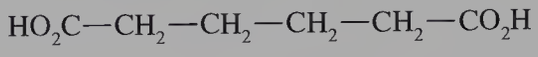
Problem 21.19

Identify the compound with molecular formula $C_4H_8O_2$ using the following hydrogen NMR spectrum.

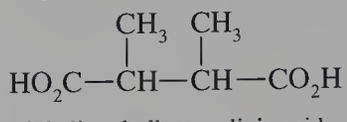


Problem 21.20

How could the following two isomers be distinguished using proton NMR spectroscopy? How could they be distinguished using carbon-13 NMR spectroscopy?



hexanedioic acid
(adipic acid)



2,3-dimethylbutanedioic acid
(α,β-dimethylsuccinic acid)

Problem 21.21

Deduce the structure of a compound with molecular formula $C_8H_8O_2$ based on the following carbon NMR data. The multiplicity is indicated within parentheses.

21.2 ppm (quartet), 128.1 ppm (doublet), 129.1 ppm (doublet), 129.4 ppm (doublet), 143.0 ppm (singlet), 167.4 ppm (singlet)

EXERCISES

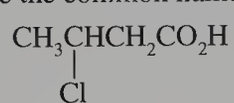
Nomenclature

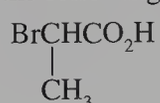
21.1 Give the common name for each of the following acids.

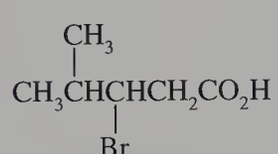
(a) $CH_3CH_2CO_2H$ **(b)** HCO_2H **(c)** $CH_3(CH_2)_4CO_2H$

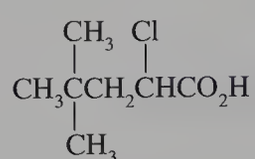
(d) $CH_3(CH_2)_{10}CO_2H$ **(e)** $CH_3(CH_2)_{16}CO_2H$ **(f)** $CH_3(CH_2)_{14}CO_2H$

21.2 Give the common name for each of the following acids.

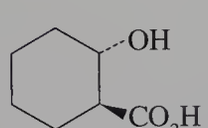
(a) 

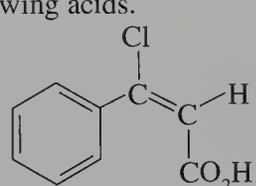
(b) 

(c) 

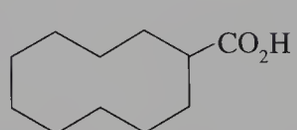
(d) 

21.3 Give the IUPAC name for each of the following acids.

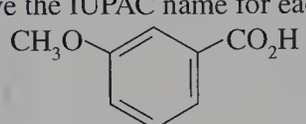
(a) 

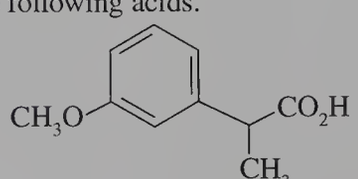
(b) 

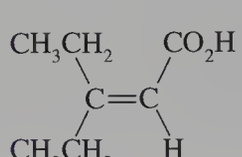
(c) $HC{\equiv}C{-}CH_2CH_2CH_2CO_2H$

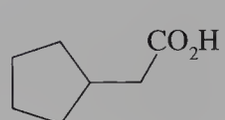
(d) 

21.4 Give the IUPAC name for each of the following acids.

(a) 

(b) 

(c) 

(d) 

21.5 The IUPAC name of ibuprofen, the analgesic in Motrin, Advil and Nuprin, is 2-(4-isobutylphenyl)propanoic acid. Draw the structure.

21.6 10-Undecenoic acid is the antifungal agent contained in Desenex and Cruex. Write the structure.

Molecular Formulas

21.7 What is the general molecular formula for each of the following classes of compounds?
(**a**) saturated acyclic carboxylic acid
(**b**) saturated acyclic dicarboxylic acid
(**c**) saturated monocyclic carboxylic acid
(**d**) monounsaturated acyclic carboxylic acid

21.8 Draw the structure of all isomers having the following characteristics.
(**a**) dicarboxylic acids with molecular formula $C_4H_4O_4$
(**b**) carboxylic acids with molecular formula $C_4H_8O_2$
(**c**) carboxylic acids with molecular formula $C_5H_{10}O_2$
(**d**) saturated carboxylic acids with molecular formula $C_5H_8O_2$

Properties of Acids

21.9 Explain why 1-butanol is less soluble in water than butanoic acid.

21.10 Explain why adipic acid is much more soluble in water than hexanoic acid.

21.11 Explain why the boiling point of decanoic acid is higher than that of nonanoic acid.

21.12 Explain why the boiling point of 2,2-dimethylpropanoic acid (164 °C) is lower than that of pentanoic acid (186 °C).

21.13 Explain why the boiling point of 4-methoxybenzoic acid (278 °C) is higher than that of 2-methoxybenzoic acid (200 °C).

21.14 Explain why the boiling point of *trans*-2-butenoic acid (185 °C) is higher than that of *cis*-2-butenoic acid (169 °C).

Acidity of Carboxylic Acids

21.15 The K_a of methoxyacetic acid is 2.7×10^{-4}. Explain why this value differs from the K_a of acetic acid (1.8×10^{-5}).

21.16 The K_a values of benzoic acid and *p*-nitrobenzoic acid are 6.3×10^{-5} and 3.8×10^{-4}, respectively. Explain why these values differ.

21.17 Estimate the pK_a values of the two carboxyl groups in 3-chlorohexanedioic acid.

21.18 The pK_a of 3-cyanobutanoic acid is 4.44. Using the pK_a values of chlorine-substituted butanoic acids as a guide, estimate the pK_a of 2-cyanobutanoic acid.

21.19 The pK_a for the first dissociation of dicarboxylic acids levels off at approximately 4.85. The pK_a of long-chain carboxylic acids levels off at approximately 4.55. What relationship exists between these two numbers? What structural features are responsible for this difference?

21.20 The difference between the pK_a values for dissociation of the first and second protons of the long-chain dicarboxylic acids is about 1 unit. The difference between the pK_a values for both oxalic and malonic acids is about 3 units. Explain these data, focusing on the pK_a for the second step.

21.21 The methoxy group is an effective donor of electrons and as a consequence is an activating group in electrophilic aromatic substitution. Explain why the pK_a of methoxyacetic acid (3.5) is less than that of acetic acid (4.7).

21.22 The pK_a values of cyanoacetic acid and nitroacetic acid are 2.45 and 1.65, respectively. What do these data indicate about the substituent properties of —CN and $—NO_2$?

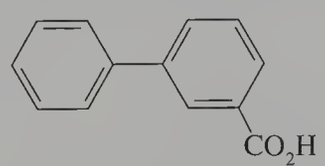
21.23 The substituent effects of the hydroxyl and methoxy groups are quite similar, as evidenced by the pK_a values of *p*-hydroxy- and *p*-methoxybenzoic acids, which are 4.48 and 4.47, respectively. However, the pK_a values of *o*-hydroxy- and *o*-methoxybenzoic acids are 2.97 and 4.09, respectively. Explain why the values for the ortho isomers are so different.

21.24 The pK_a values of para-substituted benzoic acids for the $-PCl_2$ and $-Si(CH_3)_3$ groups are 3.6 and 4.3, respectively. Based on these data, determine whether these groups are activating or deactivating in electrophilic aromatic substitution.

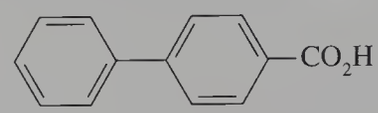
21.25 *p*-Methoxybenzoic acid is a weaker acid than benzoic acid, but *p*-(methoxymethyl)benzoic acid is a stronger acid than *p*-methylbenzoic acid. Why does the methoxy group have opposite effects in these two cases?

21.26 The van der Waals radii of fluorine and hydrogen atoms are similar. The pK_a values of *o*-, *m*-, and *p*-fluorobenzoic acids are 4.1, 3.9, and 3.3, respectively. The pK_a value of benzoic acid is 4.2. Explain the order of the pK_a values of the fluorobenzoic acids. Estimate the contribution of fluorine as an electron donor by way of resonance.

21.27 Compare the pK_a values of biphenyl-3-carboxylic acid (4.14) and biphenyl-4-carboxylic acid (4.21) to that of benzoic acid (4.20) and explain the different effect of the phenyl group on the pK_a values.



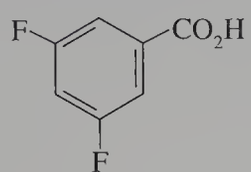
biphenyl-3-carboxylic acid



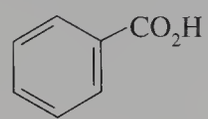
biphenyl-4-carboxylic acid

21.28 Which is the stronger acid in each of the following pairs of aromatic carboxylic acids? Explain why.

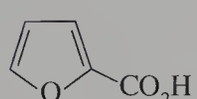
(a)



or



(b)



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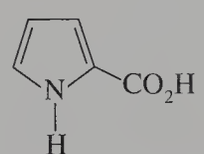

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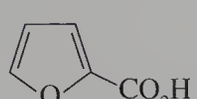

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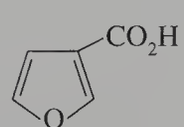
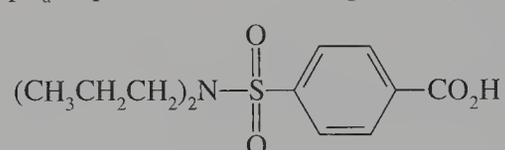
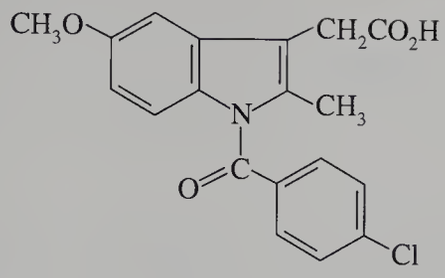


21.29 The pK_a of benzoic acid is 4.2. The pK_a of probenecid is 3.4. Explain why.



21.30 Predict the pK_a of indomethacin, an anti-inflammatory agent.



Carboxylate Ions

21.31 Are penicillins such as penicillin G (pK_a = 2.8) more soluble in stomach acid (pH ≈ 2) or in blood (pH = 7.4)?

21.32 Sodium benzoate is used as a preservative in foods, but only if the pH is greater than 5. In what form is the compound?

21.33 Explain why benzoic acid with an ^{18}O isotopic label in the hydroxyl oxygen atom can be prepared but then cannot then be used in mechanistic studies in aqueous solutions.

21.34 Draw representations of all of the molecular orbitals of a carboxylate ion. What is the electron distribution in each orbital. Which molecular orbital accounts for the shortened carbon–oxygen bond? Which molecular orbital explains the charge distribution in the ion?

Synthesis of Carboxylic Acids

21.35 Outline the steps required to prepare cyclohexanecarboxylic acid from each of the following reactants.
(**a**) bromocyclohexane (**b**) cyclohexanol (**c**) cyclohexene
(**d**) vinylcyclohexane (**e**) cyclohexylmethanol

21.36 Outline the steps required to prepare hexanoic acid from each of the following reactants.
(**a**) 1-chloropentane (**b**) 1-hexanol (**c**) hexanal
(**d**) 1-hexene (**e**) 1-heptene

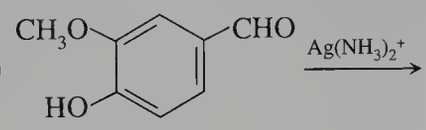
21.37 Outline the steps required to convert methylenecyclohexane to each of the following compounds.
(**a**) cyclohexanecarboxylic acid (**b**) cyclohexylacetic acid
(**c**) 1-methylcyclohexanecarboxylic acid

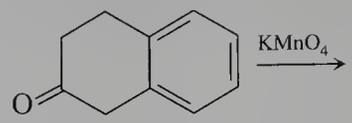
21.38 Outline the steps required to convert p-ethylanisole into each of the following compounds.
(**a**) *p*-methoxybenzoic acid (**b**) 2-(*p*-methoxyphenyl)propanoic acid
(**c**) 3-(*p*-methoxyphenyl)butanoic acid

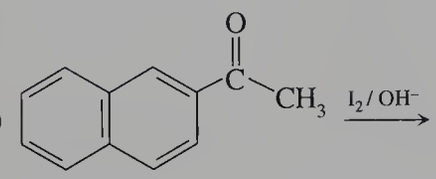
21.39 Fatty acids from natural sources are long-chain unbranched carboxylic acids that contain an even number of carbon atoms. Outline steps to convert the readily available dodecanoic acid (lauric acid) into the rare tridecanoic acid.

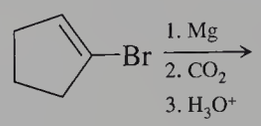
21.40 Pivalic acid, $(CH_3)_3CCO_2H$, can be prepared from *tert*-butyl chloride. What method should be used?

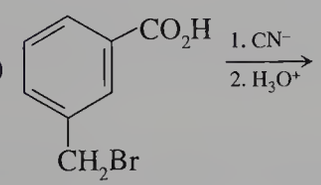
21.41 Draw the structure of the product of each of the following reactions.

(a) 

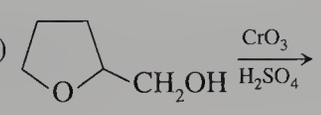
(b) 

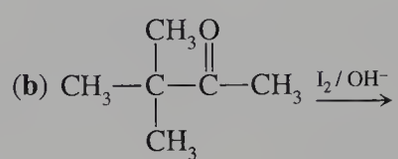
(c) 

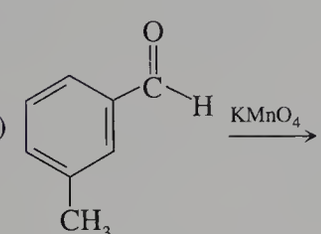
(d) 

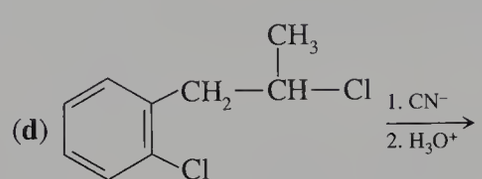
(e) 

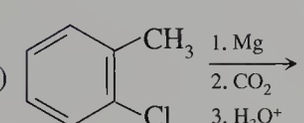
21.42 Draw the structure of the product of each of the following reactions.

(a) 

(b) 

(c) 

(d) 

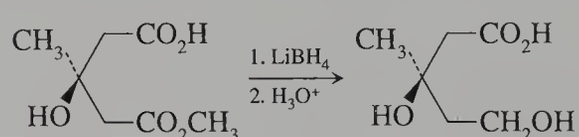
(e) 

Reduction of Carboxylic Acids

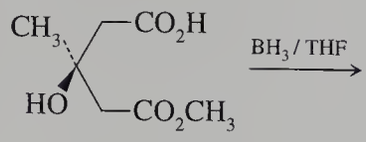
21.43 Metal hydride reductions occur by nucleophilic attack at the carbonyl carbon atom of acyl derivatives. Reduction of carboxylic acids with hydride reagents occurs slowly, but reduction by diborane occurs rapidly. Based on the structure of BH_3, the active reagent in diborane reductions, suggest the structure of the first intermediate formed in the reaction.

21.44 Diborane slowly reduces nitriles to amines, but rapidly reduces aldehydes and ketones. Using the structure of BH_3 and your mechanism developed in Exercise 21.43, explain why nitriles react more slowly than aldehydes and ketones.

21.45 Lithium borohydride is a more active reducing agent than sodium borohydride, but less active than lithium aluminum hydride. Lithium borohydride reduces the ester group of the following compound selectively. Explain this selectivity.



21.46 Draw the structure of the product of the following reaction. What relationship exists between this compound and the product of the reaction of Exercise 21.45?

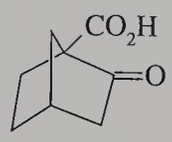


Decarboxylation

21.47 Could the Hunsdiecker reaction be used to decarboxylate an unsaturated carboxylic acid?

21.48 Which carboxylic acid should decarboxylate the more easily in a Hunsdiecker reaction, benzoic acid or cyclohexanecarboxylic acid?

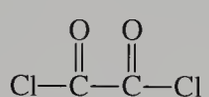
21.49 The following β-keto acid does not decarboxylate on heating. Based on the mechanism for the reaction, explain this observation.



21.50 Saturated carboxylic acids do not decarboxylate, but β,γ-unsaturated carboxylic acids do. Explain why, using a mechanism to show the decarboxylation of 3-butenoic acid. Use your mechanism to predict the product of decarboxylation of *(E)*-4-methyl-3-pentenoic acid.

Acyl Halides and Acid Anhydrides

21.51 Acyl halides can be prepared by reaction of a carboxylic acid with one equivalent of oxalyl chloride. The by-products of the reaction are HCl, CO_2, and CO. Write a mechanism for this reaction.



21.52 Acyl halides of hydroxy acids cannot be prepared using thionyl chloride. Explain why.

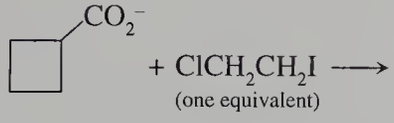
21.53 Heating octanedioic acid yields a polymeric substance. Explain why a cyclic anhydride doesn't form.

21.54 Explain how the isomeric 1,2-cyclobutanedicarboxylic acids could be distinguished from each other based on their behavior upon heating.

Synthesis of Esters

21.55 Draw the structure of the product of each of the following reactions.

(a)



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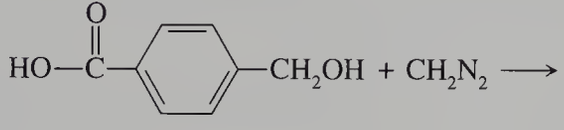
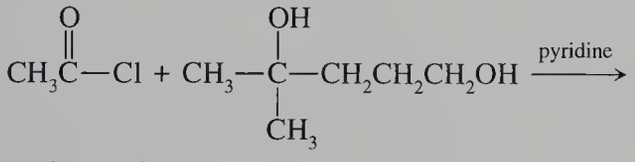


(c)



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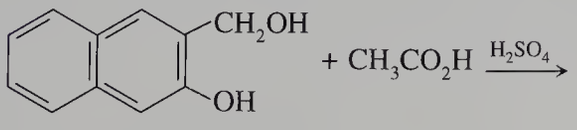
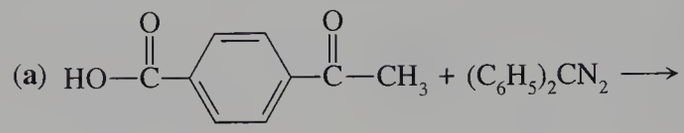
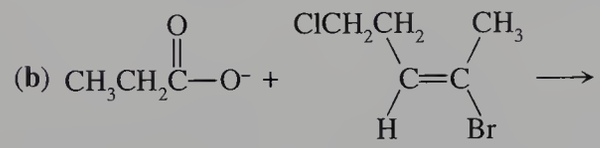
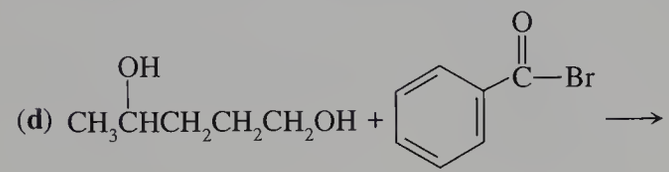


21.56 Draw the structure of the product of each of the following reactions.

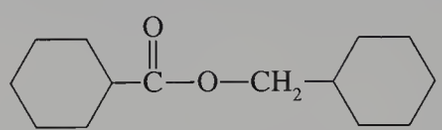
(a) 

(b) 

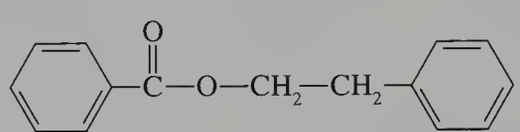
(c) $CH_3C{\equiv}CCH_2CO_2H + CH_3OH \xrightarrow{H^+}$

(d) 

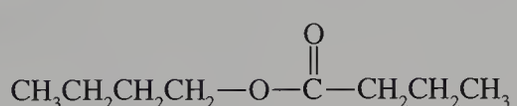
21.57 Outline the steps necessary to prepare the following compound from cyclohexanecarboxylic acid.

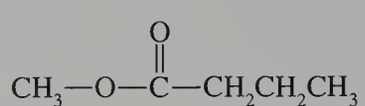


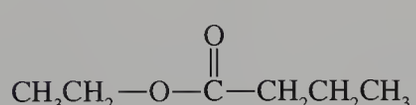
21.58 Outline the steps necessary to prepare the following compound from benzoic acid.



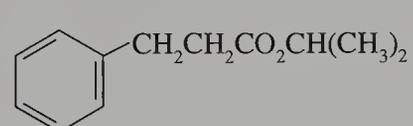
21.59 What alcohol and acid are required to form each of the following esters by Fischer esterification?

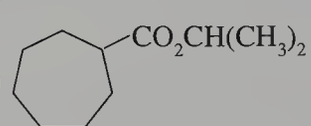
(a) 

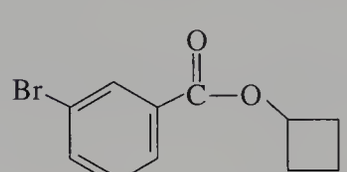
(b) 

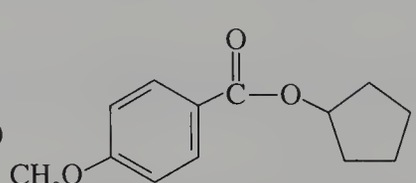
(c) 

21.60 What alcohol and acid or acyl derivative are required to form each of the following esters?

(a) 

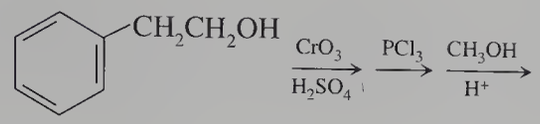
(b) 

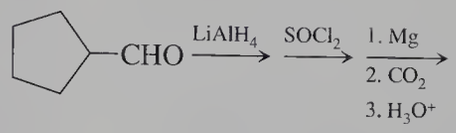
(c) 

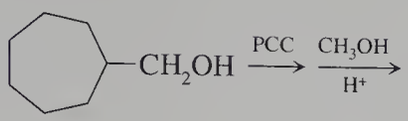
(d) 

Multistep Synthesis

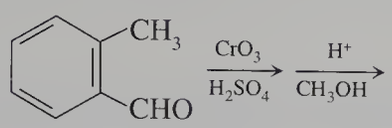
21.61 Write the structure of the final product of each of the following sequences of reactions.

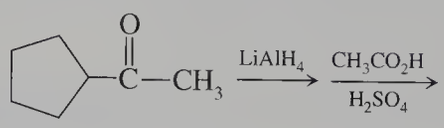
(a) 

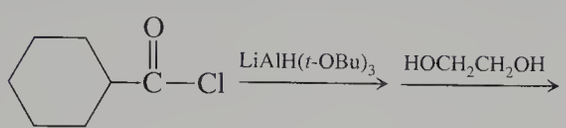
(b) 

(c) 

21.62 Write the structure of the final product of each of the following sequences of reactions.

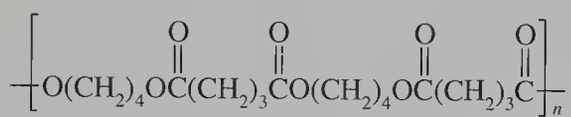
(a) 

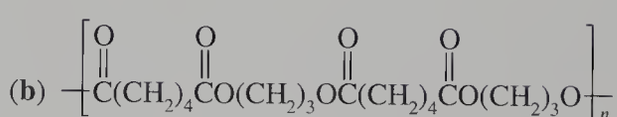
(b) 

(c) 

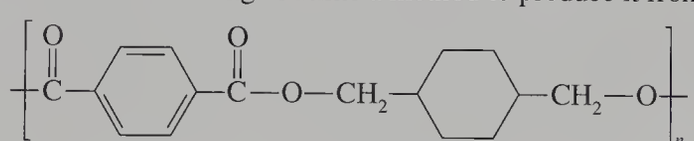
Polyesters

21.63 What monomers are needed to form the following polyesters?

(a) 

(b) 

21.64 Kodel is a commercial polyester used in clothing. Outline a method to produce it from *p*-xylene.



Kodel

21.65 Each of the following compounds has a resonance due to a single hydrogen atom at a lower field position than 10 δ. Based on the molecular formula and the indicated remaining resonances, propose a structure for each compound. The number of hydrogen atoms and multiplicity are given in parentheses.

(a) $C_5H_{10}O_2$; 1.25 ppm (9, singlet)
(b) $C_3H_5ClO_2$; 1.75 ppm (3, doublet), 4.45 ppm (1, quartet)
(c) $C_8H_8O_2$; 1.4 ppm (3, singlet), 7.25 ppm (2, doublet), 8.0 ppm (2, doublet)
(d) $C_3H_6O_3$; 3.4 ppm (2, singlet), 4.0 ppm (3, singlet)
(e) $C_9H_{10}O_3$; 2.7 ppm (2, triplet), 4.2 ppm (2, triplet), 7.4 ppm (5, complex multiplet)

21.66 Each of the following compounds has a resonance due to a single hydrogen atom at a lower field position than 10 δ. Based on the molecular formula and the indicated remaining resonances, propose a structure for each compound. The number of hydrogen atoms and multiplicity are given in parentheses.

(a) $C_6H_{12}O_2$; 1.07 ppm (9, singlet), 2.21 ppm (2, singlet)
(b) $C_3H_5ClO_2$; 2.85 ppm (2, triplet), 3.80 ppm (2, triplet)
(c) $C_8H_8O_2$; 3.6 ppm (2, singlet), 7.25 ppm (5, singlet)
(d) $C_4H_8O_3$; 1.27 ppm (3, triplet), 3.55 ppm (2, quartet), 4.13 ppm (2, singlet)
(e) $C_9H_{10}O_3$; 1.72 ppm (3, doublet), 4.95 ppm (2, quartet), 7.4 ppm (5, complex multiplet)

21.67 Deduce the structure of each of the following compounds based on the molecular formula and the carbon-13 NMR data. The multiplicity is indicated in parentheses.

(**a**) $C_6H_{12}O_2$; 9.3 ppm (quartet), 24.6 ppm (quartet), 33.5 ppm (triplet), 42.7 ppm (singlet), 185.5 ppm (singlet)

(**b**) $C_6H_6O_2$; 128.7 ppm (doublet), 129.6 ppm (doublet), 131.2 ppm (doublet), 133.0 ppm (singlet), 167.7 ppm (singlet)

(**c**) $C_4H_8O_2$; 13.4 ppm (quartet), 18.5 ppm (triplet), 36.3 ppm (triplet), 179.6 ppm (singlet)

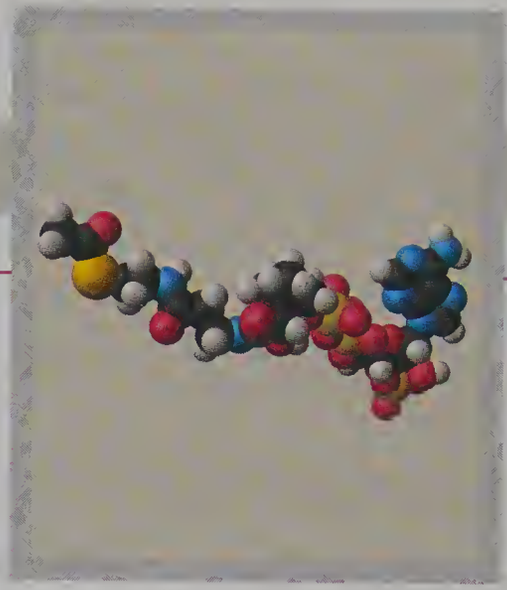
21.68 Deduce the structure of each of the following compounds based on the molecular formula and the carbon NMR data. The multiplicity is indicated in parentheses.

(**a**) $C_5H_{10}O_2$; 13.5 ppm (quartet), 22.0 ppm (triplet), 27.0 ppm (triplet), 34.1 ppm (triplet), 179.7 ppm (singlet)

(**b**) $C_7H_6O_3$; 115.8 ppm (doublet), 121.9 ppm (doublet), 132.7 ppm (singlet), 162.5 ppm (singlet), 169.0 ppm (singlet)

(**c**) $C_7H_{12}O_2$; 26.0 ppm (triplet), 26.2 ppm (triplet), 29.6 ppm (triplet), 43.7 ppm (singlet), 182.1 ppm (singlet)

22

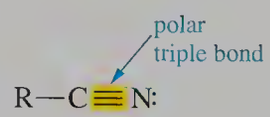


Carboxylic Acid Derivatives

22.1 Nomenclature of Carboxylic Acid Derivatives

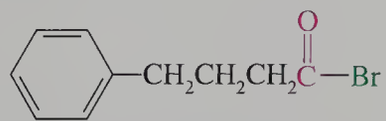
All the carboxylic acid derivatives we will consider except nitriles consist of an acyl group bonded to a halogen atom or other electronegative group, such as oxygen or nitrogen, that has additional atoms bonded to it. These derivatives are named by identifying the acyl group and modifying its name to indicate the groups bonded to the acyl carbon atom.

Nitriles do not contain a carbonyl group, but their reactions are closely related to those of acyl derivatives. Also, the oxidation state of carbon in the nitrile group is the same as the carbonyl carbon atom of acid derivatives. Both acyl derivatives and nitriles have three bonds to electronegative elements.

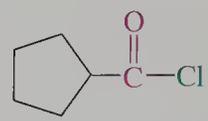


Names of Acid Halides

In an acid halide, a halogen atom is attached to an acyl group. The IUPAC names of acid halides have the ending *-oyl halide* replacing the ending *-oic acid* of carboxylic acids. The name of the halide is appended as a separate word. An acid halide functional group bonded to a cycloalkane ring is named as a *carbonyl halide*. Common names of acid halides replace the *-ic acid* ending with *-yl halide*.



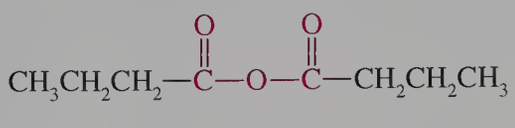
4-phenylbutanoyl bromide



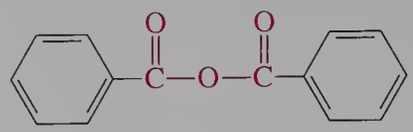
cyclopentanecarbonyl chloride

Names of Acid Anhydrides

An acid anhydride consists of two acyl groups bonded through a bridging oxygen atom. Although acid anhydrides can have two different acyl groups, compounds containing identical acyl groups are more common. They are named by replacing the suffix *-oic acid* with *-oic anhydride*. Common names are derived by replacing the term *acid* with *anhydride*.



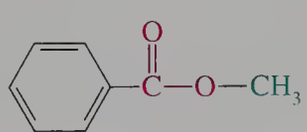
butanoic anhydride



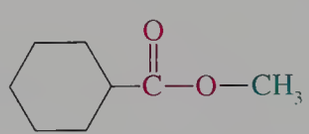
benzoic anhydride

Names of Esters

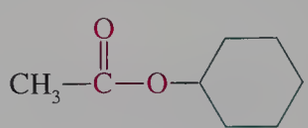
To name an ester, we first write the name of the alkyl group bonded to oxygen (—OR or —OAr). The acyl portion of the ester is named as a carboxylate in which *-ate* replaces *-ic acid*. In the three examples given below, the alkyl portion of each molecule is shown on the right side of each structure. However, the alkyl name is written first in the name of the ester regardless of how the structure is drawn.



methyl benzoate

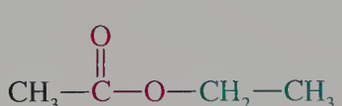


methyl cyclohexanecarboxylate

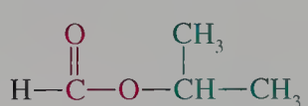


cyclohexyl ethanoate

As we observed for carboxylic acids, common names are often used for esters. This is especially true of esters derived from acetic acid and formic acid.

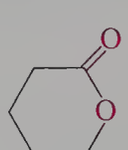


ethyl acetate

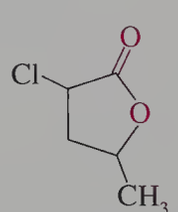


isopropyl formate

Lactones are cyclic esters of hydroxy acids. Five- and six-membered lactones commonly occur in nature, although lactones with more members also occur. The IUPAC name of a lactone is constructed by adding *lactone* to the name of the related hydroxy acid. The common name is derived by changing the suffix *-ic acid* to *-olactone*. A Greek letter designates the position of the bridging oxygen atom that closes the lactone ring.



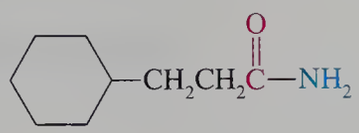
5-hydroxypentanoic acid lactone
(δ-valerolactone)



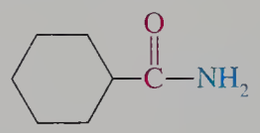
4-hydroxy-2-chloropentanoic acid lactone
(α-chloro-γ-valerolactone)

Names of Amides

In an amide, a group such as $—NH_2$, —NHR, or $—NR_2$ is attached to an acyl group. Amides are named by replacing the suffix for the acid (*-oic acid*) with the name *-amide*. The suffix *-carboxamide* indicates amides derived from cycloalkanecarboxylic acids.

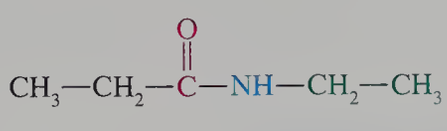


3-cyclohexylpropanamide

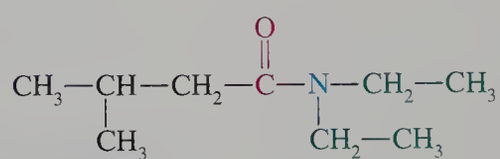


cyclohexanecarboxamide

For secondary and tertiary amides, the prefix *N-* indicates that the alkyl or aryl groups are bonded to the nitrogen atom.

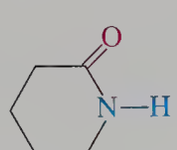


N-ethylpropanamide
(*N*-ethylpropionamide)

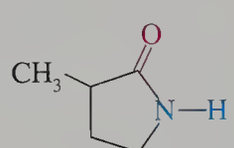


N,N-diethyl-3-methylbutanamide
(*N,N*-diethyl-β-methylbutyramide)

Lactams are cyclic amides formed from amino acids. The IUPAC name of a lactam is obtained by adding *lactam* to the name of the related amino acid. The common name is derived by changing the suffix *-ic acid* to *-olactam*. A Greek letter designates the position of the bridging nitrogen atom closing the lactone ring. The prefix *N-* indicates substituents on the nitrogen atom.



5-aminopentanoic acid lactam
(δ-valerolactam)

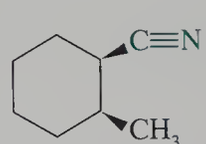


4-amino-2-methylbutanoic acid lactam
(α-methyl-γ-butyrolactam)

Names of Nitriles

Acyclic nitriles are named by adding *-nitrile* as a suffix to the alkane name that includes the carbon atom of the nitrile. The carbon atom of the nitrile is designated C-1. Cyclic compounds with the —CN group bonded to the ring are named using *carbonitrile*. The ring carbon bearing the —CN group is C-1, but that number is not included in the name.

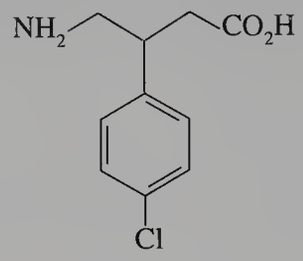
4-chlorobutanenitrile



cis-2-methylcyclohexanecarbonitrile

Problem 22.1

Write the IUPAC name for baclofen, a muscle relaxant.

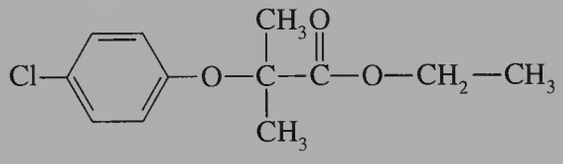


Sample Solution

The parent chain of baclofen is butanoic acid. It contains an amino group and an aryl group. The amino group is located at the C-4 atom. The aryl group located at the C-3 atom is named *p*-chlorophenyl. Placing the groups in alphabetical order, the name is 4-amino-3-(*p*-chlorophenyl)butanoic acid. The name of the aryl group is written within parentheses to clearly identify it.

Problem 22.2

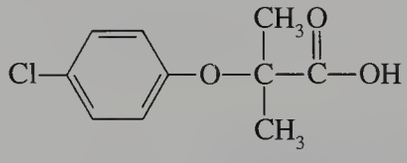
Assign the IUPAC name to clofibrate, a drug used to lower the concentration of blood triglycerides and cholesterol.



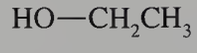
clofibrate

Sample Solution

First, identify the alcohol portion of the ester; it is located at the right of the molecule. The alcohol portion contains two carbon atoms, so the compound is an ethyl ester.



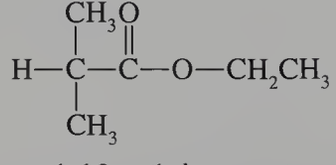
acid portion of ester



ethanol

The acid portion is a substituted propanoic acid with a methyl group and an aryl-containing group at the C-2 atom. Imagine removing the aryl-containing group from the acid and adding a hydrogen atom to its oxygen atom. The resulting compound is *p*-chlorophenol. The original group is *p*-chlorophenoxy.

p-chlorophenol



ethyl 2-methylpropanoate

The name of the acid is 2-(*p*-chlorophenoxy)-2-methylpropanoic acid. Now change the -ic ending of the acid to -ate and write the name of the alkyl group of the alcohol as a separate word in front of the modified acid name. The ester is named ethyl 2-(*p*-chlorophenoxy)-2-methylpropanoate.

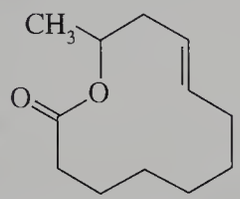
Problem 22.3

Write the structure of each of the following compounds.

(a) benzyl 2-methylbutanoate
(b) *N*,*N*-dimethylcyclobutanecarboxamide
(c) 2-chlorobutanoyl bromide
(d) 4-ethoxyhexanenitrile
(e) 3,3,3-trifluoropropanoic anhydride
(f) 6-aminohexanoic acid lactam

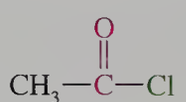
Problem 22.4

What is the name of the following large-ring lactone, which has been isolated from a species of fungus?

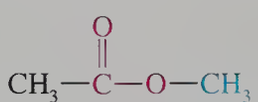


22.2 Physical Properties of Acyl Derivatives

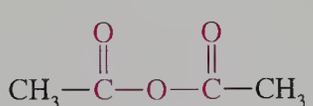
Acyl halides, such as acetyl chloride, and acid anhydrides, such as acetic anhydride, are used exclusively as reagents rather than as solvents. Consequently, their physical properties, such as boiling points and dielectric constants, are of less interest than those of other acyl derivatives. Because neither acyl halides nor acid anhydrides form intermolecular hydrogen bonds, their boiling points are similar to structurally related carbonyl compounds of approximately the same molecular weight.



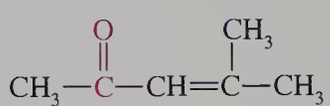
mol wt 68.6
bp 50.9 °C



mol wt 74
bp 57 °C



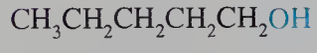
mol wt 102
bp 140 °C



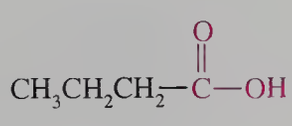
mol wt 94
bp 130 °C

Esters

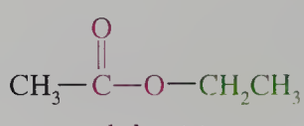
Esters are polar molecules, but their boiling points are lower than those of carboxylic acids and alcohols of similar molecular weight because there is no intermolecular hydrogen bonding between ester molecules.



1-pentanol
bp 138 °C



butanoic acid
bp 164 °C



ethyl acetate
bp 77 °C

Esters can form hydrogen bonds through their oxygen atoms to the hydrogen atoms of water molecules. As a result, esters are slightly soluble in water. However, because esters do not have a hydrogen atom to form a hydrogen bond to an oxygen

atom of water, they are less soluble than carboxylic acids. Table 22.1 lists the solubilities and boiling points of some esters.

Table 22.1
Physical Properties of Esters

Name	*Boiling point (°C)*	*Solubility (g/100 g H_2O)*
methyl methanoate	32	miscible
methyl ethanoate	57	24.4
methyl propanoate	80	1.8
methyl butanoate	102	0.5
methyl pentanoate	126	0.2
methyl hexanoate	151	0.06
ethyl methanoate	54	miscible
ethyl ethanoate	77	7.4
ethyl propanoate	99	1.7
ethyl butanoate	120	0.5
ethyl pentanoate	145	0.2
propyl ethanoate	102	1.9
butyl ethanoate	125	1.0
methyl benzoate	199	0.1
ethyl benzoate	213	0.08

The odors of esters are distinctly different from those of the corresponding acids. Acids have unpleasant smells, but esters have fruity smells. In fact, the odors of many fruits are due to esters. For example, ethyl ethanoate occurs in pineapples, 3-methylbutyl ethanoate in apples and bananas, 3-methylbutyl 3-methylbutanoate in apples, and octyl ethanoate in oranges.

The demand in our society for processed foods that are expected to taste and smell "fresh" has created problems for the food industry. Esters have low boiling points and evaporate during heating. To make processed food more attractive, processors add esters back to the food. In some cases the esters are the same as those lost in heating. Nevertheless, government regulations require that the added esters be identified as additives on the label. Thus, some individuals claim that the product is not "natural", and should not be consumed.

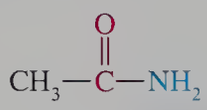
The esters used in some products are not necessarily the same as those in natural fruits, but they produce the same odor or taste. The choice of esters may be dictated by their cost and availability. Table 22.2 lists some of these esters. Although the esters are not the same as those that occur naturally in the fruit, the product is not dangerous. The structures are similar to those of "natural" esters.

Table 22.2
Esters Used as Flavoring Agents

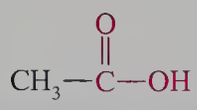
Name	*Formula*	*Flavor*
methyl butanoate	$CH_3CH_2CH_2CO_2CH_3$	apple
pentyl butanoate	$CH_3CH_2CH_2CO_2CH_2(CH_2)_3CH_3$	apricot
pentyl ethanoate	$CH_3CO_2CH_2(CH_2)_3CH_3$	banana
octyl ethanoate	$CH_3CO_2CH_2(CH_2)_6CH_3$	orange
ethyl butanoate	$CH_3CH_2CH_2CO_2CH_2CH_3$	pineapple
ethyl methanoate	$HCO_2CH_2CH_3$	rum

Amides

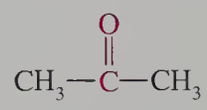
Amides form strong intermolecular hydrogen bonds between the amide hydrogen atom of one molecule and the carbonyl oxygen atom of a second molecule (C=O···H—N). This intermolecular interaction is responsible for the high melting and boiling points of primary amides compared to other compounds of similar molecular weight and structure.



bp 221 °C
mp 82 °C

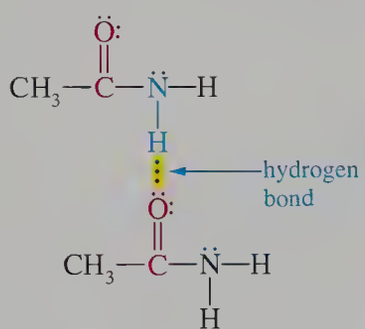


bp 118 °C
mp 16.7 °C

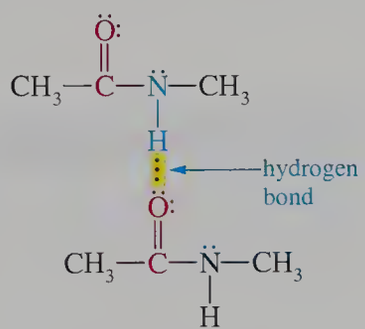


bp 56.5 °C
mp –94 °C

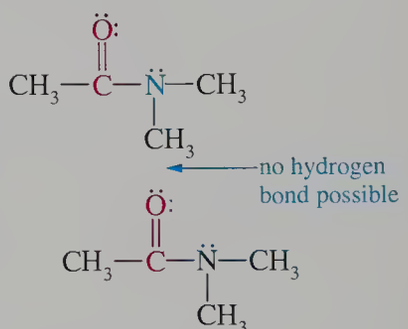
Substitution of the hydrogen atoms on the nitrogen atom by alkyl or aryl groups reduces the number of possible intermolecular hydrogen bonds and lowers the melting and boiling points. Tertiary amides cannot form intermolecular hydrogen bonds.



bp 221 °C
mp 82 °C

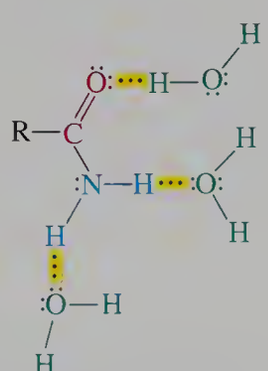


bp 204 °C
mp 28 °C



bp 166 °C
mp –20 °C

Amides having low molecular weights readily dissolve in water because hydrogen bonds form between the amide group and water. Even low molecular weight tertiary amides dissolve in water because the carbonyl oxygen atom can form hydrogen bonds to the hydrogen atoms of water.



The dielectric constants of amides are higher than those of carboxylic acids and esters of similar structure. The dielectric constants of formamide and dimethylformamide are 111 and 37, respectively. Dimethylformamide (DMF) is an excellent polar aprotic solvent. It dissolves inorganic salts such as halides used in S_N2 displacement reactions.

Nitriles

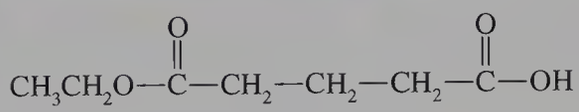
Nitriles are very polar compounds because the carbon–nitrogen triple bond includes three pairs of shared electrons, polarized toward the electronegative atom. Even

though oxygen is more electronegative than nitrogen, the bond moment of the carbonyl group is smaller than that of the nitrile group. The dipole moment of acetonitrile is 3.4 D.

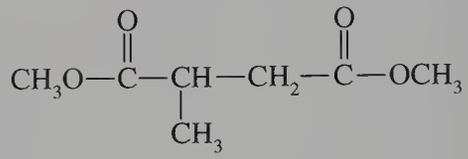
Although nitriles have an unshared pair of electrons, they are not effective hydrogen bond acceptors because the electrons occupy an *sp*-hybridized orbital. However, because acetonitrile is very polar, it is miscible in water. Propionitrile is moderately soluble in water. Acetonitrile is an excellent polar, aprotic solvent. It has a relatively high boiling point (81.5 °C) for a low molecular weight compound and a high dielectric constant (38).

Problem 22.5

Which of the following compounds would be more soluble in water? Why?



I



II

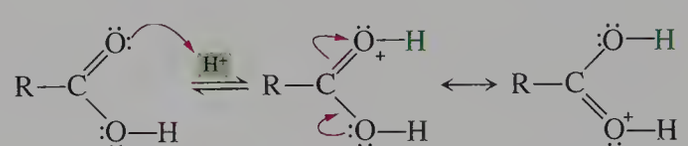
Problem 22.6

Explain why the dipole moment of methyl acetate (1.7 D) is smaller than the dipole moment of acetone (2.9 D).

22.3 Basicity of Acyl Derivatives

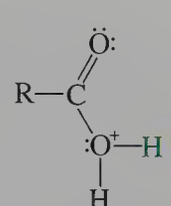
We recall that the first step in the acid-catalyzed addition reaction of carbonyl compounds is protonation of the carbonyl oxygen atom. However, the carbonyl oxygen atom is a weak base because its lone pair electrons occupy an sp^2-hybridized orbital and are therefore more strongly attracted to the nucleus than lone pair electrons in an sp^3-hybridized atom.

Protonation of a carboxylic acid occurs at the carbonyl oxygen atom because the resulting conjugate acid is resonance stabilized.



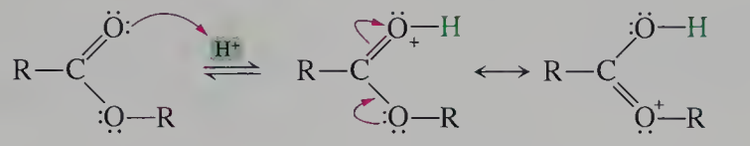
resonance-stabilized conjugate acid
$pK_a \approx -6$

Protonation does not occur at the hydroxyl oxygen atom, even though the lone pair electrons occupy an sp^3-hybridized orbital, because the resulting conjugate acid is not resonance stabilized.



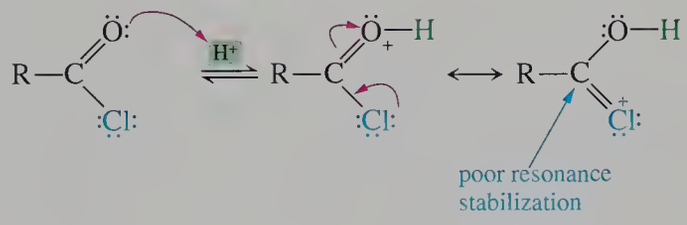
localized cation

The basicity of an ester approximately equals that of the structurally related carboxylic acid.

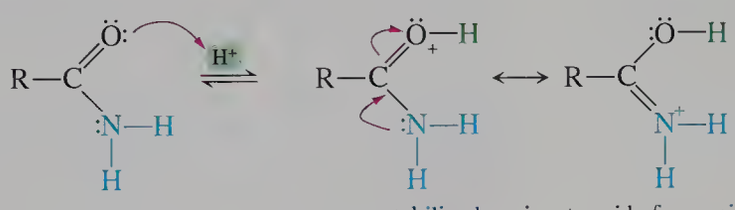


resonance-stabilized conjugate acid of an ester
$pK_a \approx -6$

Acyl chlorides should be much less basic than carboxylic acids or esters because the chlorine atom is not effective at stabilizing the conjugate acid by resonance. An inductive effect destabilizes the conjugate acid.

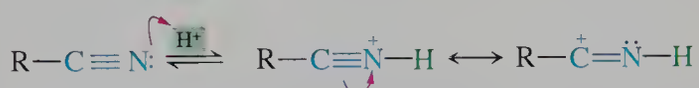


Amides are the most basic of the acid derivatives because the nitrogen atom effectively resonance stabilizes the positive charge of the conjugate acid.



resonance-stabilized conjugate acid of an amide
$pK_a \approx -1$

Nitriles are extremely weak bases. Consequently, the conjugate acids are very strong. The low basicity of nitriles reflects the hybridization of the orbital containing the lone pair electrons. Even though nitrogen is more basic than oxygen, the *sp* orbital holds electrons close to the nucleus, so they are less available to form a conjugate acid. Also, the alternate resonance form of the conjugate acid does not have a Lewis octet at each atom.



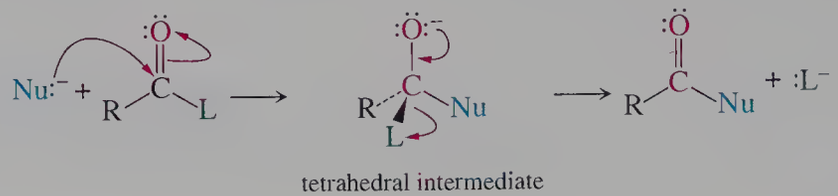
resonance forms of a conjugate acid of a nitrile
$pK_a \approx -10$

Problem 22.7

The pK_a of the conjugate acid of propanone is –7.1. Why is this species a stronger acid than the conjugate acid of ethanoic acid ($pK_a = -6$)?

22.4 Nucleophilic Acyl Substitution

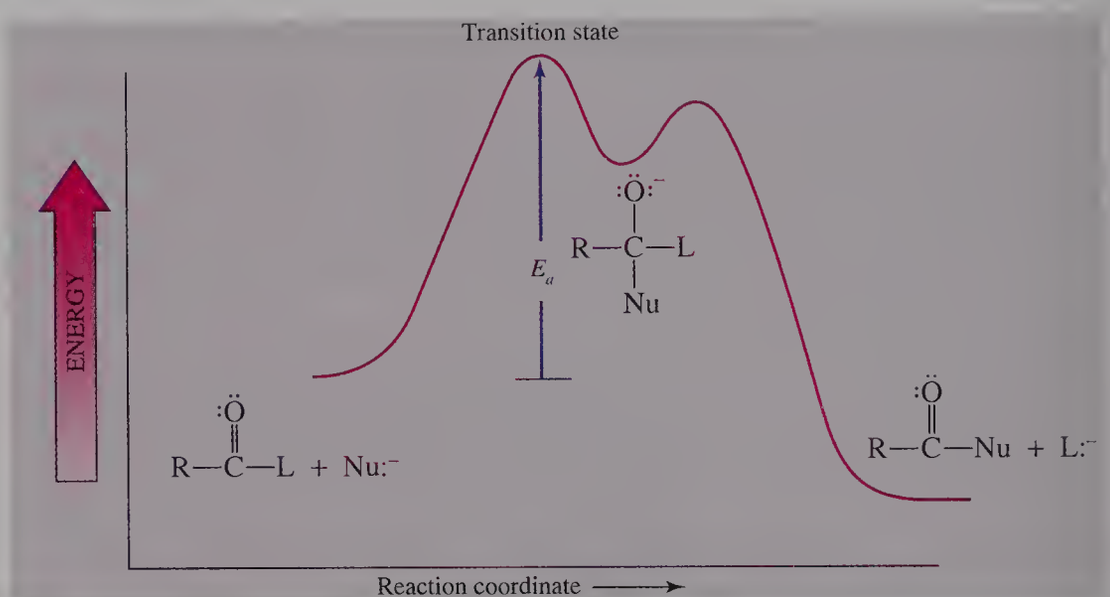
Acyl derivatives react with nucleophiles in an addition reaction to generate an unstable tetrahedral intermediate. The intermediate decomposes by an elimination reaction in which a group leaves to form a different acyl derivative. The overall process is called **nucleophilic acyl substitution**. The process is also called an **acyl transfer reaction** because it transfers an acyl group from one group (the leaving group) to another (the nucleophile).



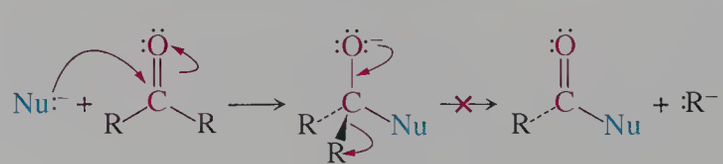
tetrahedral intermediate

The net result is a substitution reaction whose stoichiometry resembles that of an S_N2 substitution reaction of haloalkanes. However, the resemblance is only superficial. An S_N2 reaction is a single-step process in which the nucleophile bonds to the carbon atom as the leaving group leaves. Nucleophilic acyl substitution occurs in two steps (Figure 22.1). The rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. The loss of the leaving group occurs in a second, faster step.

FIGURE 22.1
Mechanism of Nucleophilic Acyl Substitution



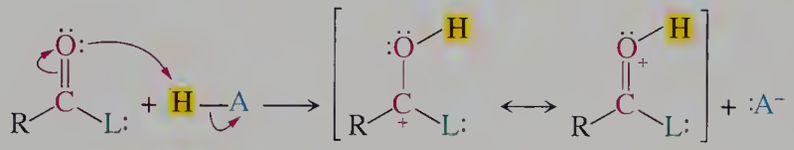
Why don't acyl derivatives behave like aldehydes and ketones and form stable tetrahedral products? The answer is that the intermediate formed from an acyl derivative has a good leaving group. In the case of an acid chloride, the leaving group is the weakly basic chloride ion. We recall that leaving group abilities are inversely related to base strength. An intermediate derived from a ketone does not have a good leaving group. A carbanion, the conjugate base of a hydrocarbon, is an extremely strong base and, therefore, a very poor leaving group.



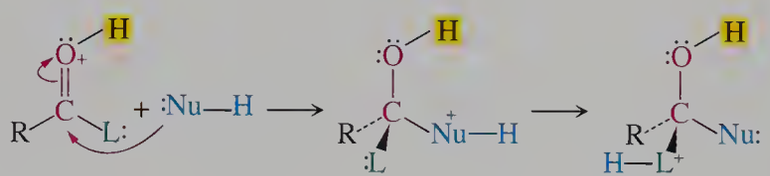
The mechanism of nucleophilic acyl substitution reactions depends on the identity of the nucleophile and the leaving group and is different for acid and base catalysts. We now consider both acid- and base-catalyzed nucleophilic acyl substitution.

Acid-Catalyzed Reactions

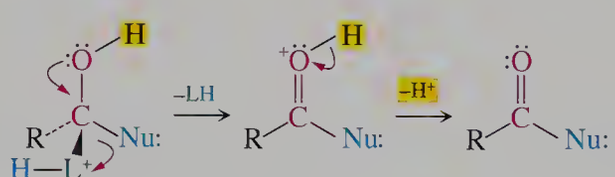
An acid, H—A, protonates the oxygen atom of an acyl group to form a resonance-stabilized carbocation intermediate that is more electrophilic than the original acyl derivative.



As a result of increased electrophilicity, a neutral nucleophile that does not react with the original acyl derivative can now react with the protonated species. Solvent-mediated proton transfers can occur between two sites in the tetrahedral intermediate.



Loss of the leaving group (as its conjugate acid) occurs to give the protonated acyl derivative product, which subsequently is deprotonated.

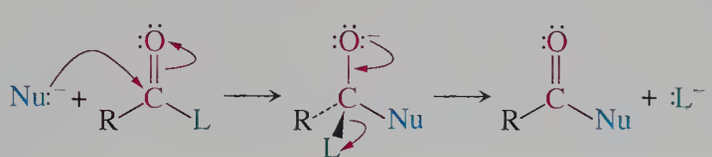


Base-Catalyzed Reactions

A base first deprotonates a reagent represented by H—Nu to give its conjugate base, which is a nucleophile.

$$B:^- + H{-}Nu \rightleftharpoons B{-}H + {}^-{:}Nu$$

The nucleophile attacks the carbonyl carbon atom, yielding a tetrahedral intermediate that can eliminate the nucleophile to regenerate the reactant or can eliminate a leaving group bonded to the carbonyl carbon atom to give the product.



Finally, an acid–base reaction between the leaving group and the conjugate acid of the base regenerates the base.

$$L:^- + H{-}B \rightleftharpoons L{-}H + {}^-:B$$

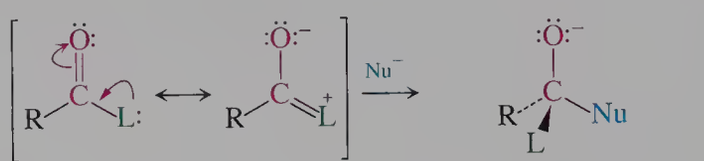
Relative Reactivity of Acyl Derivatives

The order of reactivity of acyl derivatives toward a common nucleophile such as water in a hydrolysis reaction is acid chloride > acid anhydride > ester > amide. The relative rate constants for hydrolysis are

	acid chloride	acid anhydride	ester	amide
relative rate	10^{13}	10^{9}	10^{2}	1

This order of reactivity might appear to reflect the leaving group abilities, which we also know are related to their basicities. We know, for example, that HCl is a strong acid and NH_3 is a very weak acid. Consequently, Cl^- is a weak base, NH_2^- is a strong base, and Cl^- is a better leaving group than NH_2^-. However, acyl substitution occurs in two steps (Figure 22.1) and the rate-determining step is usually nucleophilic attack at the carbonyl carbon atom to form a tetrahedral intermediate. Because the characteristics of the leaving group affect only the second step, they do not affect the observed order of reactivity.

The order of reactivities parallels resonance stabilization of the reactant. Donation of an electron pair of the atom bonded to the acyl carbon atom decreases the partial positive charge on the carbon atom and decreases its electrophilicity. Resonance stabilization is impossible in the tetrahedral intermediate. Consider the general equation for the first step of the reaction.



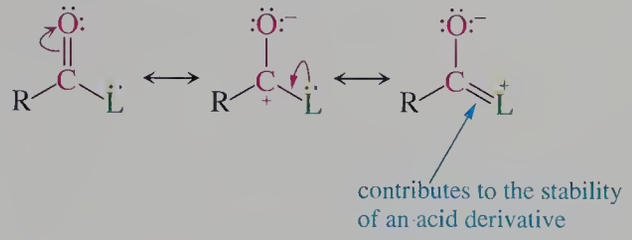
resonance-stabilized reactant — no resonance stabilization

We can explain the effect of the group bonded to the acyl carbon atom on the observed order of reactivity using concepts developed for substituent effects on electrophilic aromatic substitution (Section 14.6) We recall that electronegative second-row elements, such as oxygen and nitrogen, inductively withdraw electron density from the aromatic ring, but donate electron density to the aromatic ring by resonance. Furthermore, nitrogen is a better resonance electron donor than oxygen because nitrogen is less electronegative and can more effectively share its nonbonded electrons. We also recall that chlorine, a third-row element, is not effective in donating electrons by resonance because of unfavorable overlap between its 3*p* orbital and the 2*p* orbital of carbon.

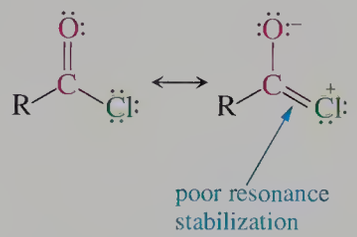
Inductive electron withdrawal from the acyl carbon atom by an electronegative atom destabilizes the acyl derivative. A reaction that leads to another acyl derivative with less severe electron withdrawal from the carbonyl carbon atom tends to be thermodynamically favorable.

destabilized by electron withdrawal

However, donation of electrons by resonance stabilizes the carbonyl group. A reaction that leads to an acid derivative with more effective donation of electrons to the carbonyl carbon atom is thermodynamically favored.



Resonance stabilization of an acyl chloride by chlorine is not effective. As a consequence, normal inductive electron withdrawal is the dominant effect of the chlorine substituent, and the acyl chloride is the least stable of the acid derivatives.



Now let's compare the stabilities of amides and acyl chlorides. Nitrogen and chlorine have approximately the same electronegativity, and both should inductively destabilize their respective derivatives. However, nitrogen is a second-row element and is a better resonance electron donor.

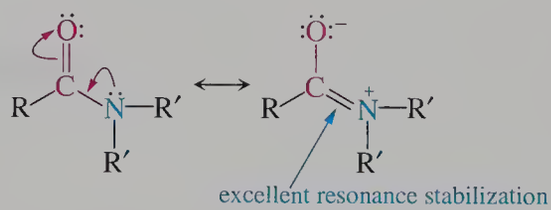


Figure 22.2 shows reaction coordinate diagrams for a reaction of a nucleophile with both an acid chloride and an amide. The relative energies of the two tetrahedral

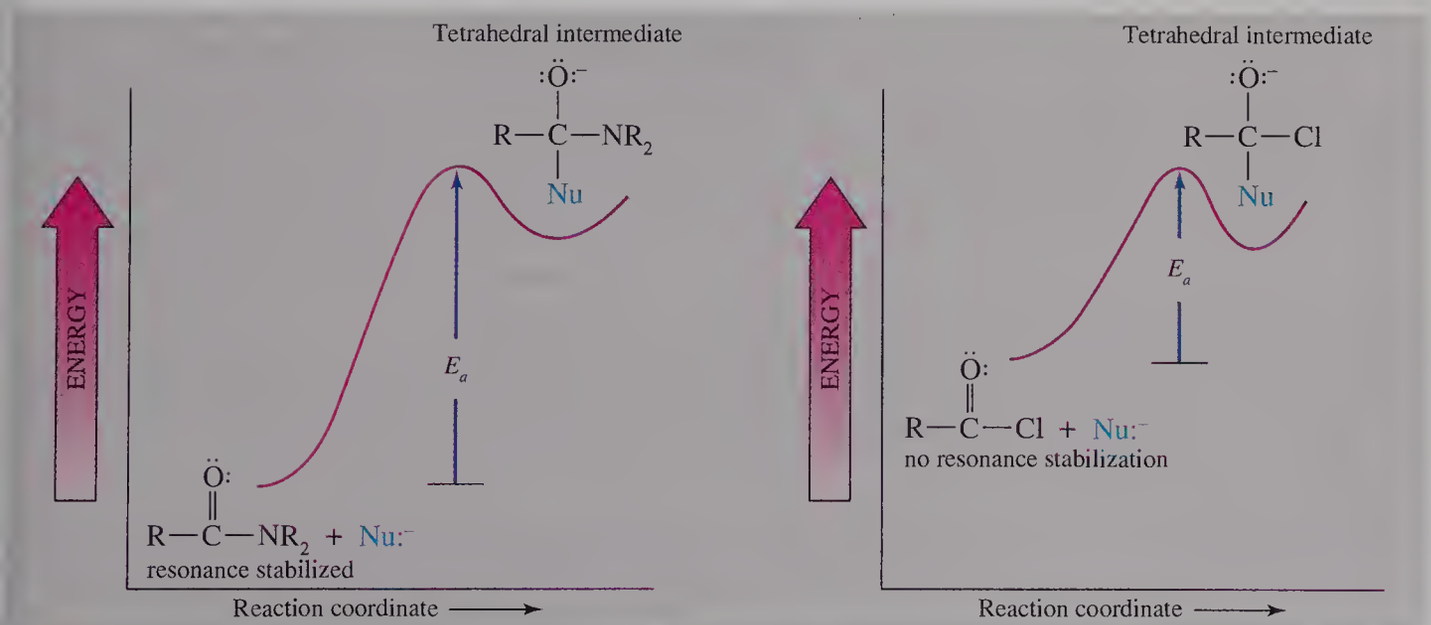
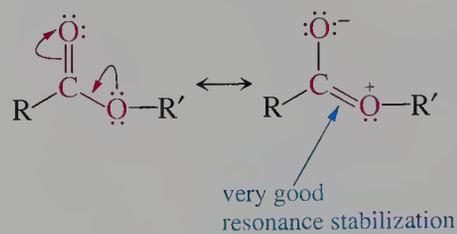


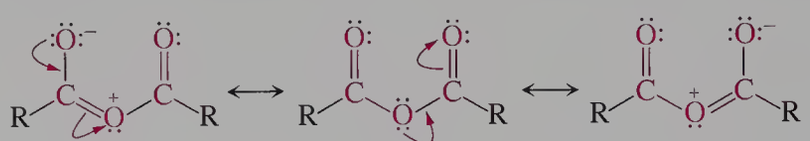
FIGURE 22.2 Reactivity of Acyl Derivatives

intermediates and the transition state energies leading to these intermediates are approximately equal because neither intermediate is resonance stabilized. However, because the amide is resonance stabilized, its energy is lower than that of the acid chloride. As a consequence, the activation energy for reaction of the amide is higher than the activation energy for reaction of the acid chloride.

Next, let's consider acyl derivatives containing oxygen. Esters and anhydrides are both more reactive than amides, and anhydrides are more reactive than esters. We can explain these facts using the resonance contribution of the nonbonded electrons of oxygen. Oxygen is a second-row element like nitrogen, but oxygen does not donate electron density in resonance forms as well as the less electronegative nitrogen. We could characterize the donation of electrons by oxygen as "very good."



The oxygen atom of an anhydride is less effective than the oxygen atom of an ester in supplying electrons by resonance because the second carbonyl carbon atom also competes for the same lone pair electrons of oxygen. Neither carbonyl group is as stable as the single carbonyl group of an ester.

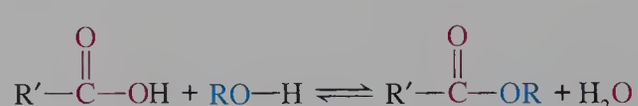


good resonance stabilization

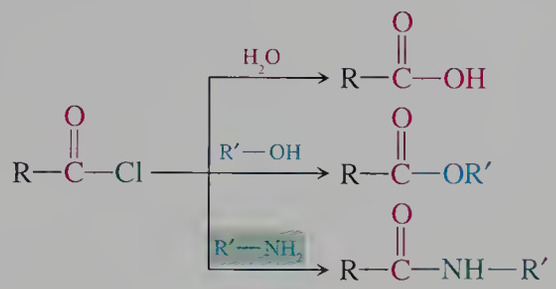
Predicting the Direction of a Reaction

The relative stabilities of acyl derivatives allow us to predict the equilibrium position of a nucleophilic acyl substitution reaction. The same factors that affect the relative reactivity of acyl derivatives also control the stability of these compounds. The identity of the groups bonded to the tetrahedral carbon atom affects the stabilities of the reactants and products. Thus, destabilizing the reactant and stabilizing the product increases the equilibrium constant. We conclude that the less stable acyl derivative is more reactive and can be converted into a more stable, less reactive acyl derivative. The relative stabilities of acyl derivatives enable us to understand most of the chemical reactions presented in this chapter.

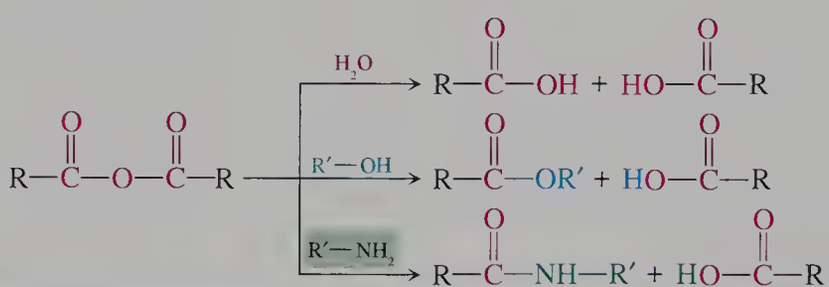
Because acids and esters have similar reactivities, they can be readily interconverted in equilibrium processes. The reaction conditions may be selected to favor either the esterification of an acid or the hydrolysis of an ester.



Acid chlorides react rapidly and quantitatively with most nucleophiles, and they are hydrolyzed by the moisture in air. Reaction of an acid chloride with an alcohol gives an ester. Reaction with acid chlorides readily converts amines into amides.



Acid anhydrides are less reactive than acid chlorides, but they are still very active acylating agents. Water hydrolyzes acid anhydrides to acids; alcohols react to give esters; and amines give amides. Note that the by-product in each case is one molar equivalent of a carboxylic acid.



Problem 22.8

Which member of each of the following pairs of compounds reacts faster with water?

(a) $CH_3—C(=O)—Cl$ or $CH_3—C(=O)—S—CH_3$ (b) $CH_3—C(=O)—Cl$ or $CH_3—C(=O)—Br$

Problem 22.9

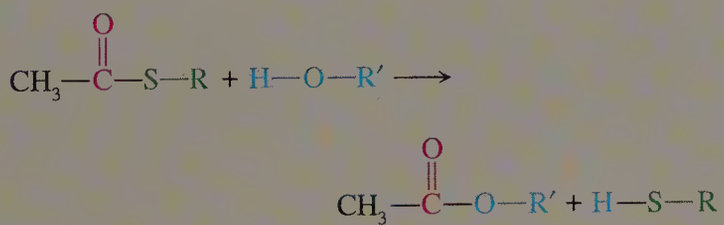
Explain why the carbonyl carbon–oxygen single bond of esters is about 7 pm shorter than the carbon–oxygen bond of an ether. Using this interpretation, determine whether the difference between the carbonyl carbon–nitrogen bond of an amide and the carbon-nitrogen bond of an amine will be larger or smaller than 7 pm.

Sample Solution

The contribution of dipolar resonance forms of esters increases the bond order of the carbonyl carbon–oxygen single bond of esters. Increased double bond character results in a decrease in bond length. The contribution of dipolar resonance forms of amides is greater than that of esters because nitrogen is more effective than oxygen in donating electrons by resonance. Thus the carbonyl carbon–nitrogen bond has more double bond character, which leads to a further decrease in bond length. The difference between the carbonyl carbon–nitrogen bond of an amide and the carbon–nitrogen bond of an amine is larger than 7 pm.

Thioesters Are Nature's Active Acyl Compounds

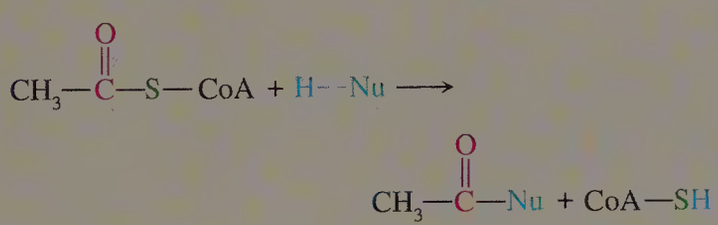
The interconversion of acyl compounds in cells occurs by transfer of an acyl group from one molecule to another. The acyl group of the donor or acceptor molecule is often in the form of a thioester. Thus, cells use thioesters as acyl transfer agents. Thioesters are more reactive than esters, and an alkoxy group from an alcohol easily replaces the thiol group.

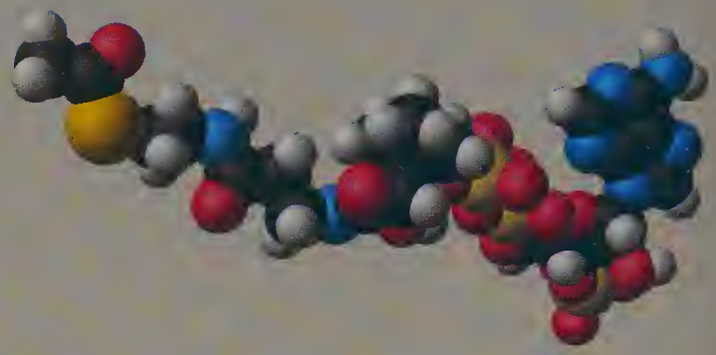


The most important thioester, acetyl coenzyme A, is formed from the thiol group of coenzyme A, a complex thiol that we will abbreviate as CoA—SH. The thiol group of CoA—SH is bonded to an acyl group in acyl S—CoA derivatives.

When an acetyl group is linked to CoA—SH, the addition compound, or adduct, is acetyl coenzyme A. This extremely important metabolite results from the degradation of long-chain carboxylic acids contained in fats. Acetyl CoA also results from metabolic degradation of many amino acids and carbohydrates. Acetyl CoA is a donor of the two-carbon acetyl group in the biosynthesis of long-chain carboxylic acids.

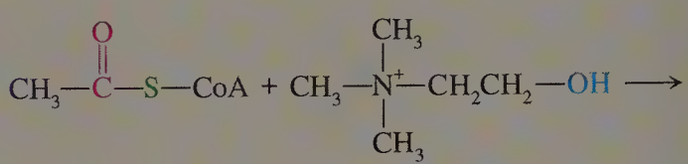
Acetyl coenzyme A reacts with nucleophiles in biological reactions to give new acyl compounds.



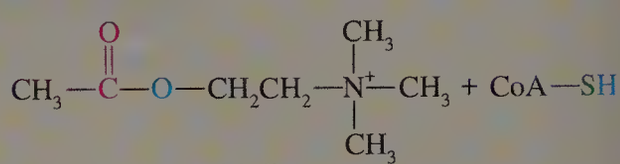


acetyl coenzyme A

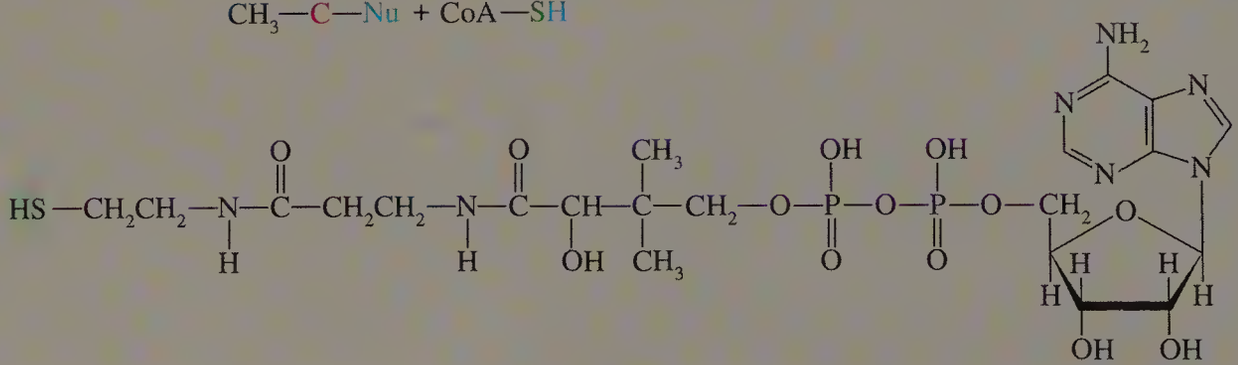
For example, acetyl coenzyme A provides the acetyl group in the biosynthesis of the neurotransmitter acetylcholine. Choline contains a hydroxyl group that is acetylated by acetyl coenzyme A to make acetylcholine.



choline



acetylcholine



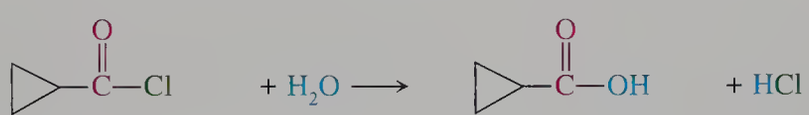
coenzyme A (CoA—SH)

22.5 Hydrolysis of Acyl Derivatives

The hydrolysis of acyl derivatives yields an acid as one of the products. Recalling the order of reactivity of acyl derivatives, we expect the reaction of acyl chlorides and anhydrides to be spontaneous. The reaction of an ester with water is an equilibrium reaction that can be forced to completion by using favorable experimental conditions and taking into account Le Châtelier's principle. Amides are so stable that the hydrolysis requires harsh conditions to drive the reaction to completion. It is also difficult to hydrolyze nitriles.

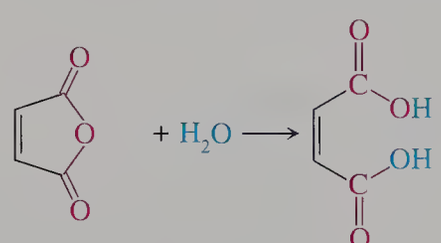
Acid Chlorides and Anhydrides

An acid chloride reacts spontaneously with water to give a carboxylic acid and HCl. The reaction requires no acid or base catalyst. There is no synthetic advantage to this reaction because acid chlorides are prepared from carboxylic acids. Because of their reactivity with water, acid chlorides must be protected even from the moisture in air.



cyclopropanecarbonyl chloride — cyclopropanecarboxylic acid

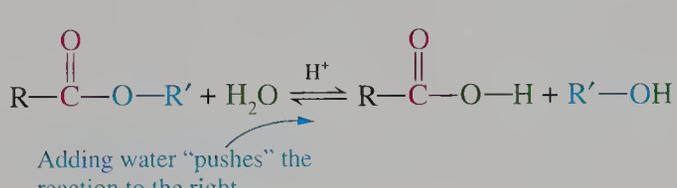
Although acid anhydrides are less reactive than acid chlorides, they still react spontaneously with water.



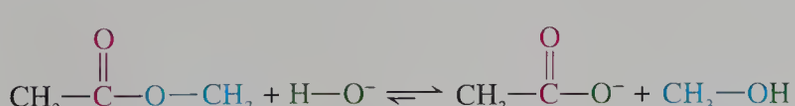
maleic anhydride — maleic acid

Esters

The acid-catalyzed hydrolysis of an ester produces an acid and an alcohol. Ester hydrolysis, then, is just the reverse of the Fischer esterification reaction, which is also catalyzed by strong acids. A large excess of water favors the reaction.

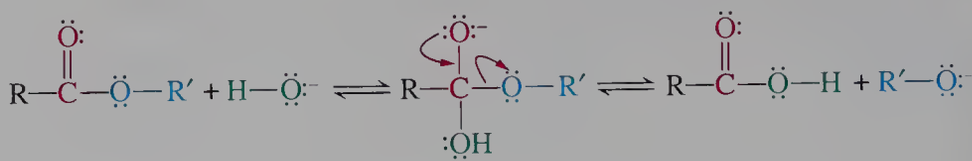


The hydrolysis of an ester by a strong base is called **saponification** (from Latin *sapon*, soap) because this reaction is used to make soaps from esters of long-chain carboxylic acids. Methyl acetate reacts with a strong base to give acetate ion and methanol.

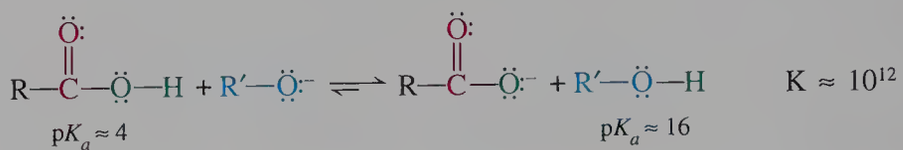


There is an important difference between hydrolysis and saponification. In hydrolysis, the hydronium ion acts as a catalyst, whereas in saponification the hydroxide ion is a reagent. The hydroxide ion is not a catalyst because it is consumed in the reaction. Equal numbers of moles of hydroxide and ester react, and, because hydroxide is a strong base, the position of equilibrium lies overwhelmingly to the right. As a consequence, the saponification of an ester is driven to the product.

The saponification of an ester occurs by nucleophilic attack of hydroxide ion at the carbonyl carbon atom to form a tetrahedral intermediate. The intermediate can then eliminate hydroxide ion to regenerate the ester or eliminate an alkoxide to give a carboxylic acid.

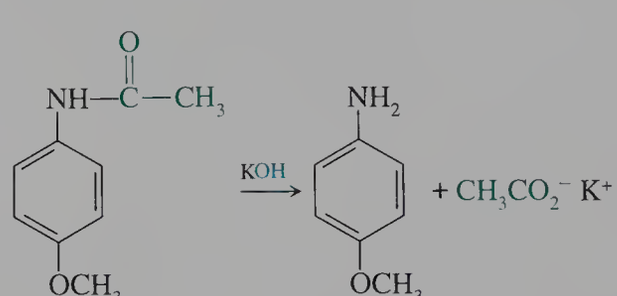


Because the alkoxide formed is a stronger base than a carboxylate ion, an acid–base reaction occurs to give a carboxylate ion and an alcohol. This spontaneous reaction drives the overall saponification reaction to completion.

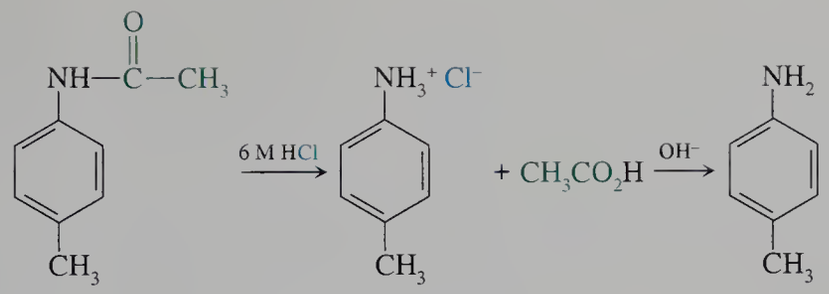


Amides

Hydrolysis of an amide breaks the carbon–nitrogen bond and produces an acid and either ammonia or an amine. This reaction resembles the hydrolysis of esters, but with important differences. The hydrolysis of esters occurs relatively easily, whereas amides resist hydrolysis, requiring heating for hours with 6 M HCl or a 40% solution of sodium hydroxide. When amide hydrolysis is carried out in basic solution, the salt of the carboxylic acid forms. A mole of base reacts with each mole of amide. As in the saponification of an ester, the formation of the carboxylate anion drives the reaction to completion.



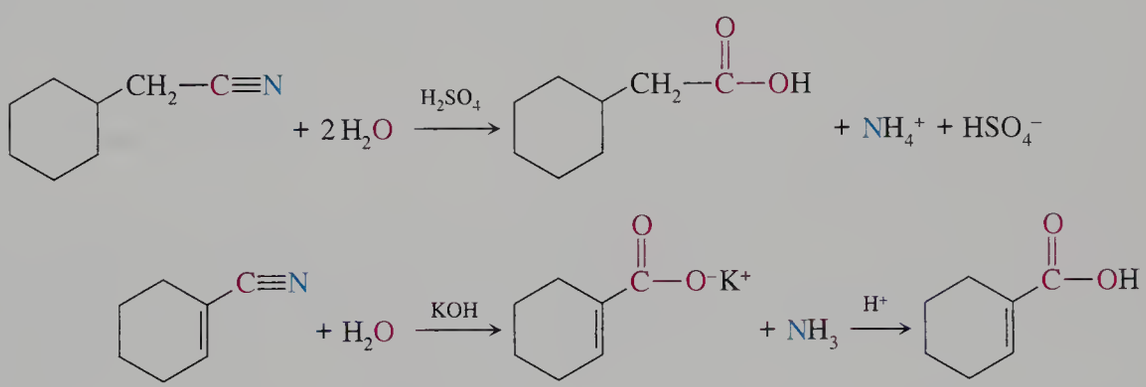
When amide hydrolysis is carried out under acidic conditions, the ammonium salt of the amine forms, and a mole of acid reacts with each mole of amide. The formation of the conjugate acid of the amine drives the reaction to completion. The free amine forms in a subsequent neutralization reaction with a base.



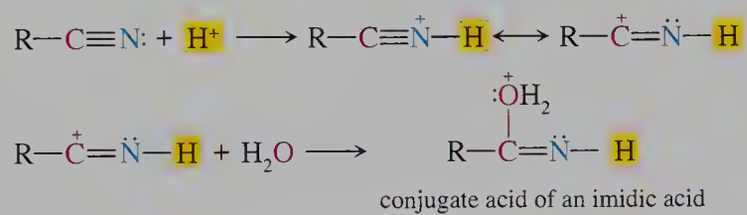
The great stability of amides toward hydrolysis has an important biological consequence, since amino acids in protein are linked by amide bonds. Because amides are stable, proteins do not readily hydrolyze at physiological pH and body temperature without an enzyme catalyst. However, in the presence of specific enzymes, the hydrolysis of amides is rapid. We will discuss these reactions in Chapter 26.

Nitriles

Nitriles hydrolyze to form carboxylic acids when treated with either concentrated acid or concentrated base. As in the case of amides, the reaction is slow and requires high temperatures. The amides that form in the hydrolysis reaction are further hydrolyzed to the carboxylic acid.

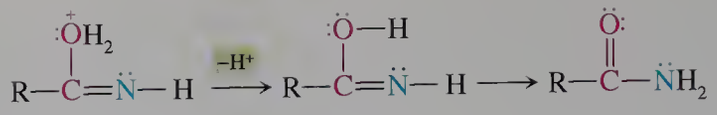


The mechanisms of the acid- and base-catalyzed reactions of the triple bond of nitriles resemble those of the acid- and base-catalyzed hydrations of the double bond of aldehydes and ketones. In the acid-catalyzed reaction, the first step is protonation of the lone pair electrons of the nitrogen atom. Nucleophilic attack of water on the electrophilic carbon atom occurs in the second step.



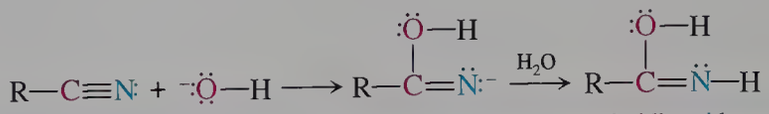
conjugate acid of an imidic acid

Transfer of a proton from the conjugate acid of the imidic acid yields an imidic acid that tautomerizes through solvent-mediated steps to give an amide that hydrolyzes to give the carboxylic acid.



imidic acid

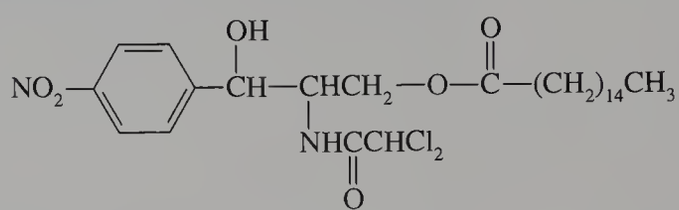
In the base-catalyzed hydration of a nitrile, like that of carbonyl compounds, the first step of the reaction is nucleophilic attack of hydroxide at the electrophilic carbon atom. Subsequent protonation of nitrogen by water yields an imidic acid. The imidic acid tautomerizes to give an amide that hydrolyzes to yield the carboxylic acid.



imidic acid

Problem 22.10

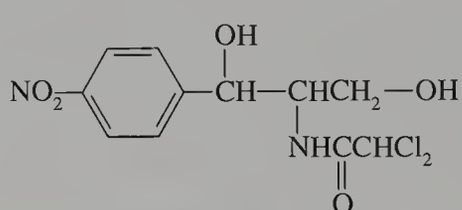
The antibiotic chloramphenicol tastes bitter. Its palatability for children is improved by using a suspension of the palmitate ester. Enzymes in the intestine hydrolyze the ester. Given the structure of the ester, write the structure of the antibiotic.



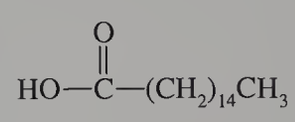
chloramphenicol palmitate

Sample Solution

First locate the ester functional group by examining the carbonyl carbon atoms. The carbonyl group at the bottom of the structure is bonded to a nitrogen atom. This is an amide. The carbonyl carbon atom toward the right of the structure is bonded to an oxygen atom. This is the ester functional group. The carbon chain to the right of the carbonyl group is part of the acid, which contains a total of 16 carbon atoms. Chloramphenicol is bonded in the ester through its primary hydroxyl group.



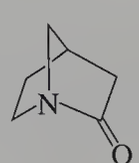
chloramphenicol



hexadecanoic acid
(palmitic acid)

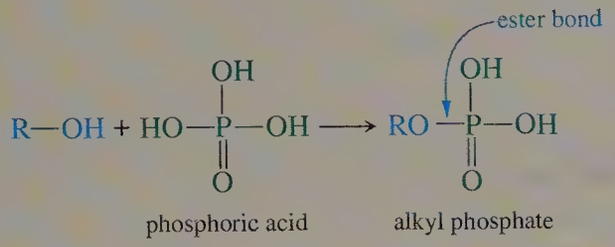
Problem 22.11

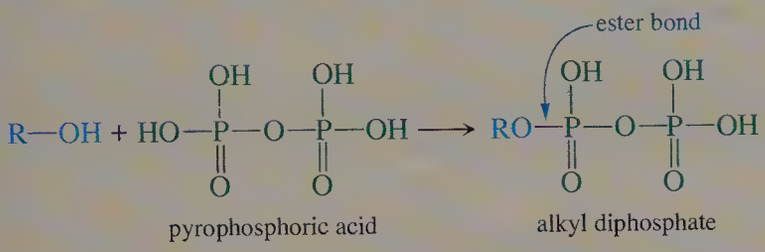
Give two reasons why the following bicyclic amide is easily hydrolyzed.

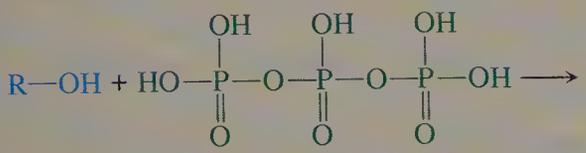


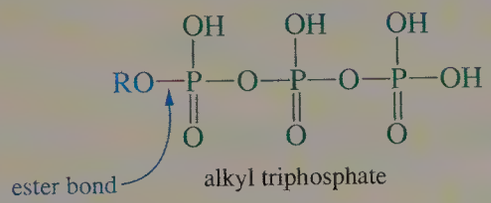
Esters and Anhydrides of Phosphoric Acid

Phosphoric acid, pyrophosphoric acid, and triphosphoric acid occur in living cells as esters. Just as alcohols react with carboxylic acids, they also react with phosphoric acid, pyrophosphoric acid, and triphosphoric acid.



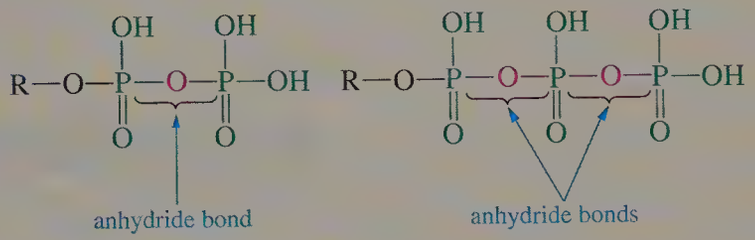




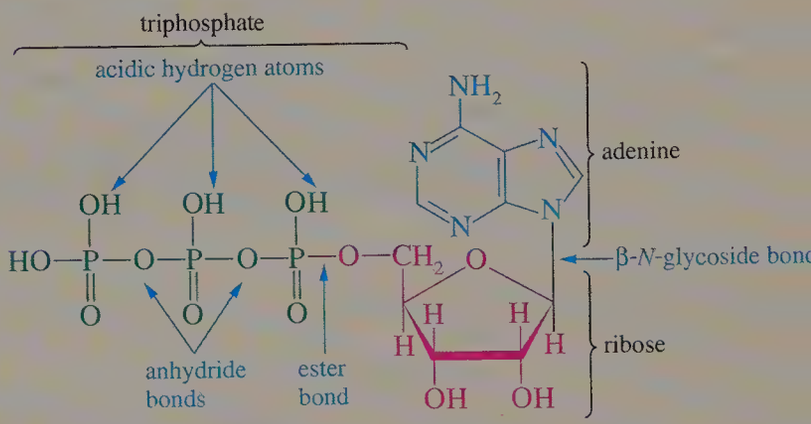


Note that these esters are also acids. The protons in the —OH groups of these esters exist as ions at physiological pH. That's why phosphoric acid derivatives are soluble in the aqueous environment of living systems.

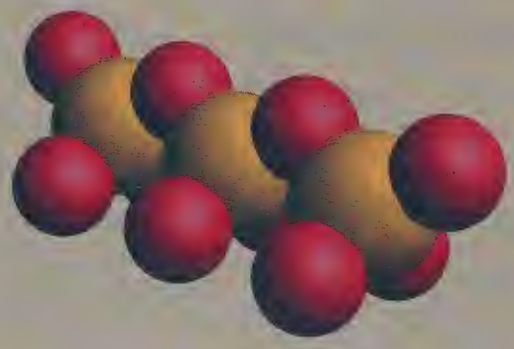
Two of the esters are also acid anhydrides of phosphoric acid. The oxygen atom between the phosphorus atoms constitutes the anhydride bond. These compounds are analogs of acid anhydrides of carboxylic acids.



The anhydride bonds of diphosphates and triphosphates are hydrolyzed in many biological reactions.



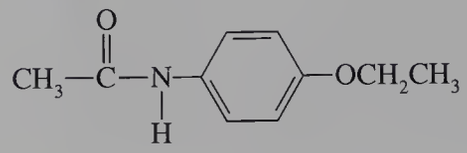
Adenosine triphosphate (ATP), a triphosphate ester of adenosine, stores some of the energy released in the degradation of carbohydrates, fats, and amino acids. When one anhydride bond of ATP is hydrolyzed, adenosine diphosphate (ADP) results. This reaction has a standard free energy change of –30.5 kJ mole^{-1} (–7.3 kcal mole^{-1}) at pH 7.



triphosphate ion

Problem 22.12

What are the products of the hydrolysis of phenacetin by a base? Phenacetin was formerly used in APC analgesic tablets consisting of aspirin, phenacetin, and caffeine.



phenacetin

Problem 22.13

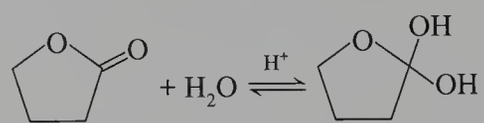
The principal component of the wax of the sperm whale is an unbranched ester that hydrolyzes to $C_{16}H_{34}O$ and $C_{16}H_{32}O_2$. Write the structure of the ester.

Problem 22.14

The lactone of 4-hydroxybutanoic acid is stable in aqueous acid solution. However, when dissolved in aqueous acid labeled with ^{18}O, the lactone incorporates ^{18}O. Which oxygen atom of the lactone is labeled?

Sample Solution

Protonation of the carbonyl oxygen atom and attack of a nucleophilic oxygen atom of water at the carbonyl carbon atom give a tetrahedral intermediate that is a hydrate of the ester.



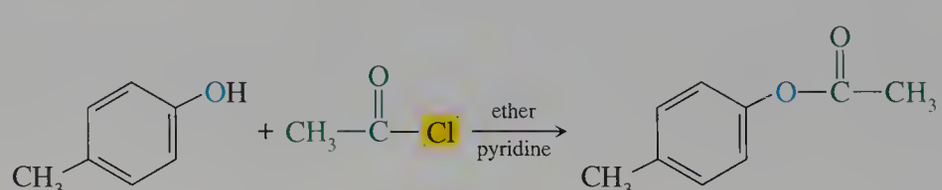
Both hydroxyl groups are structurally equivalent. Thus the reverse of the hydration reaction can eliminate either group in the water released. The ^{18}O can be retained in the carbonyl group or released back into the solution.

22.6 Reaction of Acyl Derivatives with Alcohols

The mechanism of the reaction of alcohols with each of the acyl derivatives is similar to the corresponding mechanism for the hydrolysis of acyl derivatives.

Acid Chlorides

We recall that esters of alcohols can be prepared by Fischer esterification (Section 21.12). Esters of phenols cannot be prepared by this method because the equilibrium constant is not favorable. However, esters of both alcohols and phenols can be prepared using acid chlorides. The reaction produces HCl, and pyridine is added to the reaction mixture to neutralize the HCl.

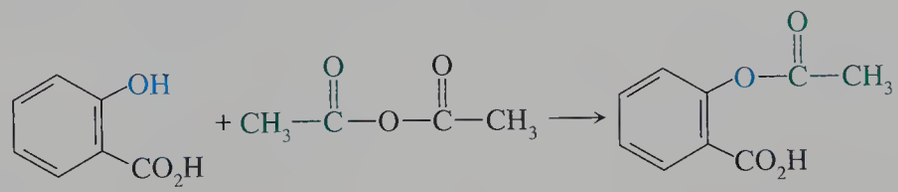


4-methylphenol

4-methylphenyl ethanoate

Acid Anhydrides

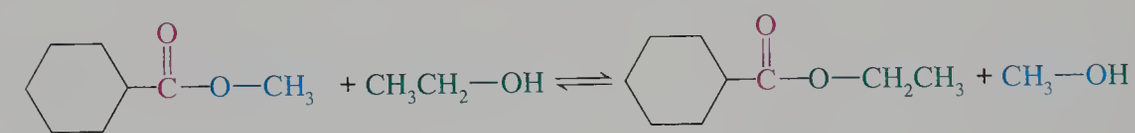
Acid anhydrides react with alcohols in much the same way as do acid chlorides. However, only one of the two acyl groups of the anhydride reacts with nucleophiles. Because an acid anhydride is usually prepared from two equivalents of a carboxylic acid, one of those equivalents is wasted when the acid anhydride reacts with an alcohol. Acetic anhydride, an inexpensive and commercially available reagent, is used in industry to acetylate alcohols and phenols. Drug manufacturers prepare aspirin from salicylic acid by this method.



salicylic acid aspirin

Esters

The reaction of an ester with an alcohol in an acid-catalyzed reaction yields an ester of the alcohol by an exchange of alkoxy groups. This transesterification reaction has little synthetic utility because any desired ester can usually be prepared in better yield from another acid derivative, such as an acid chloride.



methyl cyclohexanecarboxylate ethyl cyclohexanecarboxylate

Thus, whenever an ester reacts in an alcohol solvent, the same alcohol as contained in the ester must be used to avoid transesterification. Otherwise, a mixture of derivatives of two esters would result.

Problem 22.15

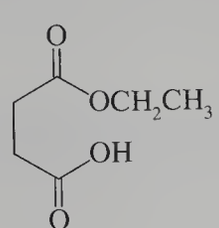
Why are the esters of tertiary alcohols prepared by reaction with acid chlorides rather than by the Fischer esterification method?

Problem 22.16

Write the product of the reaction of succinic anhydride with ethanol.

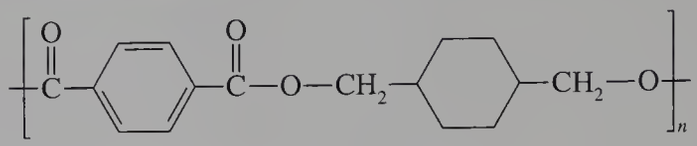
Sample Solution

Reaction of an alcohol with an acyclic anhydride to form an ester releases one equivalent of a carboxylic acid. Because succinic anhydride is a cyclic anhydride, the carboxyl group is not released. It remains as part of the ester. Because carboxylic acids are less reactive than anhydrides, the carboxyl group does not react with a second equivalent of ethanol. The product is



Problem 22.17

The polyester Kodel is prepared by heating a mixture of dimethyl terephthalate with 1,4-di(hydroxymethyl)cyclohexane. Explain how the reaction may be driven to completion.



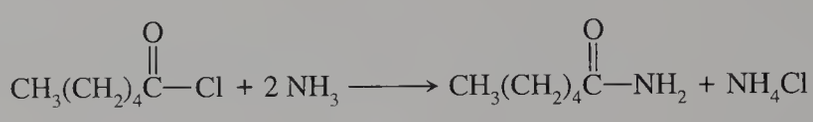
Kodel

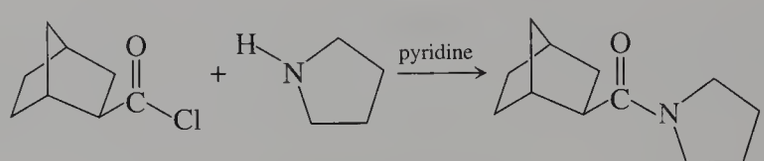
22.7 Reaction of Acyl Derivatives with Amines

Ammonia and amines are better nucleophiles than water or alcohols because the nitrogen atom is less electronegative than oxygen and, therefore, a stronger base. Because amides are the most stable of the acyl derivatives, ammonia and amines react with all other acyl derivatives.

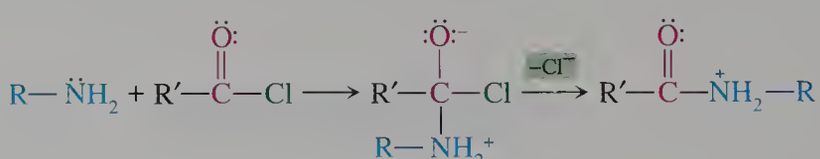
Acid Chlorides

Acid chlorides react with ammonia, a primary amine, or a secondary amine to give primary, secondary, and tertiary amides, respectively. Tertiary amines do not react with acid chlorides to give amides.

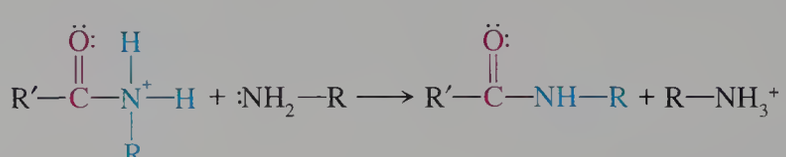




Tertiary amines such as pyridine are added to the reaction mixture of an acid chloride and amine. Let's look at the mechanism to see why pyridine is used.



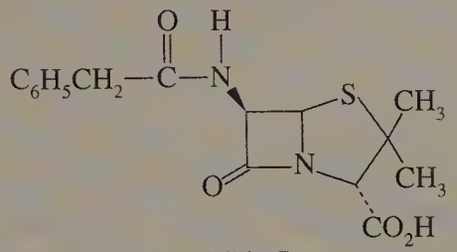
An amide is a weak base. Thus, the conjugate acid of the amide formed in the synthetic reaction transfers a proton to the reactant amine.



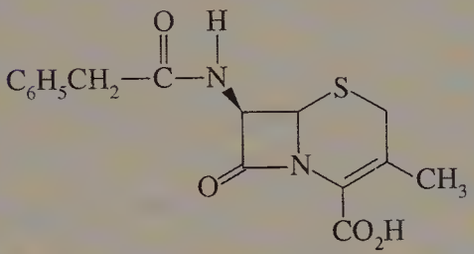
The ammonium ion, unlike the original amine, is not nucleophilic. Therefore, one equivalent of amine is "lost" for every equivalent of amine converted to the amide.

Action of Bactericides

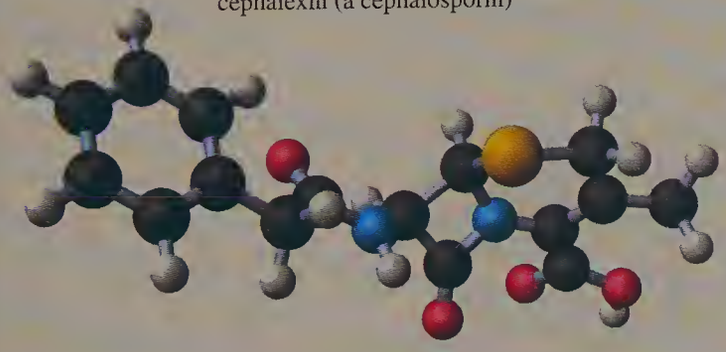
Penicillins and cephalosporins are two classes of bactericides that contain a four-membered lactam (β lactam). Although representatives of both types of compounds were originally isolated from fungi, derivatives are now produced by structural modification in the laboratory.



penicillin G



cephalexin (a cephalosporin)

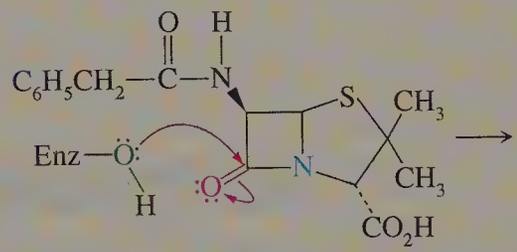


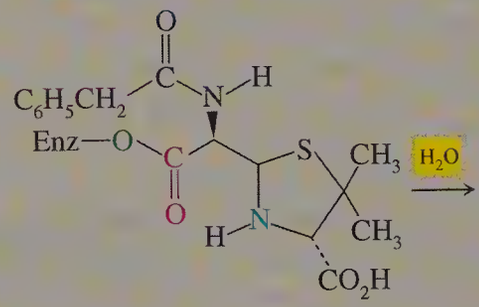
cephalexin

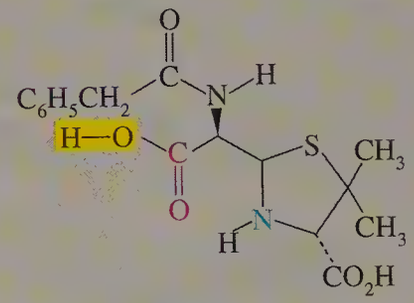
These two bactericides inhibit the synthesis of bacterial cell walls, causing growing cells to burst. The enzyme transpeptidase catalyzes reactions that form the cell wall. The enzyme complexes with both penicillins and cephalosporins, and the carbonyl group of the bactericide acylates a serine hydroxyl group contained in the active site of the enzyme.

Most amides are ineffective acylating agents. However, the four-membered ring of a β lactam is strained. Relief of strain provides the driving force for its reaction with nucleophiles.

Penicillin-resistant strains of one type of bacteria, staphylococci, have developed as the result of overuse of bactericides. These strains have enzymes called penicillases that hydrolyze penicillins to yield penicilloic acids, which are not bactericides. The rate of this deactivation of penicillin varies with its substituents. Thus, to stay one step ahead of the mutation of bacteria, a series of substituted penicillins has been developed. Another class of compounds, the cephalosporins, has been developed to kill bacteria that have developed a resistance to penicillins.





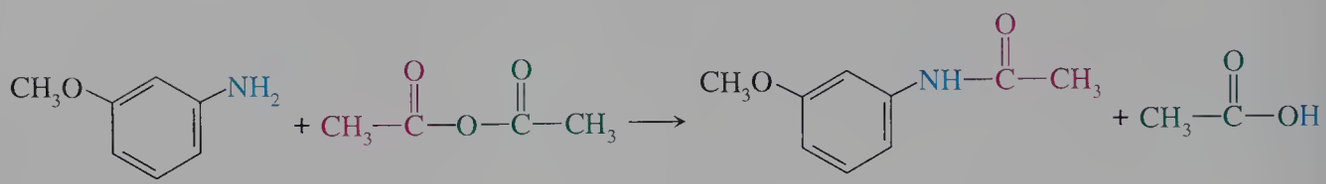


(a penicilloic acid)

Such a process is wasteful, and impractical for all but the least expensive amines. Therefore, a tertiary amine, such as pyridine, is used to react with the proton released in the reaction.

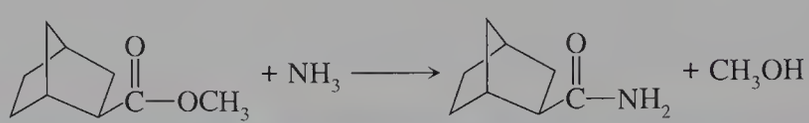
Acid Anhydrides

Ammonia, primary amines, and secondary amines all react easily with acid anhydrides to form amides. As noted for the reaction of acid anhydrides with alcohols, one of the acyl carbon atoms is "wasted". The by-product is the carboxylic acid used to originally form the anhydride. Acetic anhydride in acetic acid is an inexpensive reagent for the acetylation of amines.



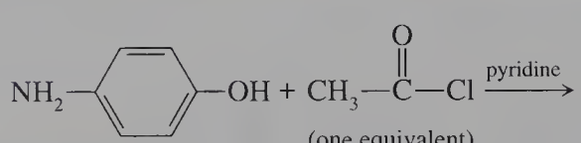
Esters

Esters react with ammonia or primary or secondary amines to yield amides by the same generalized mechanism as for the reaction of nitrogen compounds with acid chlorides or acid anhydrides. However, the method is not used synthetically because amides are better prepared by reaction with the more reactive acyl derivatives.



Problem 22.18

Draw the structure of the product of the following reaction.



Problem 22.19

Draw the structure of the product of the reaction of maleic anhydride with methylamine (CH_3NH_2).

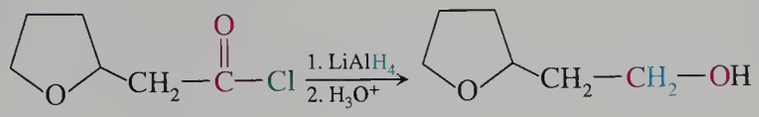
22.8 Reduction of Acyl Derivatives

Carboxylic acids and their acyl derivatives are relatively difficult to reduce, requiring strong reducing agents. In this section, we will review some of these reductions, which we studied earlier as methods to synthesize alcohols and aldehydes. We also consider the reduction of additional acyl derivatives.

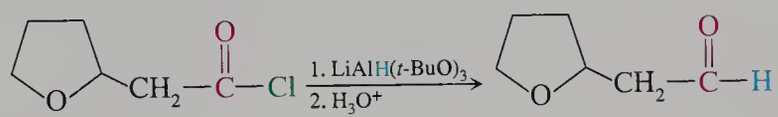
Reduction of Acid Chlorides

Acid chlorides are the most reactive acyl derivatives toward the nucleophilic hydride ion provided by metal hydrides. As a consequence, acid chlorides are rapidly reduced to aldehydes. However, lithium aluminum hydride is such a strong reducing agent

that the aldehydes produced from acid chlorides are further reduced to primary alcohols under the reaction conditions.

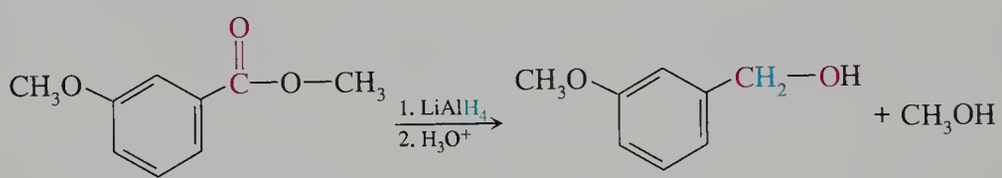


The milder reducing agent lithium aluminum tri(tert-butoxy) hydride reduces acid chlorides to yield aldehydes. However, this less reactive hydride reagent reduces the aldehyde less rapidly. Thus, the aldehyde is obtained without further reduction to an alcohol.



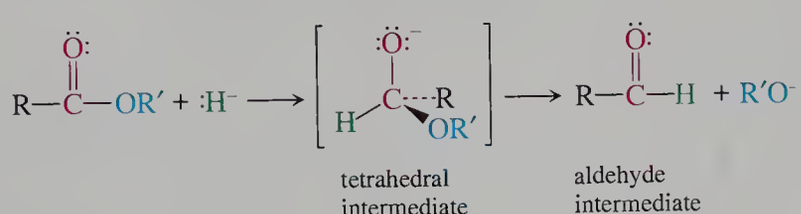
Reduction of Esters

The reduction of esters requires the strong reducing agent lithium aluminum hydride. The milder reagent sodium borohydride does not reduce esters.

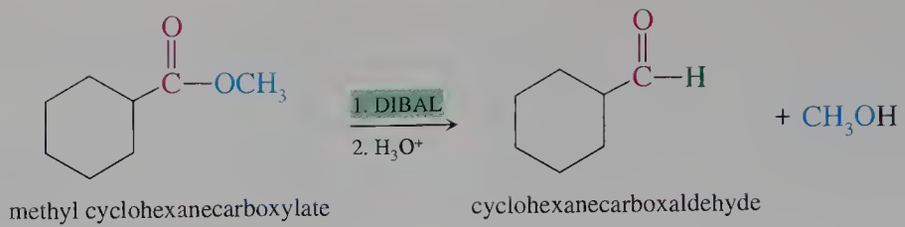


Note that the alcohol portion of the ester is a by-product of the reaction. The esters typically reduced by lithium aluminum hydride contain a low molecular weight alkyl group introduced in the conversion of an acid to an ester. The alcohol obtained by reduction of the acid portion of the ester is easily separated from the low molecular weight, water-soluble alcohol.

The mechanism of the reduction of an ester is pictured as a nucleophilic attack of a one molar equivalent of a "hydride" ion on the carbonyl carbon atom. However, the aluminum atom is bonded to the oxygen atom and participates in the reaction. For simplicity, the structures do not show the aluminate ion. Attack by the hydride ion produces a tetrahedral intermediate whose negatively charged oxygen atom is bonded to the aluminum atom. The tetrahedral intermediate loses an alkoxide ion, and the resulting aldehyde is even more rapidly reduced than the original ester by a second molar equivalent of hydride ion. In total, two molar equivalents of hydride ion or one-half molar equivalent of lithium aluminum hydride is required for the reduction.



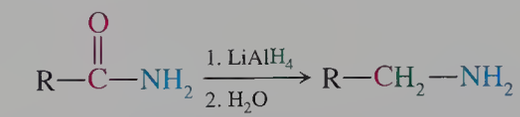
Esters are reduced to aldehydes using the mild reducing agent diisobutylaluminum hydride (DIBAL). To avoid subsequent reduction of the aldehyde, exactly one equivalent of the reagent is used, and the reaction is carried out at –78 °C.



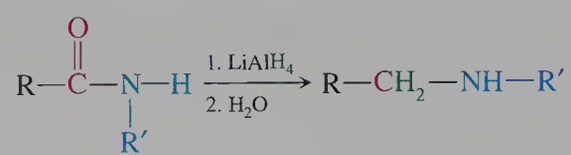
methyl cyclohexanecarboxylate cyclohexanecarboxaldehyde

Reduction of Amides

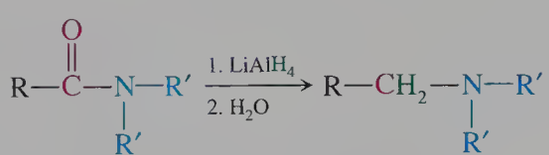
Amides are reduced by lithium aluminum hydride to yield amines regardless of the degree of substitution of the amide. Primary, secondary, and tertiary amides yield primary, secondary, and tertiary amines, respectively.



primary amide primary amine



secondary amide secondary amine

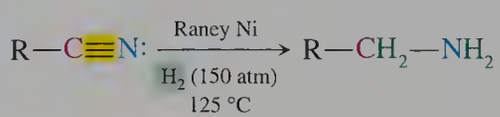


tertiary amide tertiary amine

There is an important difference between the reductions of esters and of amides. In esters, the oxygen atom retained in the product is the original carbonyl oxygen atom. The bridging oxygen atom to the alkyl group leaves as an alkoxy group. If a similar mechanism occurred with amides, the nitrogen atom would leave, but it does not. In the reduction of amides, the carbonyl oxygen atom is replaced.

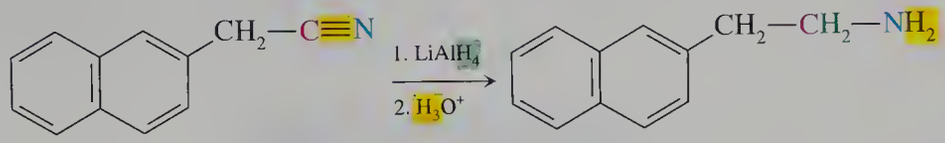
Reduction of Nitriles

Nitriles are difficult to reduce by catalytic hydrogenation. The conditions of high temperature and high pressure of hydrogen are similar to those required to catalytically reduce carbonyl compounds.

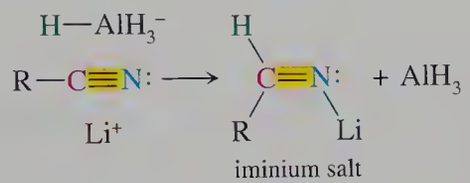


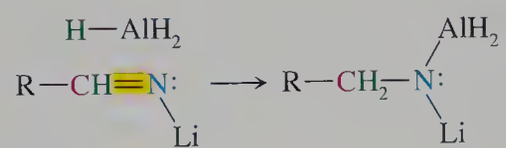
The intermediate in the reaction is an imine, which is more rapidly reduced than the nitrile.

Nitriles are reduced directly to primary amines by lithium aluminum hydride. The aqueous workup is a conventional one for reductions by this metal hydride.

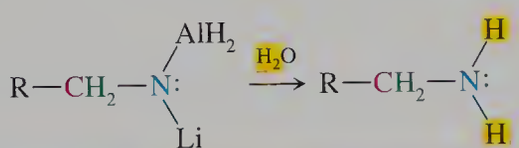


The first step in the mechanism of the reduction of a nitrile produces a lithium iminium compound, which then reacts with a second equivalent of hydride.



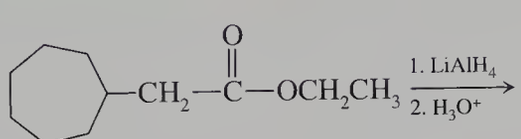


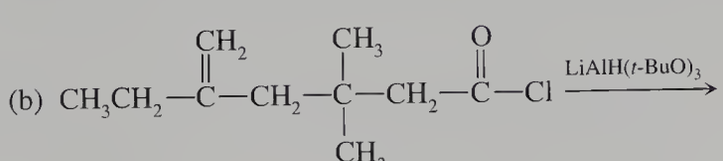
The N—Li and the N—Al bonds are protonated in the subsequent hydrolysis step.

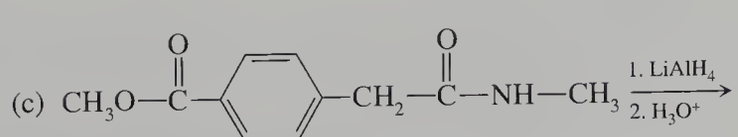


Problem 22.20

Draw the structure of the product of each of the following reactions.

(a) 

(b) 

(c) 

(d) 

Problem 22.21

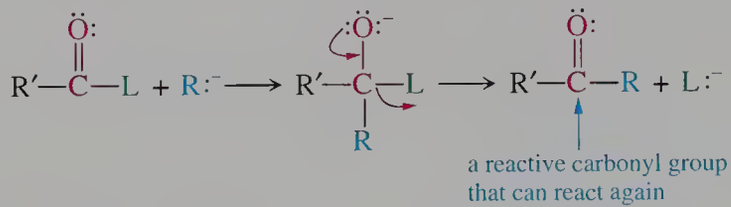
Reduction of cyclohexanecarboxamide with $LiAlD_4$ followed by aqueous workup gives $C_7H_{13}D_2N$. What is the structure of the product? Why does the amine product contain two deuterium and two hydrogen atoms more than the amide?

Problem 22.22

Reduction by $LiAlH_4$ of a substance with molecular formula $C_{12}H_{20}O_2$ obtained from a fungus gives (*E*)-4-dodecene-2,12-diol. Write the structure of the compound.

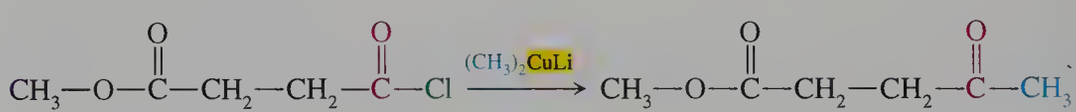
22.9 Reaction of Acyl Derivatives with Organometallic Reagents

The carbonyl group of acid derivatives reacts with the nucleophilic carbanion available from organometallic reagents. However, the reactions of the individual classes of compounds are not as straightforward as the addition reactions of organometallic compounds with aldehydes and ketones. Addition of a carbanion to the acyl carbon atom generates a tetrahedral intermediate that can decompose to give a ketone that will react further with another equivalent of the carbanion.



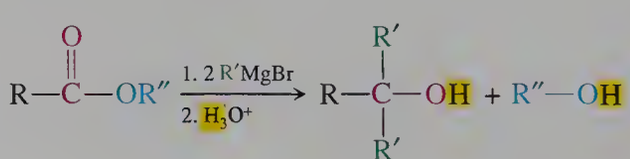
Acid Chlorides

Addition reactions of Grignard reagents to acid chlorides are not useful synthetic procedures because the reactions are difficult to control. However, lithium dialkylcuprates (Gilman reagents) are less reactive, and probably react by a different mechanism than Grignard reagents. These reagents replace chloride by a "carbanion" to give a ketone. Because these reagents react only slowly with ketones, the reaction can be stopped at this stage. The method is an excellent way to prepare ketones. The Gilman reagent does not react with esters because they are less susceptible to nucleophilic acyl substitution than acid chlorides.

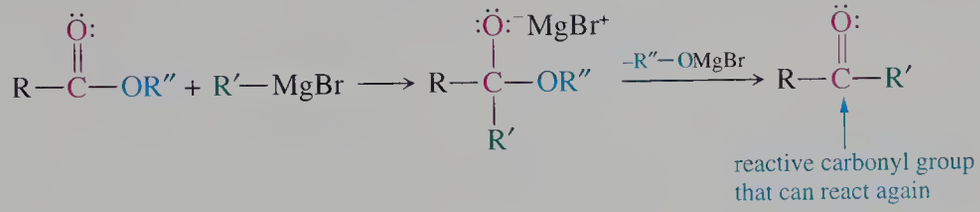


Esters

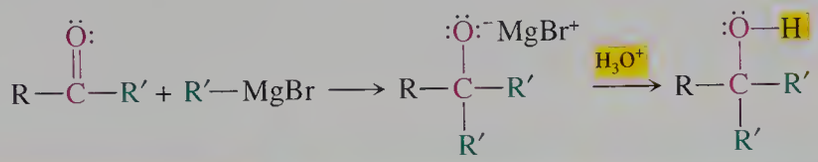
The reaction of an ester with a Grignard reagent to give a tertiary alcohol that contains two equivalents of the alkyl group of the organometallic reagent is an important synthetic procedure.



The first step of the reaction is addition of the Grignard reagent to the carbonyl group to give a tetrahedral intermediate. It subsequently releases an alkoxide ion complexed with magnesium bromide. Thus, the reaction is a typical nucleophilic acyl substitution reaction.



Because the carbon atom of the carbonyl group of ketones is more electrophilic than the acyl carbon atom of esters, a subsequent addition step yields a tertiary alcohol.

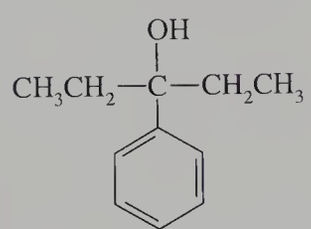


Problem 22.23

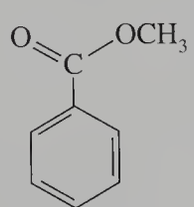
Propose a synthesis of 3-phenyl-3-pentanol using the addition reaction of a Grignard reagent to an ester.

Sample Solution

The carbon atom that bears the hydroxyl group has two ethyl groups and a phenyl group bonded to it.



The two ethyl groups can come from a Grignard reagent that can add to the carbonyl carbon of an ester. The ester must have a phenyl group bonded to the carbonyl carbon atom—a benzoate ester. The benzoate ester can contain any alkyl group such as in methyl benzoate or ethyl benzoate.



methyl benzoate

Problem 22.24

Explain how symmetrical secondary alcohols of the type R_2CHOH can be prepared by adding a Grignard reagent to an ester.

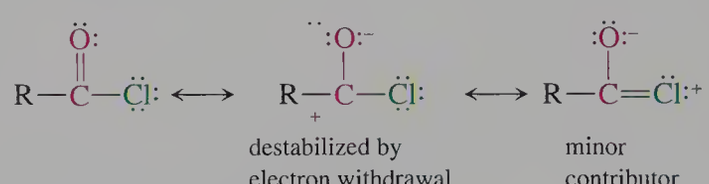
22.10 Spectroscopy of Acid Derivatives

Infrared Spectroscopy

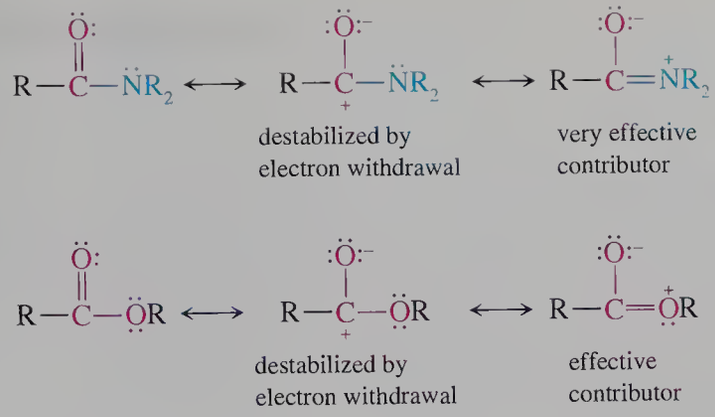
The C≡N stretching absorption occurs in the 2200–2250 cm^{-1} region, a rather isolated part of the spectrum, where the C≡C stretching absorption of alkynes also occurs (2100–2200 cm^{-1}). In contrast to the C≡C absorption, which is very weak and even absent in nearly symmetrical alkynes, the C≡N stretching absorption is very intense.

All acid derivatives having a carbonyl group have strong C=O stretching absorptions in the 1700–1800 cm^{-1} region. Simple esters as well as six-membered lactones (δ lactones) have an absorption at 1735 cm^{-1}, which is at a higher wavenumber postition than aldehyde and ketone absorptions. The C=O stretching absorption of unsaturated esters occurs at slightly lower wavenumber (1720–1725 cm^{-1}). As in the case of ketones, a decrease in ring size increases the wavenumber position of the C=O stretching absorption. The absorptions of five-membered lactones (γ lactones) and four-membered lactones (β lactones) occur at 1770 and 1840 cm^{-1}, respectively. Esters also have a C—O stretching absorption in the 1000–1300 cm^{-1} region. Because other absorptions also occur in this region, such data is useful only as a confirmation when an ester is suspected from other data such as the carbonyl stretching absorption. We recall that both alcohols and ethers, as well as carboxylic acids, have C—O absorptions in the same region.

Acyl chlorides have C=O stretching absorptions at higher wavenumber position (1800 cm^{-1}) than esters, whereas amides have C=O stretching absorptions at lower wavenumber position (1650–1655 cm^{-1}). These different values reflect the contribution of inductive and resonance effects in the stabilization of the Lewis structure of a carbonyl group compared to the dipolar resonance form. In the case of acyl chlorides, the chlorine atom is inductively electron withdrawing and destabilizes the dipolar resonance form, thus leading to an increase in the double bond character of the carbonyl group. We recall, based on our study of electrophilic aromatic substitution (Section 14.6), that the 3*p* lone pair electrons of chlorine cannot be donated effectively by resonance.



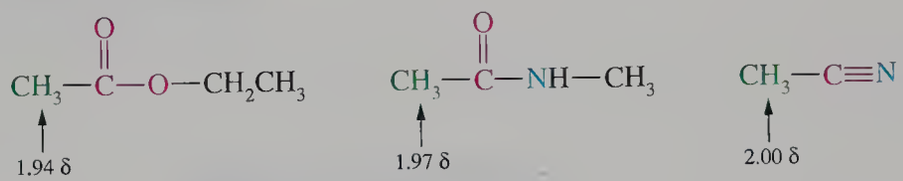
The position of the C=O stretching absorption of amides, like that of esters, reflects contributions of both inductive electron withdrawal by electronegative atoms and donation of electron density by resonance. The oxygen atom of esters and the nitrogen atom of amides destabilize the dipolar resonance form compared to that of ketones as a result of inductive withdrawal of electron density. As a consequence, both classes of compounds would have C=O stretching absorptions at higher wavenumber positions than ketones, as is indeed observed for acyl chlorides. However, unlike chlorine, both nitrogen and oxygen can donate electrons by resonance and stabilize a dipolar resonance form that has a C—O single bond. As a consequence the C=O stretching absorptions of esters and amides occur at higher wavenumber than acyl chlorides. Because nitrogen is less electronegative than oxygen, nitrogen supplies its lone pair electrons more easily and the dipolar resonance form is better stabilized in amides than in esters. As a consequence, the carbonyl group in amides has less double bond character than esters and less energy is required to stretch the C=O bond in amides compared to esters.



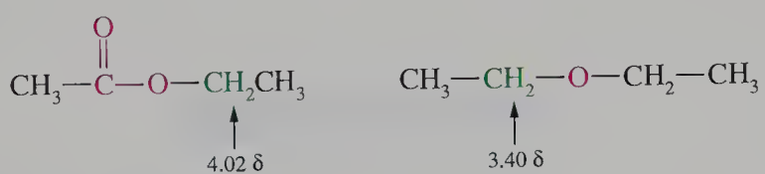
In addition to the characteristic C=O stretching absorption of amides, these compound may also have N—H stretching absorptions in the 3200–3400 cm^{-1} region. Amides without alkyl or aryl groups bonded to nitrogen (primary amides) have two N—H absorptions; secondary amides have one N—H absorption. Of course, tertiary amides have no absorption in this region.

Proton NMR Spectroscopy

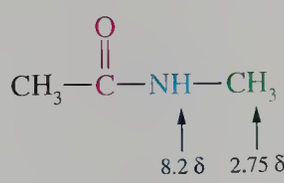
The α hydrogen atoms of all acid derivatives are somewhat deshielded by the carbonyl group, and the proton resonance occurs in the 2 δ region, as illustrated by the following simple structures. Substitution of alkyl groups on the α carbon causes a further downfield shift.



The chemical shift of hydrogen atoms on the alkyl carbon atom bonded directly to oxygen in esters is at about 0.6 ppm to lower field than the corresponding hydrogen atom of alcohols and ethers. This deshielding is the result of partial positive charge on the oxygen atom of esters that is a consequence of inductive electron withdrawal by the carbonyl carbon atom as well as donation of electrons of oxygen by resonance.

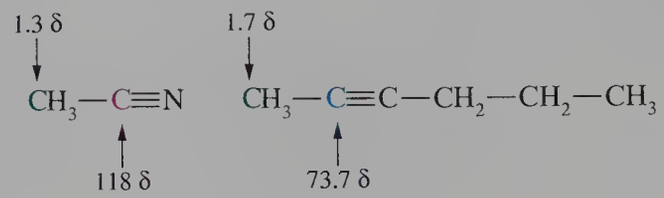


The chemical shift of hydrogen atoms on the alkyl carbon atom bonded directly to nitrogen in amides is in the 2.6–3.0 δ region. The proton(s) bonded to nitrogen are in the 7.5–8.5 δ region. Like the resonances of hydrogen atoms bonded to oxygen, the resonances of N—H groups are unsplit because of exchange of protons. In addition, these hydrogen atoms can be exchanged by deuterium using D_2O.

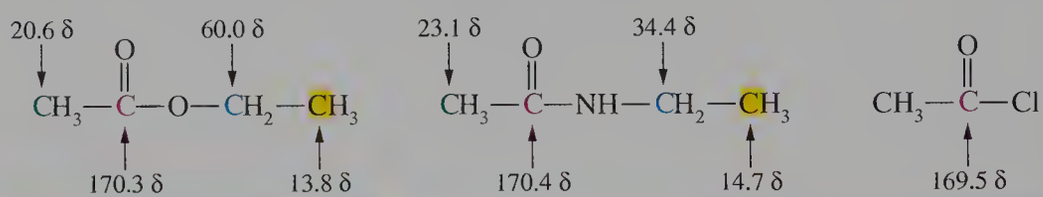


Carbon NMR Spectroscopy

The chemical shift of the carbon atom bonded to nitrogen in nitriles occurs in the 115–120 δ range. These values illustrate that the carbon atom is more deshielded than the triple-bonded carbon atom of acetylenes, a direct consequence of the electronegativity of the nitrogen atom. The chemical shift of the carbon atom bonded to the nitrile carbon atom is at high field, as is also the case for the carbon atom bonded to the acetylenic carbon atom of alkynes. The reason for this phenomenon, which is related to an effect of the π electrons of a triple bond, is a specialized topic that will not be considered in this text.

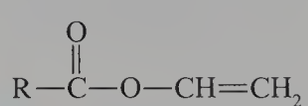


The resonance of the carbonyl carbon atom of acid derivatives, like that of carboxylic acids, occurs in the 165–180 δ region. The resonances of the α carbon atom of all acid derivatives are in the 20 δ region and at lower field with increased substitution of alkyl groups. The carbon atom bonded to oxygen of esters and the carbon atom bonded to nitrogen of amides are deshielded, compared to other saturated carbon atoms, as a result of the inductive effect of the respective electronegative atoms.



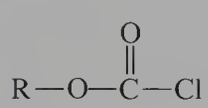
Problem 22.25

Although esters of unsaturated acids have carbonyl stretching absorptions at 1720 cm^{-1}, a lower value than the esters of saturated acids, the carbonyl stretching absorption of unsaturated esters of the following type is at 1760 cm^{-1}. Explain why.



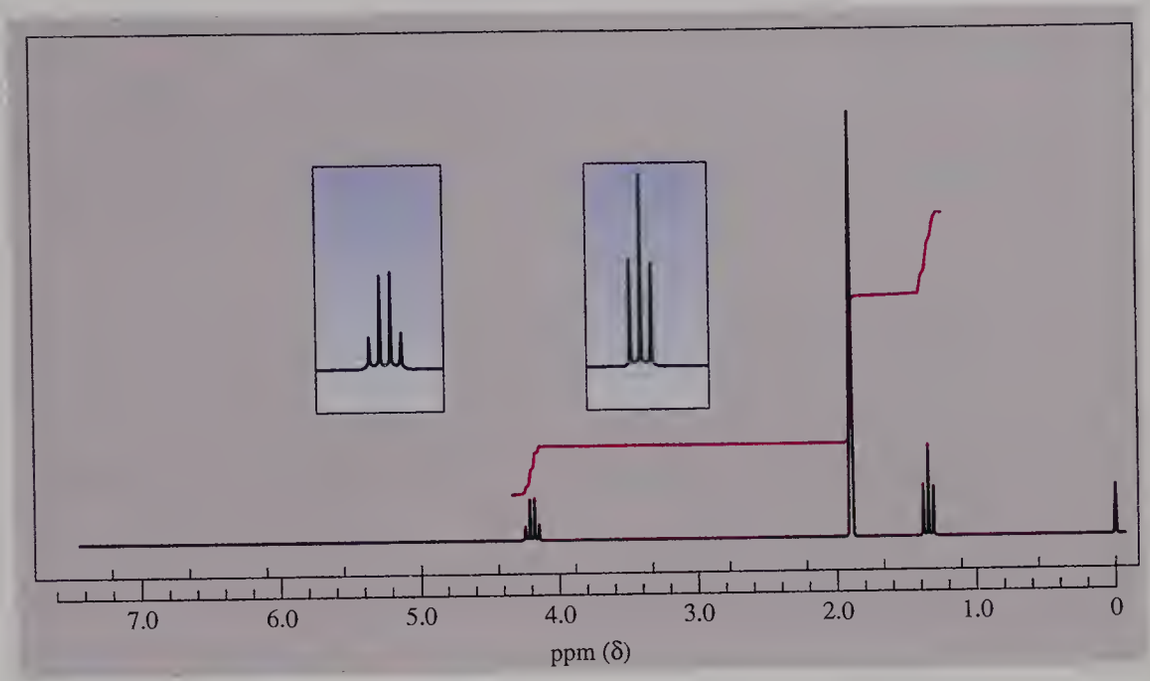
Problem 22.26

Explain why chlorocarbonates have carbonyl stretching absorptions at 1780 cm^{-1}, which is a lower wavenumber value than shown by acyl chlorides.



Problem 22.27

Deduce the structure of a compound with molecular formula $C_6H_{11}BrO_2$ with a carbonyl stretching absorption at 1730 cm^{-1} and having the following hydrogen NMR spectrum.



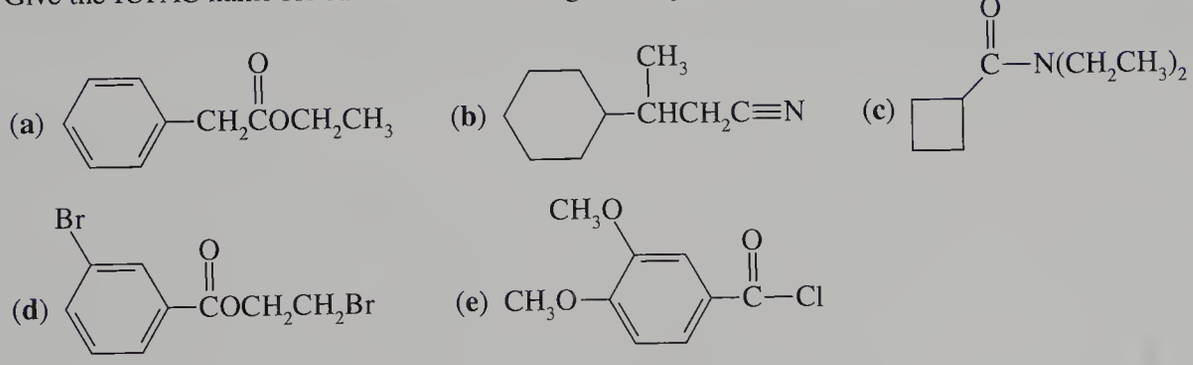
Problem 22.28

Deduce the structure of a compound with molecular formula $C_4H_6O_2$ that has a carbonyl stretching absorption and whose carbon NMR spectrum has a singlet at 178.1 ppm and triplet absorptions at 22.3, 27.8, and 68.8 ppm.

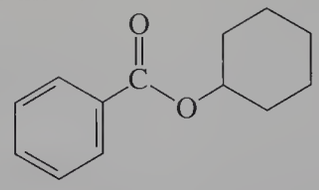
EXERCISES

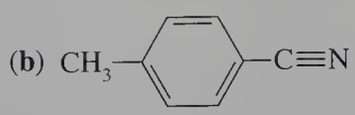
Nomenclature

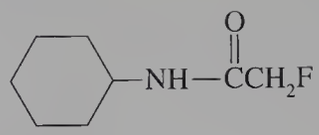
22.1 Give the IUPAC name for each of the following carboxylic acid derivatives.

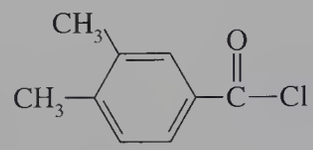


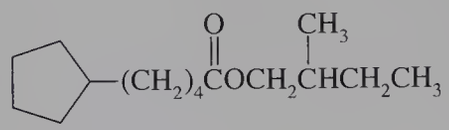
22.2 Give the IUPAC name for each of the following carboxylic acid derivatives.

(a) 

(b) 

(c) 

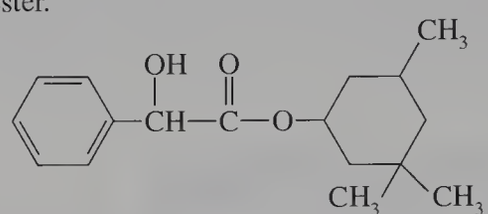
(d) 

(e) 

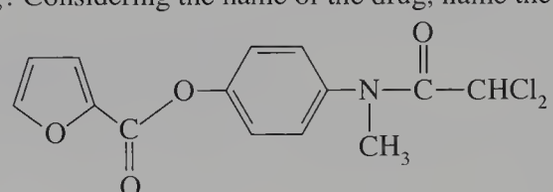
22.3 Write the structure of each of the following compounds.
(**a**) phenyl octanoate (**b**) butanoic anhydride (**c**) *N*-ethyl-4,4-dimethylcyclohexanecarboxamide
(**d**) 2-bromo-3-methylbutanoyl chloride (**e**) *trans*-4-methylcyclohexanecarbonitrile

22.4 Write the structure of each of the following compounds.
(**a**) 2-chloropropyl 3-bromobutanoate (**b**) 4-methoxyphthalic anhydride
(**c**) *N,N*-dimethyl-3-cyclopropylpentanamide (**d**) cyclobutanecarbonyl bromide
(**e**) (*R*)-2-methylbutanenitrile

22.5 The common name of the vasodilator cyclandelate is 3,5,5-trimethylcyclohexyl mandelate. Give the structure and name of the acid contained in the ester.

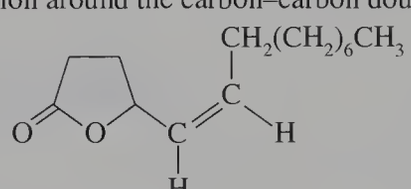


22.6 Hydrolysis in the body is required for diloxanide furanoate to be effective against intestinal amebiasis. What is the acid component of the drug? Considering the name of the drug, name the acid.

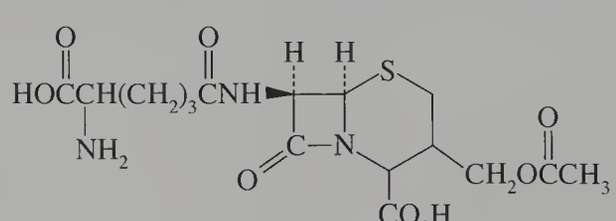


Cyclic Acyl Derivatives

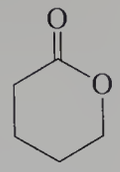
22.7 Identify the oxygen-containing functional group in the following structure of a sex pheromone of the female Japanese beetle. What is the configuration around the carbon–carbon double bond?

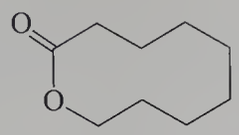


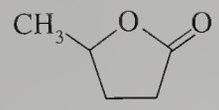
22.8 Identify the nitrogen-containing functional group within the four-membered ring of cephalosporin C, an antibiotic.



22.9 Name each of the following lactones.

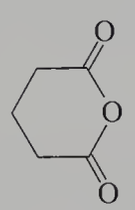
(a) 

(b) 

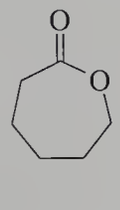
(c) 

22.10 Draw the structure of each of the following lactams.
(a) 3-aminopropanoic acid lactam (b) 4-aminopentanoic acid lactam (c) 5-aminopentanoic acid lactam

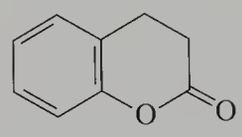
22.11 Which of the following compounds are lactones?



I

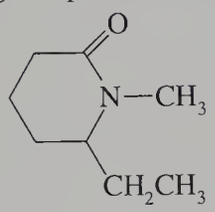


II

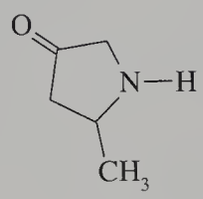


III

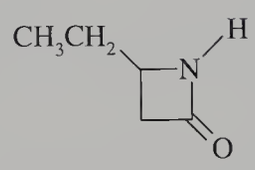
22.12 Which of the following compounds are lactams?



I



II



III

Properties of Acid Derivatives

22.13 The boiling points of methyl pentanoate and butyl ethanoate are 126 and 125 °C, respectively. Explain the similarity of these boiling points.

22.14 The boiling points of methyl pentanoate and methyl 2,2-dimethylpropanoate are 126 and 102 °C, respectively. Explain why these values differ.

22.15 The boiling points of acetonitrile and 1-propyne are 81.5 and -23 °C, respectively. Account for this difference in boiling point between two compounds with similar molecular weights.

22.16 The boiling points of acetamide and acetic acid are 221 and 118 °C, respectively. Account for this difference in boiling point between two compounds with similar molecular weights.

22.17 Explain why protonation of *N,N*-dimethylformamide occurs at the oxygen atom rather than the nitrogen atom.

22.18 The rotational barrier around the nitrogen–carbonyl carbon bond of *N,N*-dimethylformamide is approximately 87 kJ mole^{-1}. Why is this energy barrier substantially higher than values for other single bonds?

Nucleophilic Acyl Substitution

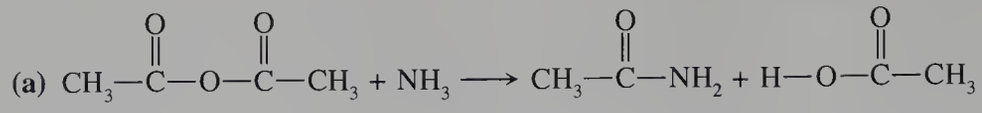
22.19 Indicate whether each of the following reactions will occur.

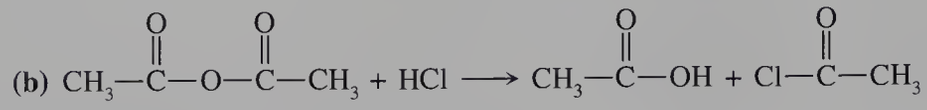
(a) $CH_3-\overset{\overset{O}{\|}}{C}-Cl + CH_3OH \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-O-CH_3 + HCl$

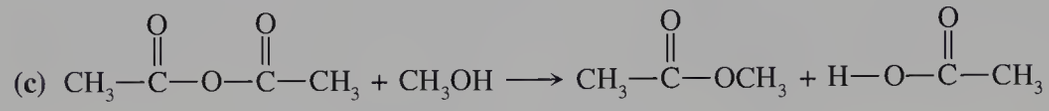
(b) $CH_3-\overset{\overset{O}{\|}}{C}-NH_2 + CH_3OH \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-O-CH_3 + NH_3$

(c) $CH_3-\overset{\overset{O}{\|}}{C}-OCH_3 + CH_3NH_2 \longrightarrow CH_3-\overset{\overset{O}{\|}}{C}-NHCH_3 + CH_3OH$

22.20 Indicate whether each of the following reactions will occur.

(a) 

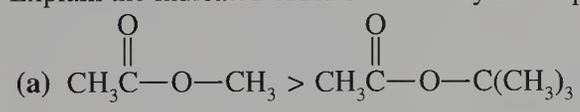
(b) 

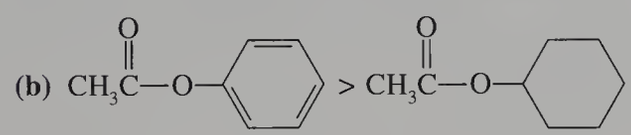
(c) 

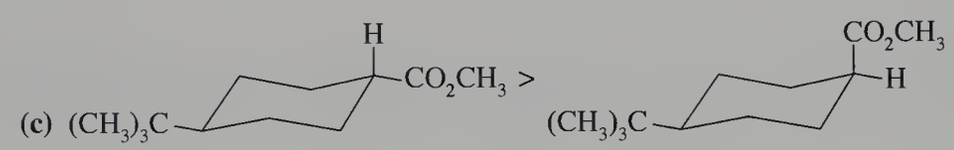
22.21 Considering the stability of the reactant, explain why thioesters react more readily than esters in acyl substitution reactions.

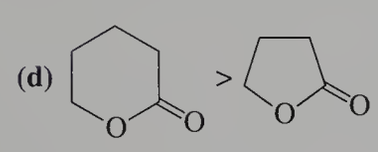
22.22 Considering the stability of the reactant, explain why thioesters are less reactive than acid chlorides in acyl substitution reactions.

22.23 Explain the indicated order of reactivity in a saponification reaction of each of the following pairs of compounds.

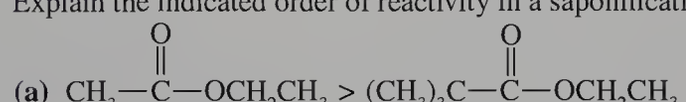
(a) 

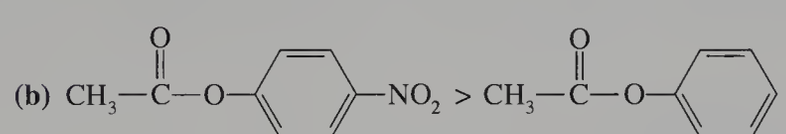
(b) 

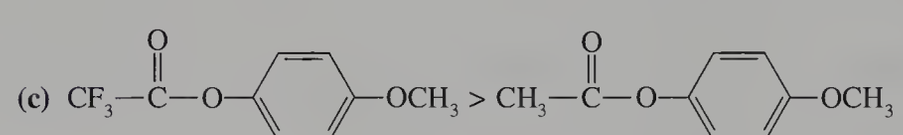
(c) 

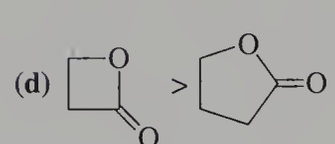
(d) 

22.24 Explain the indicated order of reactivity in a saponification reaction of each of the following pairs of compounds.

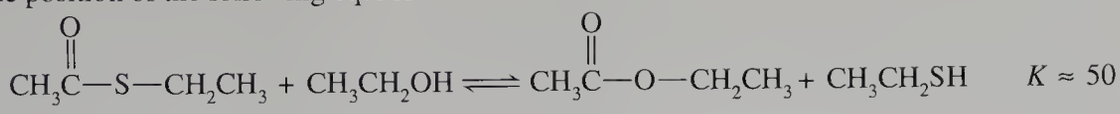
(a) 

(b) 

(c) 

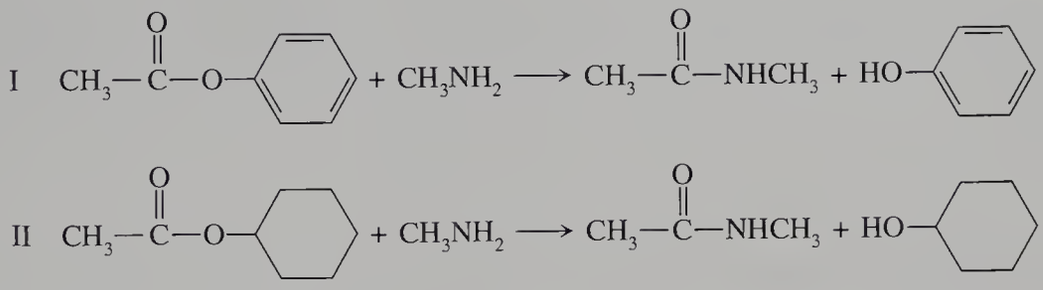
(d) 

22.25 Explain the position of the following equilibrium.



$K \approx 50$

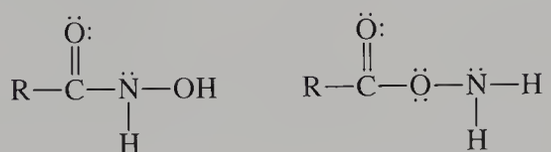
22.26 Which of the following reactions has the more negative ΔG°_{rxn}?



22.27 Explain why the tautomeric equilibrium between an imidic acid and an amide lies on the side of the amide.

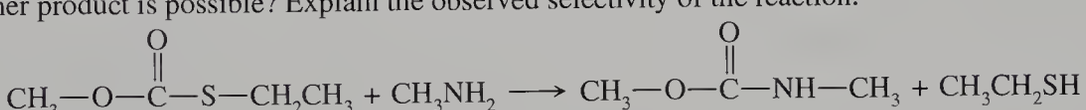
(an imidic acid) (an amide)

22.28 Explain why esters react with hydroxylamine (NH_2OH) to give hydroxamic acids rather than *O*-acyl hydroxylamines.

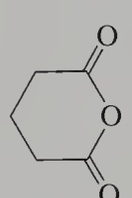


(a hydroxamic acid) (an *O*-acyl hydroxylamine)

22.29 One equivalent of methylamine reacts with *S*-ethyl-*O*-methylthiocarbonate as shown by the following equation. What other product is possible? Explain the observed selectivity of the reaction.

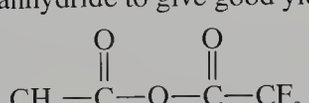


22.30 Methanol reacts with glutaric anhydride to give a good yield of a monomethyl ester. Explain why the diester does not form.

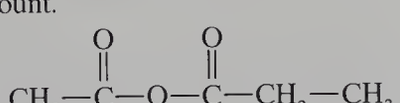


glutaric anhydride

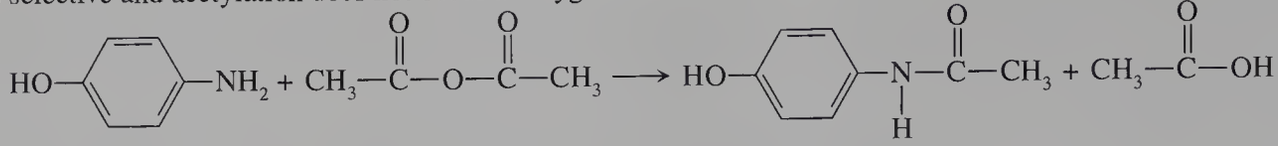
22.31 Alcohols react with the following mixed anhydride to give good yield of acetate esters. Explain why.



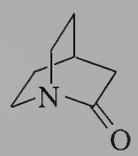
22.32 Ethanol reacts with the following mixed anhydride to give two esters in a 36:64 ratio. Predict which of the two possible esters forms in the larger amount.



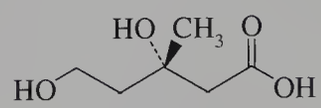
22.33 *p*-Hydroxyaniline reacts with acetic anhydride to give *N*-(4-hydroxyphenyl)acetamide. Explain why the reaction is selective and acetylation does not occur at oxygen.



22.34 Explain why the following bicyclic lactam is hydrolyzed at a significantly faster rate than 5-aminopentanoic acid lactam.

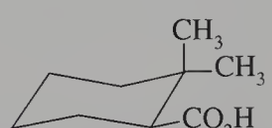


22.35 Mevalonic acid, when heated, readily forms a lactone. Draw two possible structures for the lactone. Which of the two is formed?



mevalonic acid

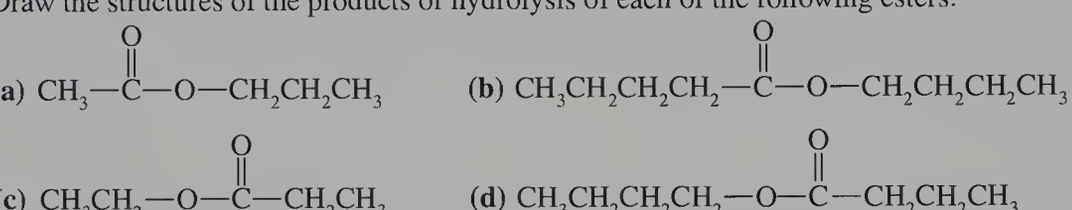
22.36 Explain why the rate of acid-catalyzed esterification of 2,2-dimethylcyclohexanecarboxylic acid is slower than that of cyclohexanecarboxylic acid.



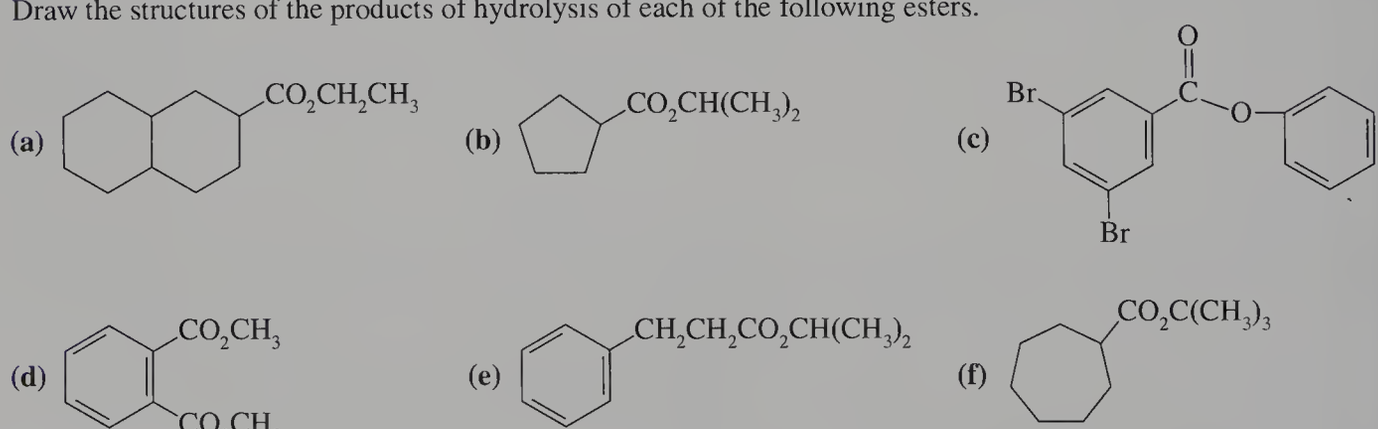
2,2-dimethylcyclohexanecarboxylic acid

Reactions of Acyl Derivatives

22.37 Draw the structures of the products of hydrolysis of each of the following esters.



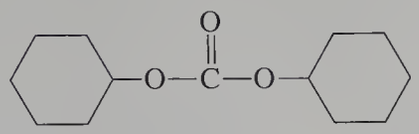
22.38 Draw the structures of the products of hydrolysis of each of the following esters.

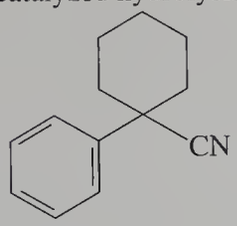


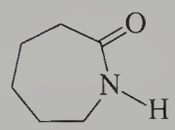
22.39 Hydrolysis of ambrettolide, contained in hibiscus, yields (*E*)-16-hydroxy-7-hexadecenoic acid. Draw the structure of ambrettolide.

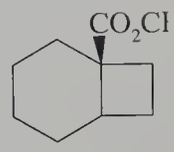
22.40 Hydrolysis of beeswax gives a mixture containing unbranched acids with 26 and 28 carbon atoms and primary unbranched alcohols with 30 and 32 carbons atoms. Draw the structures of all possible components of beeswax.

22.41 Draw the structures of the products of the acid-catalyzed hydrolysis of each of the following compounds.

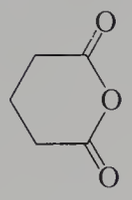
(a) 

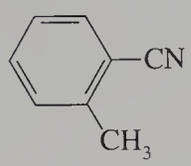
(b) 

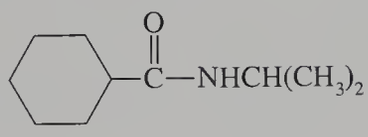
(c) 

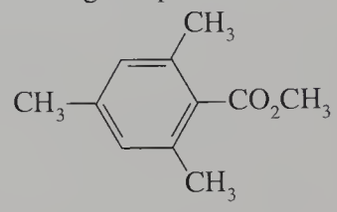
(d) 

22.42 Draw the structures of the products of the acid-catalyzed hydrolysis of each of the following compounds.

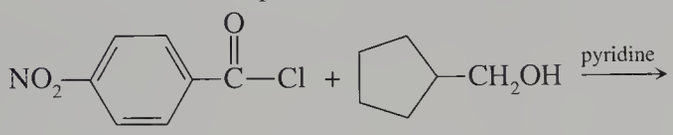
(a) 

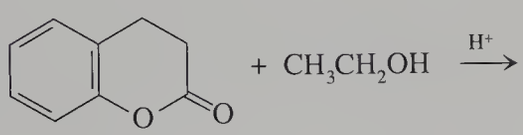
(b) 

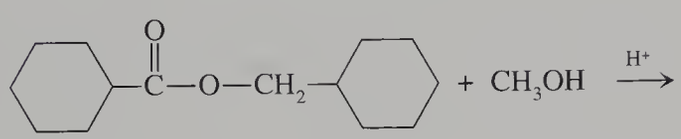
(c) 

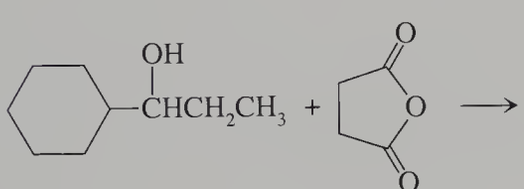
(d) 

22.43 Draw the structure of the product of each of the following reactions.

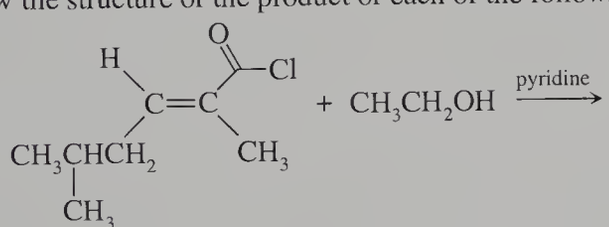
(a) 

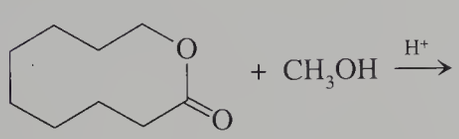
(b) 

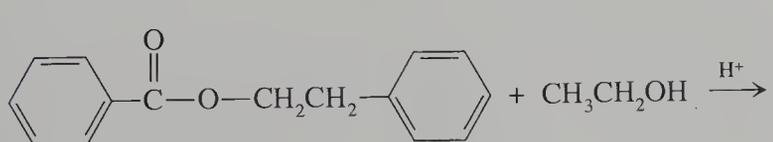
(c) 

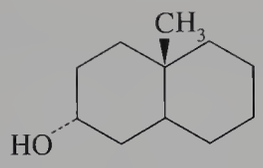
(d) 

22.44 Draw the structure of the product of each of the following reactions.

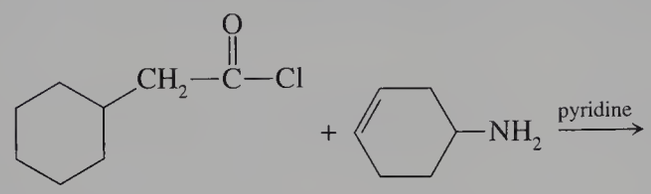
(a) 

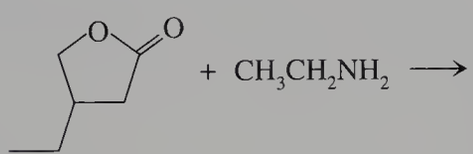
(b) 

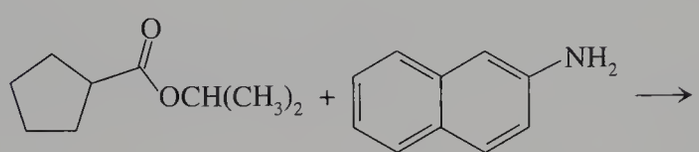
(c) 

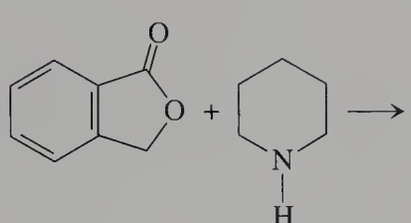
(d)  + $(CH_3CO)_2O$ ⟶

22.45 Draw the structure of the product of each of the following reactions.

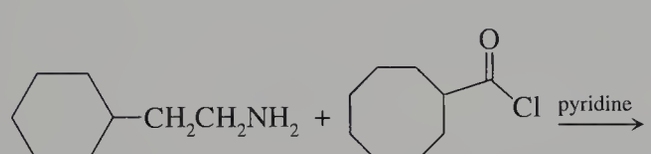
(a) 

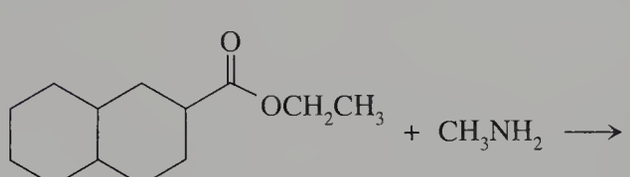
(b) 

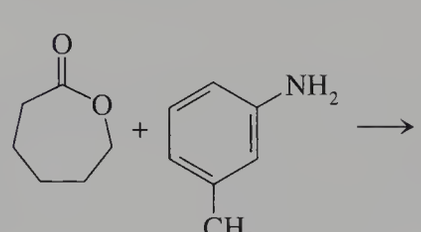
(c) 

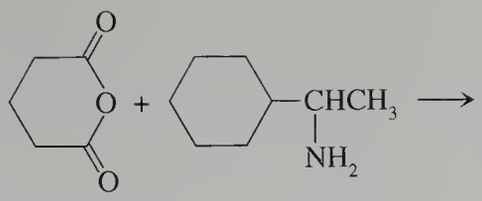
(d) 

22.46 Draw the structure of the product of each of the following reactions.

(a) 

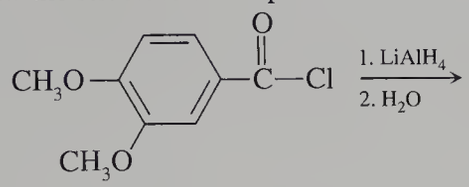
(b) 

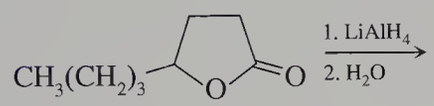
(c) 

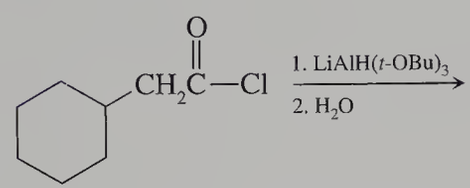
(d) 

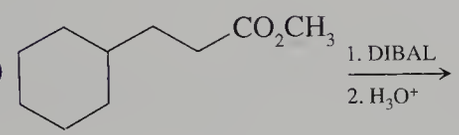
Reduction of Acyl Derivatives

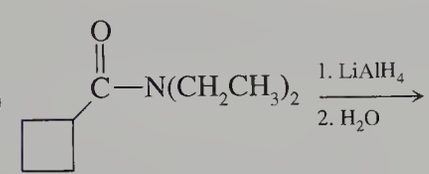
22.47 Draw the structure of the product of each of the following reactions.

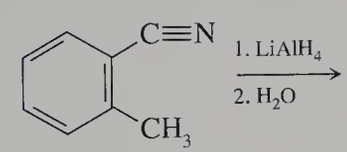
(a) 

(b) 

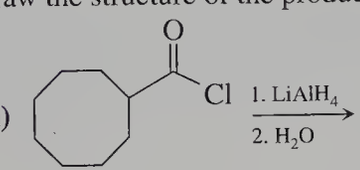
(c) 

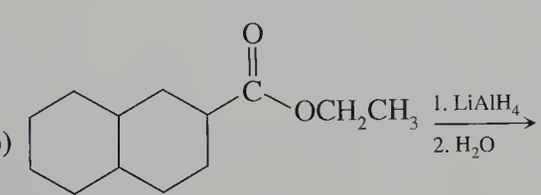
(d) 

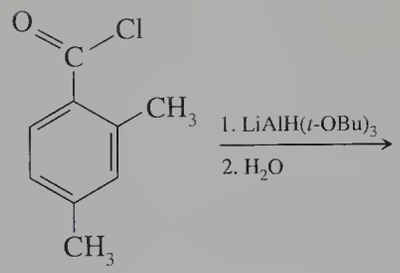
(e) 

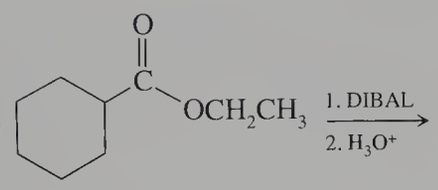
(f) 

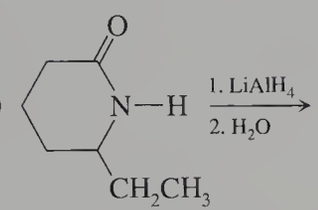
22.48 Draw the structure of the product of each of the following reactions.

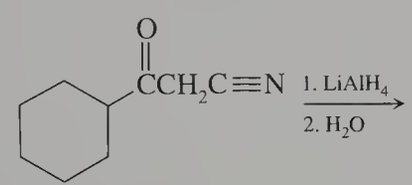
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

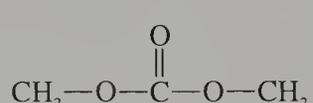
22.49 A compound obtained from the wax of the sperm whale has the molecular formula $C_{32}H_{64}O_2$. Reduction by $LiAlH_4$ gives 1-hexadecanol. Draw the structure of the compound.

22.50 A compound obtained from hibiscus has the molecular formula $C_{16}H_{28}O_2$. Reduction by $LiAlH_4$ gives (*E*)-7-hexadecen-1,16-diol. Draw the structures of two possible compounds that could yield this diol.

Reactions with Organometallic Compounds

22.51 What ester is required to produce alcohols of the general structure R_2CHOH using a Grignard reagent?

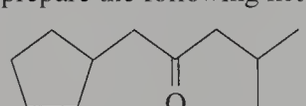
22.52 Dimethyl carbonate reacts with Grignard reagents to give tertiary alcohols with the general structure R_3COH. Write the structures of the intermediates formed after the addition of one and two moles of the Grignard reagent, respectively.



dimethyl carbonate

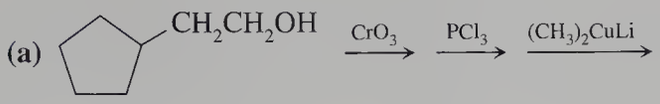
22.53 Butanoyl chloride reacts at −78 °C with one equivalent of the Grignard reagent derived from 1-iodopropane in THF to give 4-heptanone. Why doesn't a second equivalent of the Grignard reagent react?

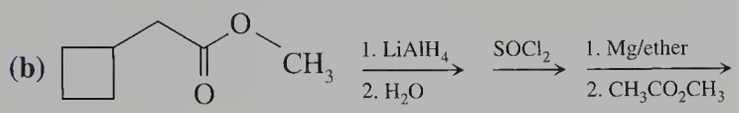
22.54 Suggest two possible synthetic routes to prepare the following ketone using a lithium dialkylcuprate.

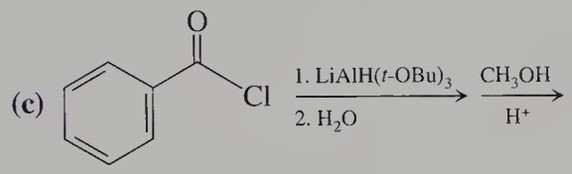


Multistep Synthesis

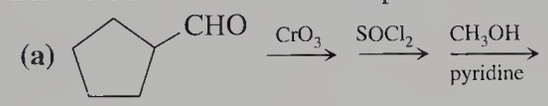
22.55 Draw the structure of the final product of each of the following sequences of reactions.

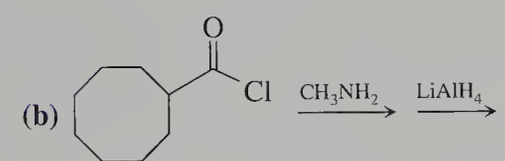
(a) 

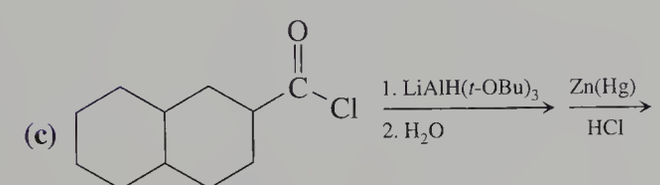
(b) 

(c) 

22.56 Draw the structure of the final product of each of the following sequences of reactions.

(a) 

(b) 

(c) 

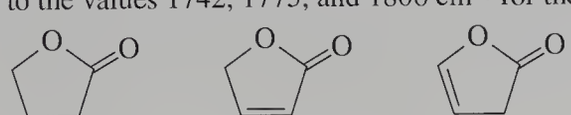
Spectroscopy of Acid Derivatives

22.57 Would you expect the carbonyl stretching absorption of acyl bromides to occur at higher or lower wavenumber than the carbonyl stretching absorption of acyl chlorides?

22.58 Explain why the carbonyl stretching absorption of thioesters occurs at 1690 cm^{-1}, whereas that of acyl chlorides occurs at 1800 cm^{-1}.

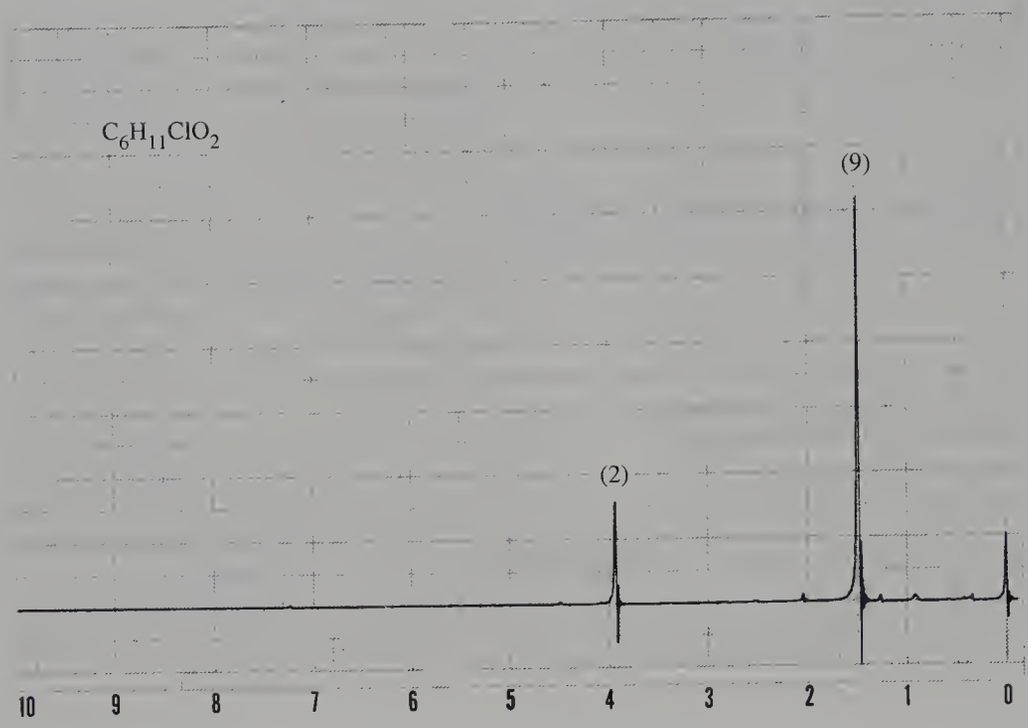
22.59 A compound with molecular formula C_4H_5N has a strong absorption at 2250 cm^{-1}. Suggest two possible structures and explain how they could be distinguished by other infrared absorptions.

22.60 Match the following structures to the values 1742, 1775, and 1806 cm^{-1} for the carbonyl stretching absorptions.

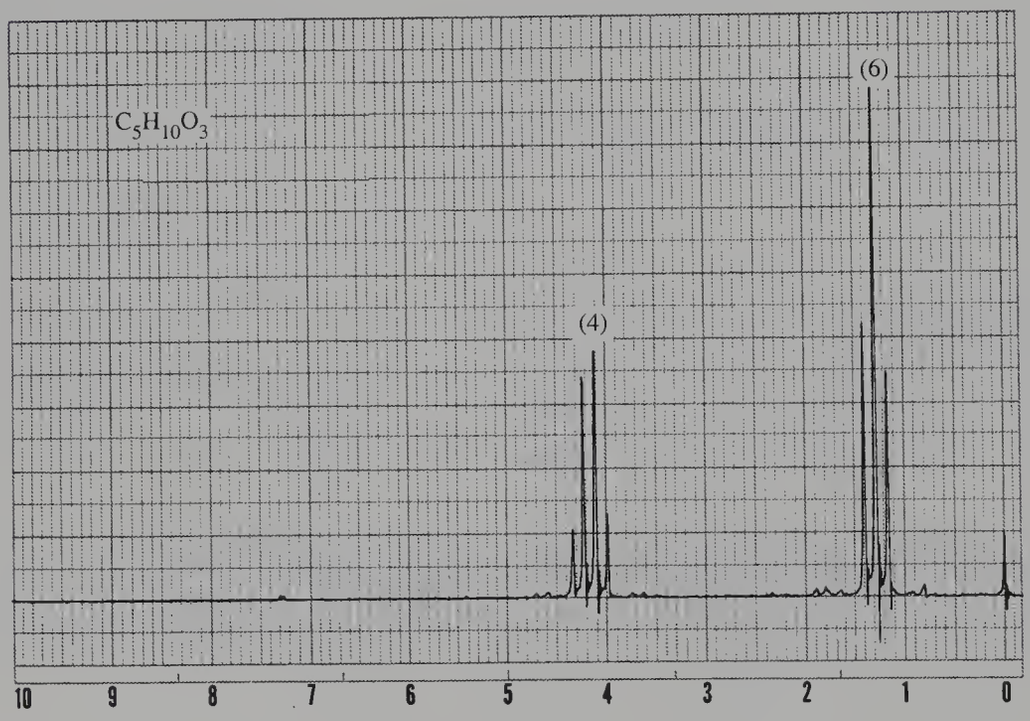


22.61 Deduce the structure of each of the following esters based on the molecular formula and the hydrogen NMR spectrum.

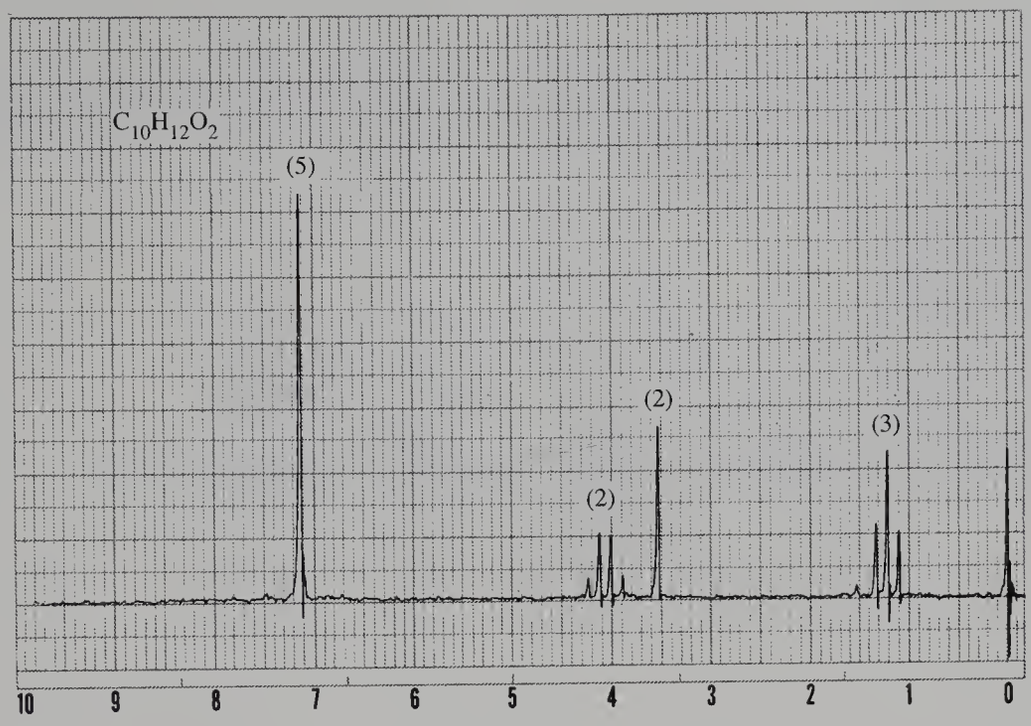
(a) $C_6H_{11}ClO_2$



(b) $C_5H_{10}O_3$

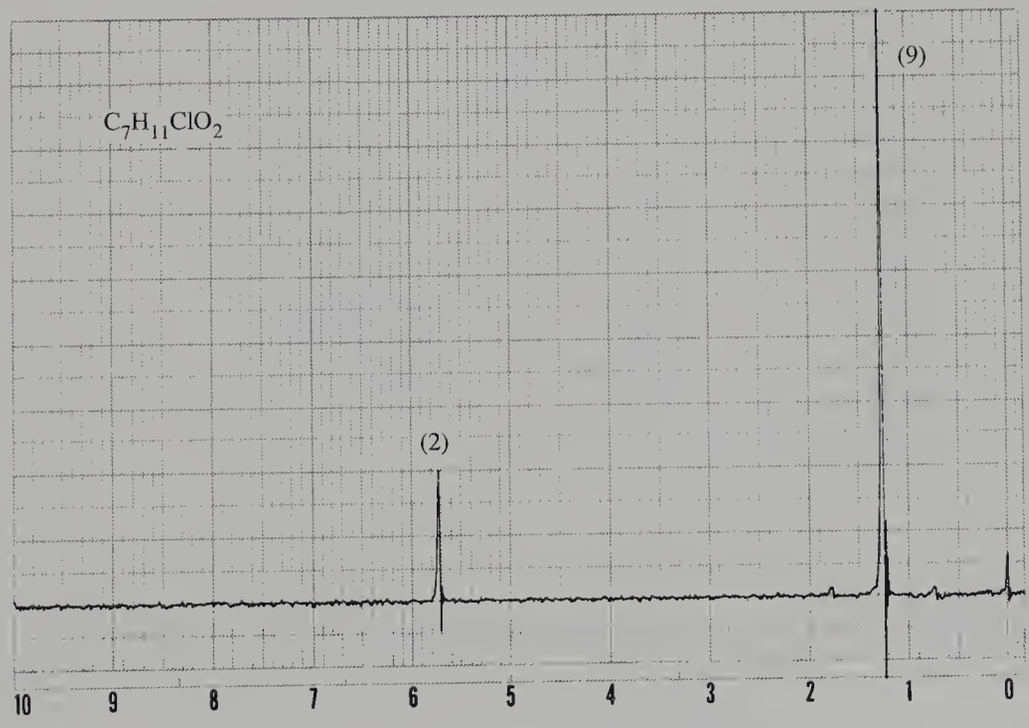


(c) $C_{10}H_{12}O_2$

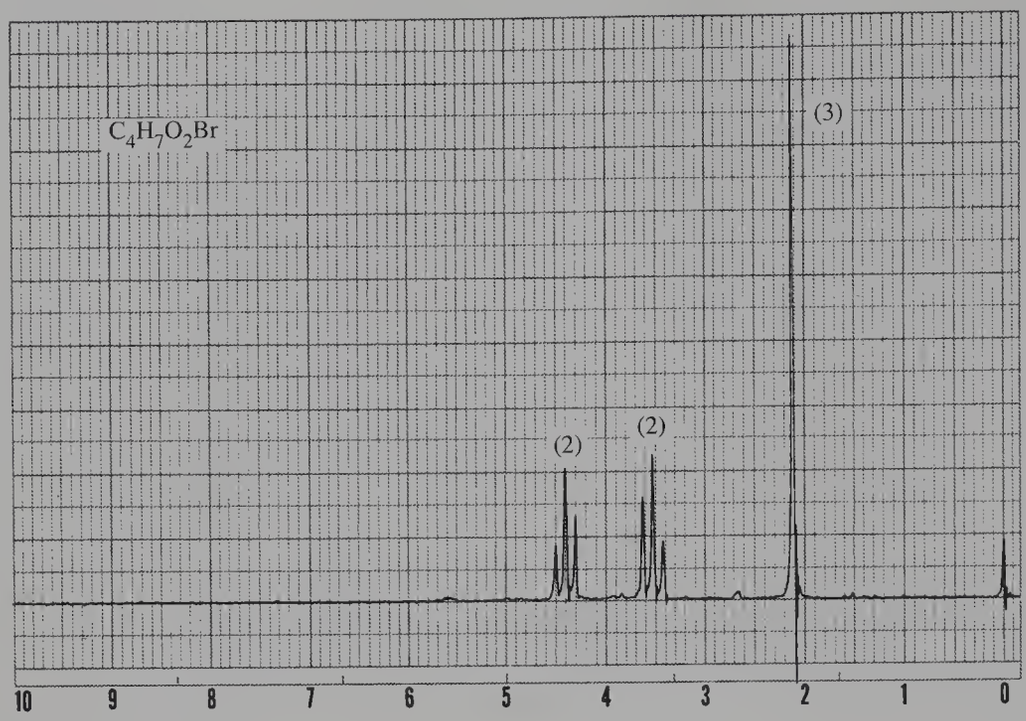


22.62 Deduce the structure of each of the following esters based on the molecular formula and the hydrogen NMR spectrum.

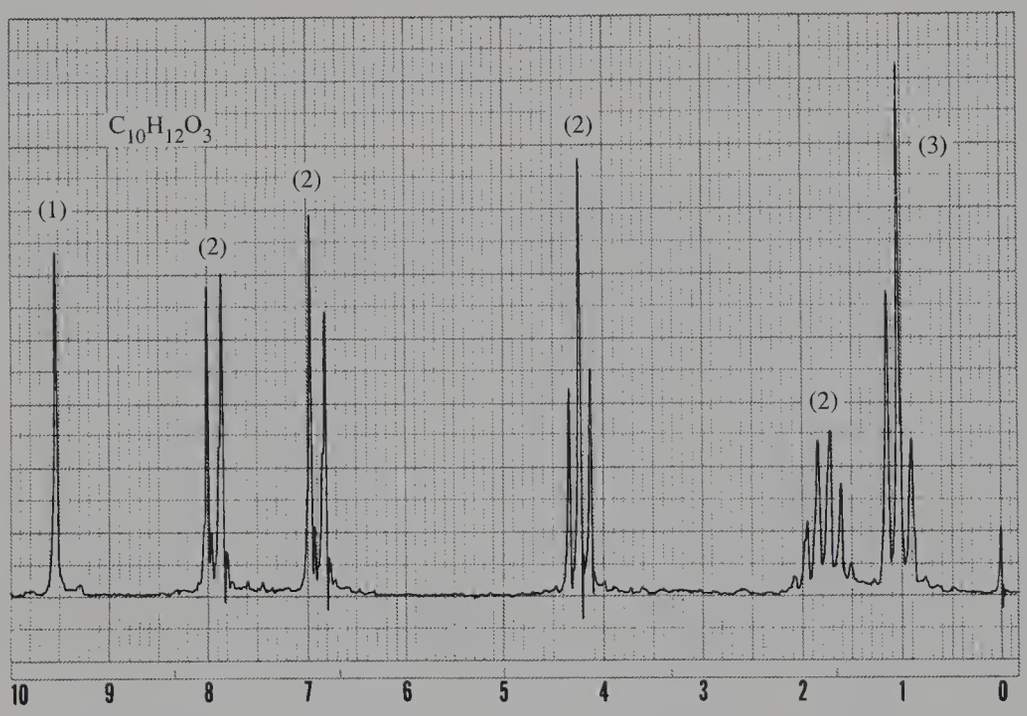
(a) $C_7H_{11}ClO_2$



(**b**) $C_4H_7O_2Br$



(**c**) $C_{10}H_{12}O_3$



22.63 Deduce the structure of each of the following compounds given the molecular formula and the absorptions for the carbon NMR specturm.

(**a**) $C_6H_{12}O_2$; 27.3 ppm (quartet), 38.7 ppm (singlet), 51.5 ppm (quartet), 178.8 ppm (singlet)

(**b**) $C_5H_8O_2$; 19.1 ppm (triplet), 22.7 ppm (triplet), 29.9 ppm (triplet), 69.4 ppm (triplet), 171.2 ppm (singlet)

(**c**) $C_9H_{10}O_2$; 20.7 ppm (triplet), 66.1 ppm (quartet), 128.1 ppm (singlet), 128.4 ppm (doublet), 128.8 ppm (doublet), 136.1 ppm (doublet), 170.6 ppm (singlet)

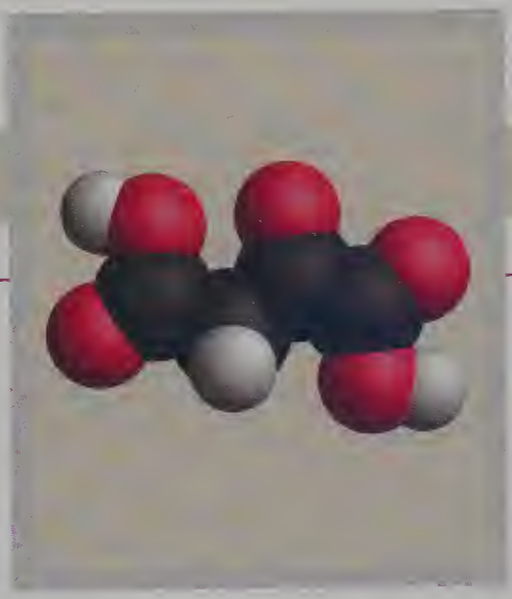
22.64 Deduce the structure of each of the following compounds given the molecular formula and the absorptions for the carbon NMR specturm.

(**a**) $C_6H_{12}O_2$; 9.4 ppm (quartet), 16.8 ppm (quartet), 27.6 ppm (triplet), 41.4 ppm (doublet), 51.1 ppm (quartet), 176.2 ppm (singlet)

(**b**) $C_6H_{10}O_2$; 18.4 ppm (triplet), 25.2 ppm (triplet), 37.9 ppm (doublet), 51.4 ppm (quartet), 175.7 ppm (singlet)

(**c**) $C_7H_{14}O_2$; 14.2 ppm (quartet), 27.2 ppm (quartet), 38.7 ppm (singlet) 60.2 ppm (quartet), 178.4 ppm (singlet)

23



Enols and Enolates—Condensation Reactions

23.1 Synthesis and Retrosynthesis

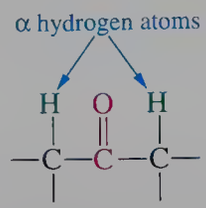
One of the goals of organic chemistry is to synthesize new compounds having properties that either duplicate or improve on naturally occurring compounds. To synthesize these compounds, which often have very complex structures, we have to use reactions that build "large" molecules from "small" molecules. Although the interconversion of functional groups plays a role in synthesis, those reactions that form new carbon–carbon bonds and extend the carbon skeleton are of greater interest. Methods of carbon–carbon bond formation discussed earlier in this text include the alkylation of alkynides and the addition of Grignard reagents to carbonyl carbon atoms. In this chapter we first explore the chemistry of the enolates of aldehydes and ketones, which react at the α carbon atom to give condensation products. Then we examine a larger number of similar reactions of the enolates of esters.

Before we add groups of reactions to the list of carbon–carbon bond-forming processes, let's consider the philosophy of designing synthetic sequences. Rather than considering all of the possible known reactions and reagents that are available for synthesis, we think "backwards" and consider the most logical precursor that could give the desired product in the last step. Then we consider how that precursor could be made. Working backwards is called **retrosynthesis**. This method is more efficient than planning a synthesis in a forward direction because there are many known combinations of reactions of small molecules, only a few which may lead to the desired product. Focusing on the number of options that can be used to make the final product in the "last" step concentrates our thinking and is ultimately more productive.

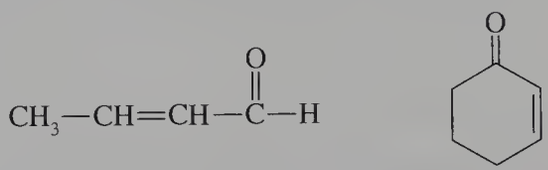
The focus in retrosynthetic analysis is on the carbon–carbon bonds in the molecule that might be formed by reactions that occur in good yield. There may be several sites, but some appear better than others based on the known facts of specific reactions. To think retrosynthetically you should learn reactions not only in the forward sense of converting a reactant to a product but in the reverse sense as well. In other words, the structural features of the product provide a clue for how the method could be used to synthesize other desirable products. In this chapter we will greatly extend our knowledge of reactions that can be used to form carbon–carbon bonds. Many of these reactions give products that also can be converted into more complex products by forming additional carbon–carbon bonds.

23.2 The α Carbon Atom of Carbonyl Compounds

In Chapters 18 and 19, we considered the reactivity of the carbonyl group itself. In this chapter we extend our discussion of carbonyl compounds to the carbon atom adjacent to the carbonyl carbon atom, the α carbon atom. The α carbon atom can also act as a reactive site in a carbonyl compound. It is bonded to hydrogen atoms, called α hydrogen atoms, removal of which gives a nucleophilic α carbon atom.



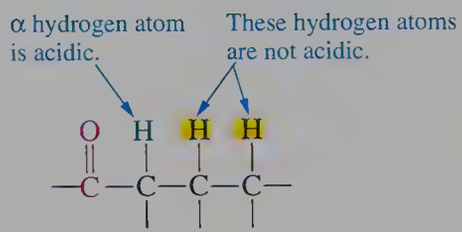
We will also consider unsaturated carbonyl compounds in which a carbon–carbon double bond and the carbonyl group are conjugated. These compounds, known as α,β-unsaturated carbonyl compounds, react in a special way that we can anticipate from our studies of conjugated alkenes (Chapter 12).



α,β-unsaturated aldehyde α,β-unsaturated ketone

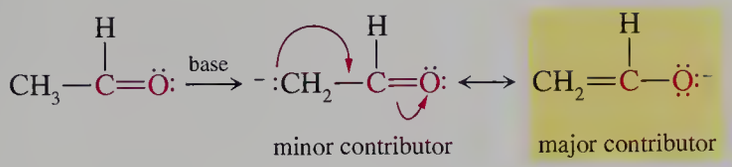
Acidity of α Hydrogen Atoms

We know that the carbonyl carbon atom has a partial positive charge, which is represented in its dipolar resonance form. This partial positive charge decreases the electron density in neighboring bonds by an inductive effect. Loss of some electron density at the α carbon atom results in a partial positive charge at that carbon atom, and the effect spreads to the C—H bonds of the α carbon atom. As a result, an α hydrogen atom is more acidic than the hydrogen atoms farther removed from the carbonyl group.



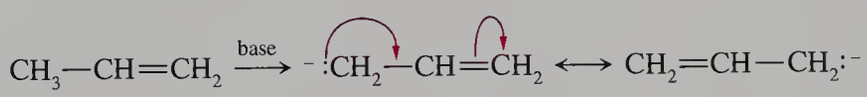
The pK_a values of acetaldehyde and acetone are 16.7 and 19, respectively. These values mean that the α hydrogen atom is over 10^{30} times more acidic than the C—H bond of alkanes, whose pK_a values are approximately 50. This tremendous difference in pK_a results from more than the inductive effect of the carbonyl group. When a carbonyl compound loses its α hydrogen atom in an acid–base reaction, the resulting anion is resonance stabilized. The resonance-stabilized anion is called an **enolate ion**. One of its contributing resonance structures has a negative charge on the oxygen atom and the other has a negative charge on the α carbon atom. Because the charge on the

anion is delocalized, an enolate anion is more stable than a carbanion, such as $CH_3CH_2^-$, in which no such resonance stabilization is possible.



resonance forms of enolate ion of acetaldehyde

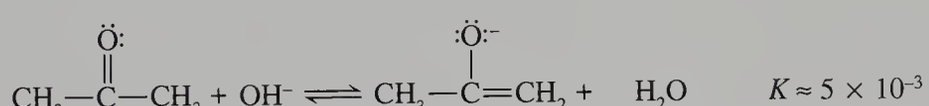
We note that the major resonance form of the enolate ion carries a negative charge on the more electronegative oxygen atom. This form contributes strongly to the stability of enolate anion, the conjugate base of the carbonyl compound. We can appreciate the significance of this stabilization by comparing the acidity of acetaldehyde to that of propene. The allylic hydrogen atom of propene has a pK_a of 42, only about 10^8 times more acidic than an alkane. Resonance stabilization of the allyl anion accounts for the greater acidity, but neither resonance form tolerates a negative charge as well as the oxygen atom of the enolate ion.



equal contributors

Formation of Enolates

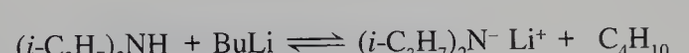
Now let's consider the strength of the base required to produce an enolate anion from a carbonyl compound. The strongest base that can exist in aqueous solution is the hydroxide ion. Because the pK_a of water is 15.7 and the pK_a of acetone is 19, the amount of the enolate anion of acetone that can form in a 1 M NaOH solution is very small. Although the concentration of enolate is low, it may be sufficient for some reactions. As the enolate reacts, more enolate forms, maintaining the equilibrium.



$pK_a = 19$ enolate of acetone $pK_a = 15.7$

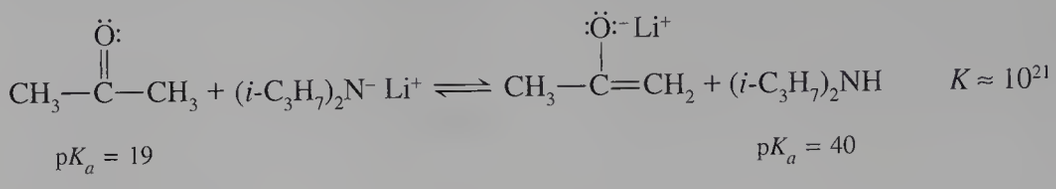
$$K = \frac{[\text{enolate}]\,[H^+]}{[\text{acetone}]} \times \frac{[H_2O]}{[H^+]\,[OH^-]} = \frac{10^{-19}}{2 \times 10^{-16}} = 5 \times 10^{-3}$$

If acetone is treated with the conjugate base of a much weaker acid than acetone, the enolate forms in high concentrations. Lithium diisopropylamide, $(i\text{-}C_3H_7)_2N^-\,Li^+$, commonly abbreviated as LDA, is such a base, prepared from diisopropylamine and butyllithium in ether as a solvent.



$pK_a = 40$ $pK_a = 50$

The enolate is produced in a stoichiometric amount when LDA is used as the base because diisopropylamine is a much weaker base than acetone.

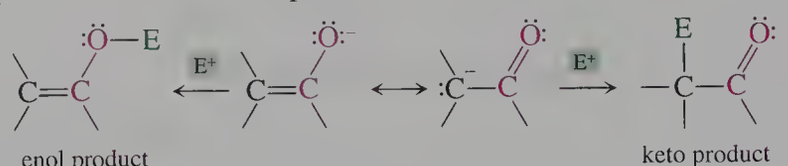


$$K = \frac{[\text{enolate}]}{[\text{acetone}]} \times \frac{[(i\text{-}C_3H_7)_2NH]}{[(i\text{-}C_3H_7)_2N^- Li^+]} = \frac{10^{-19}}{10^{-40}} \approx 10^{21}$$

Therefore, enolates may be prepared in ether solution and used in subsequent reactions. The only limitation is that the solutions must be protected from moisture or compounds that can transfer a proton to the enolate, which is a strong base.

Reactions of Enolates

The charge in enolates is distributed between two sites—a condition called ambidentate ("two fanged": Latin *ambi*, both + *dens*, tooth)—and reaction of the enolate with an electrophile may occur at either site. We recall that the resonance forms used to depict charge distribution do not exist as independent nucleophilic entities. However, we may use these forms to show how different products result by reaction at each of two sites. Thus, an electrophile can react with the nucleophilic enolate to give two possible isomeric compounds.



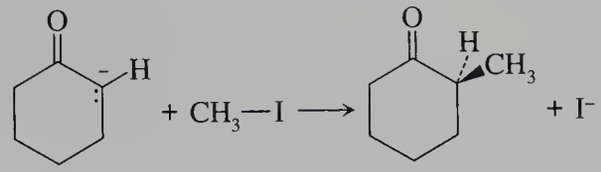
The isomeric products derived by reaction of an enolate are stable enough to isolate in some cases. Many factors determine the relative amounts of these isomers formed. We might be tempted to predict that the enol product would form readily because of the greater electron density on the oxygen atom of the enolate compared to the carbon atom. This occurs when the electrophile is a proton, but the enol product spontaneously rearranges to the isomeric keto form. For most other electrophiles, the keto product forms directly. This preference for the keto product over the enol product reflects the relative energies of the respective transition states leading to each product. Apparently the transition state energies reflect the stabilities of the products formed. So, let's consider the bonds that start to form in the transition state. For the enol isomer, formation of a single bond between oxygen and the electrophile is accompanied by formation of a carbon–carbon double bond. For the keto isomer, formation of a single bond between carbon and the electrophile is accompanied by formation of a carbon–oxygen double bond. The bond energies of C—H and O—H bonds differ, but the energy difference is much less than the difference between the bond energies of C=C and C=O bonds. We recall that the carbon–oxygen double bond is considerably stronger than a carbon–carbon double bond (Section 19.1) The keto isomer forms in preference to the enol isomer mostly because of the stability of the carbonyl group.

Problem 23.1

Draw the expected product of the reaction of the enolate of cyclohexanone with iodomethane. How might the reaction of 2-iodopropane with the same nucleophile differ from the first reaction?

Sample Solution

Both α carbon atoms of cyclohexanone are equivalent and only one enolate can form. The enolate acts as a nucleophile and displaces iodide ion from iodomethane, giving 2-methylcyclohexanone.



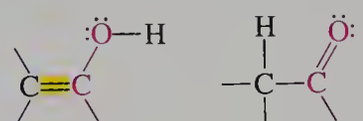
2-Iodopropane is a secondary alkyl halide and strong bases tend to give dehydrohalogenation products rather than substitution products. Propene and cyclohexanone could be the major products of the reaction.

Problem 23.2

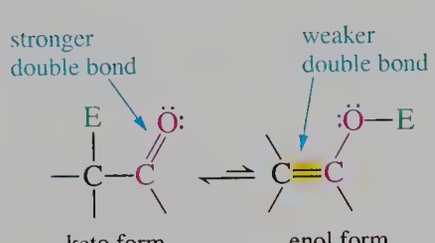
Chlorotrimethylsilane, $(CH_3)_3SiCl$, reacts with enolates to give the enol product with silicon bonded to oxygen. Draw the product of the reaction with the enolate of cyclohexanone. Explain why this product forms rather than the keto product.

23.3 Keto–Enol Equilibria of Aldehydes and Ketones

If the electrophile that reacts with an enolate is a proton, the products are called the keto and enol forms for both aldehydes and ketones. These species are isomers, not resonance forms.



It is not necessary to protonate an enolate to obtain these two isomers. They exist in equilibrium with each other by a proton transfer reaction known as **keto–enol tautomerism**. Tautomerization describes the interconversion of two isomeric structures that differ in the location of a hydrogen atom. Tautomerization requires a change in the kinds of bonds between at least two other sets of atoms in the structures. We encountered this phenomenon in the isomerization reaction of the enol formed in the hydration of an alkyne (Section 11.7). So we know that the keto form is more stable than the enol form. As we saw in the last section, this order of stabilities results primarily from the difference between the bond strengths of a carbon–oxygen double bond and a carbon–carbon double bond.

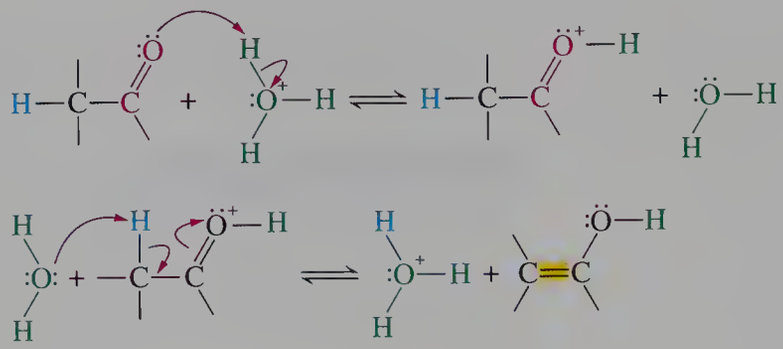


Mechanism of Tautomerization

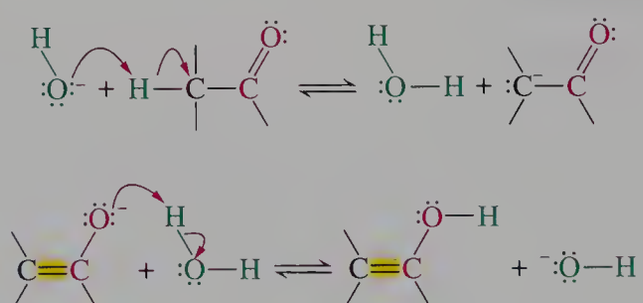
Tautomerization does not occur by the intramolecular transfer of a proton between carbon and oxygen atoms. Rather, a series of proton transfer steps between each

tautomer and the solvent occurs. The solvent acts as a mediator, accepting a proton from one form and giving it to the other form. Either acid or base can catalyze this transfer. Hence, tautomerization occurs by two different mechanisms.

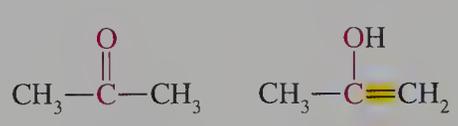
In acid-catalyzed tautomerization of the keto form, the first steps are the protonation of the carbonyl oxygen atom by hydronium ion, followed by deprotonation of the α carbon atom by water. Each of the reactions is reversible, so the acid-catalyzed conversion of the enol into the keto form occurs by the reverse of each step of the mechanism.



In the base-catalyzed tautomerization of the keto form, the first step is deprotonation of the α carbon atom by hydroxide ion, followed by protonation of the oxygen atom by water. Note that the step that forms the enolate shows one resonance form and the second step shows the alternate resonance form. That is the more appropriate form for the "electron pushing" required to write this mechanism.



You should be able to write the keto–enol forms of any aldehyde or ketone whether tautomerization occurs by acid or base catalysis. Move a proton from the α carbon atom to the oxygen atom and rewrite the necessary single and double bonds between carbon and oxygen atoms.



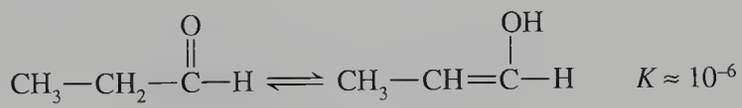
acetone (keto form) propen-2-ol (enol form)

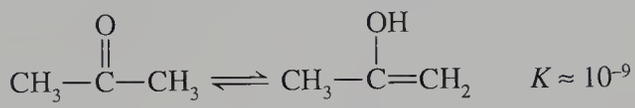
Only one enol form of acetone exists because both α carbon atoms are equivalent. Furthermore, because equivalent atoms are bonded to one of the sp^2-hybridized

carbon atoms of the enol, there are no geometric isomers for acetone. However, the enols of many aldehydes and ketones can exist as geometric isomers.

Stability of Enols

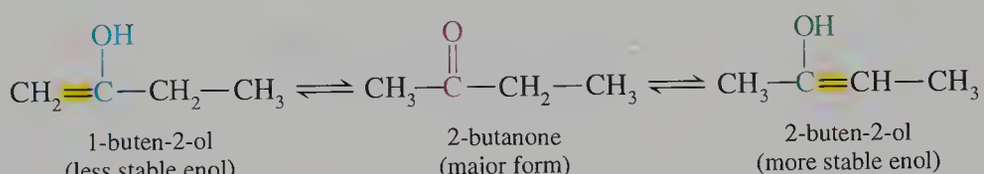
The amount of enol in equilibrium with the carbonyl compound depends on structural factors affecting the stability of both the carbonyl compound and the enol. For example, aldehydes tend to have much higher concentrations of enols than do ketones, as indicated for propanal and propanone.



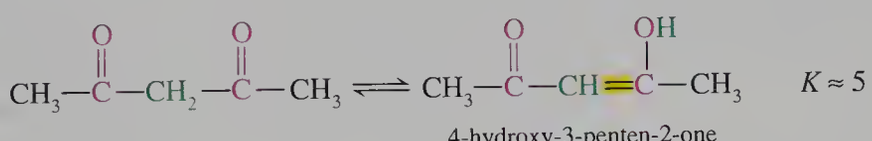


The stability of the carbonyl compound explains this difference in the two equilibrium constants. We recall that a ketone is more stable than an aldehyde because two alkyl groups donate electron density to the carbonyl carbon atom of a ketone.

Now let's consider a case where the stability of the enol affects the concentration of the enol. Only one α carbon atom exists in an aldehyde. However, two α carbon atoms may form enols of a ketone. In general, the relative stabilities of the double bonds of the two enols account for the amount of each enol formed. The enol with the more substituted double bond predominates because alkyl groups stabilize double bonds. However, the concentration of either enol is much smaller than the concentration of the keto form.

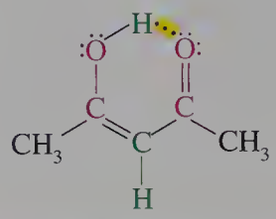


β-Diketones provide a more dramatic demonstration of the effect of stabilization of the double bond has on the concentration of the enol form. The 1,3 arrangement of the carbonyl carbon atoms in these compounds results in a conjugated system in the enol.



We recall that conjugation of two carbon–carbon double bonds of butadiene results in resonance stabilization of approximately 15 kJ mole^{-1} (3.5 kcal mole^{-1}). A similar stabilization is reasonable for a carbon–carbon double bond in conjugation with a carbonyl group. However, a second structural feature further increases the concentration of 4-hydroxy-3-penten-2-one in equilibrium with 2,4-pentanedione. There

is a strong intramolecular hydrogen bond between the enol hydrogen atom and the oxygen atom of the carbonyl group. An intramolecular hydrogen bond can stabilize a structure by approximately 20 kJ mole^{-1} (5 kcal mole^{-1}).



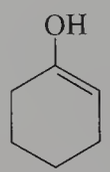
intramolecular hydrogen bond of an enol

Problem 23.3

The equilibrium constant for formation of the enol of cyclohexanone is approximately 10^{-5}. Explain why this value is larger than the equilibrium constant for acetone.

Sample Solution

The carbon–carbon double bond of the enol of cyclohexanone is more highly substituted than the carbon–carbon double bond of the enol of acetone. Thus, the double bond of the enol of cyclohexanone is more stable, and the formation of the enol is more favorable.



enol of cyclohexanone

Problem 23.4

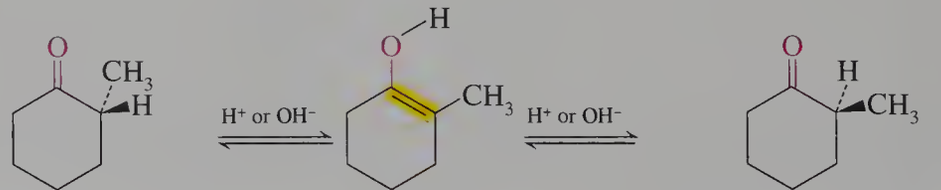
Draw three possible enols for 2-methyl-3-pentanone and describe their relative stabilities.

Problem 23.5

An alternative enol of 2,4-pentanedione can also form an intramolecular hydrogen bond. Draw its structure and explain why it occurs in substantially smaller concentration than 4-hydroxy-3-penten-2-one.

23.4 Consequences of Enolization

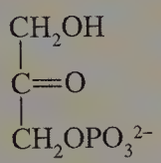
A hydrogen atom located on an α carbon atom can be lost to a solvent molecule and then regained in equilibrium reactions that occur by way of formation of the enol. This hydrogen atom is called an **enolizable hydrogen** atom. If the enolizable hydrogen atom is located at a stereogenic center, formation of the enol destroys the configuration of the center. For this reason, stereocenters located next to a carbonyl group readily racemize in enolization reactions catalyzed by both acid and base. Let's consider the equilibrium for formation of the enol of (*R*)-2-methylcyclohexanone.



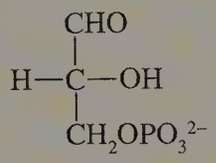
(*R*)-2-methylcyclohexanone achiral enol (*S*)-2-methylcyclohexanone

Tautomerization and Metabolism

Tautomerism is important in the chemistry and metabolism of carbohydrates (Chapter 20). For example, glyceraldehyde 3-phosphate and dihydroxyacetone phosphate are two intermediates produced in the sequence of steps known as glycolysis.

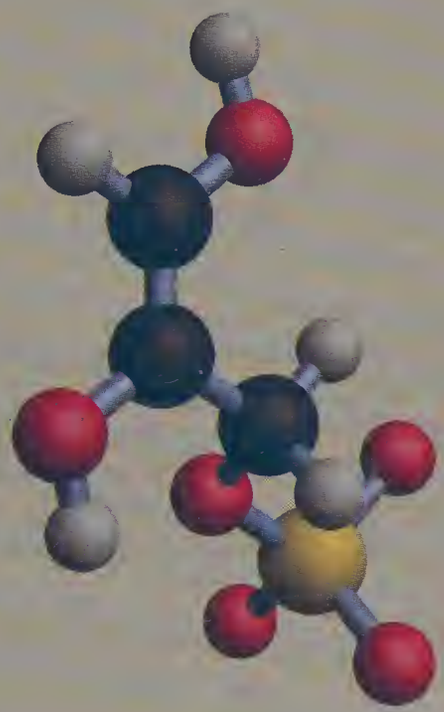


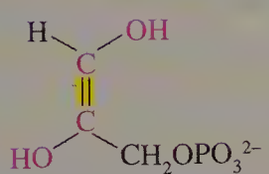
dihydroxyacetone phosphate



glyceraldehyde 3-phosphate

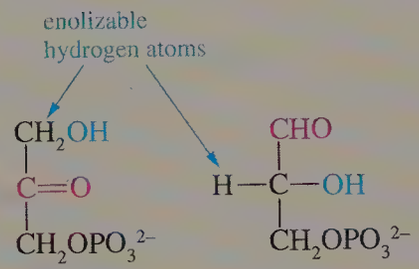
These two compounds are isomers, and they are interconverted enzymatically by way of an **enediol intermediate**. This intermediate is an enol with an extra hydroxyl group located on the α carbon atom of both the ketone and the aldehyde.





an enediol intermediate

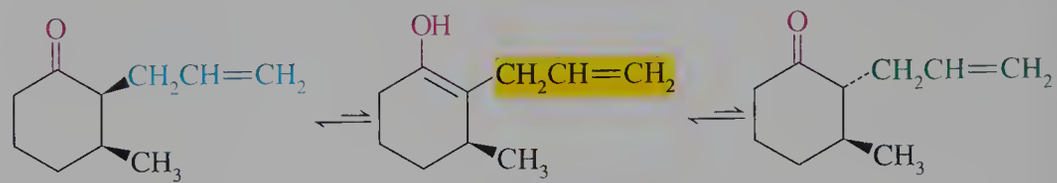
The enediol intermediate is produced from dihydroxyacetone phosphate by transfer of a proton from the α carbon atom bearing the hydroxyl group to water and a transfer of a proton from water to the carbonyl oxygen atom. Similarly, the enediol intermediate is also produced from glyceraldehyde 3-phosphate by transfer of a proton from its α carbon atom to water and a transfer of a proton from water to the carbonyl oxygen atom.



Because dihydroxyacetone phosphate and glyceraldehyde 3-phosphate give a common intermediate, they exist in equilibrium with each other. The enzyme triose phosphate isomerase efficiently catalyzes the isomerization. Although the enediol intermediate is achiral, the enzyme forms only the *R* enantiomer of glyceraldehyde 3-phosphate. In aqueous solution, an acid-catalyzed reaction would yield a racemic mixture of glyceraldehyde 3-phosphate.

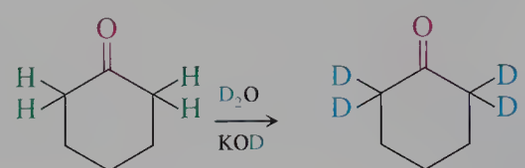
At equilibrium, a mixture contains 96% dihydroxyacetone phosphate because the ketone carbonyl group is more stable than the aldehyde carbonyl group of glyceraldehyde 3-phosphate. Only glyceraldehyde 3-phosphate reacts in subsequent steps of the glycolysis mechanism. However, as it is removed from the equilibrium mixture, more dihydroxyacetone phosphate is converted to glyceraldehyde 3-phosphate. Similar isomerization reactions occur in many enzyme-catalyzed reactions of carbohydrates.

Because there is no stereogenic center in the enol of 2-methylcyclohexanone, the transfer of a proton back to the C-2 atom can occur equally well from either side of the plane of the double bond to give a racemic mixture of enantiomers. If stereogenic centers occur elsewhere in the molecule, the result is an unequal mixture of diastereomers. For example, the enolization of *cis*-2-allyl-3-methylcyclohexanone, which has two stereogenic centers, gives the less sterically hindered trans isomer by way of an enol. In the enol, the C-2 atom is no longer a stereogenic center. The enol can be protonated from either of two sides. However, attack at the top of the ring is not equivalent to attack at the bottom because of a stereogenic center at C-3. Hence, the two isomers do not form in equal amounts.



less stable isomer — enol — more stable isomer

The proton transfer equilibrium between a carbonyl compound and its enol is useful in the synthesis of isotopically labeled aldehydes or ketones. If the carbonyl compound is dissolved in deuterium oxide (heavy water) or in an aprotic solvent containing D_2O, an exchange of α hydrogen atoms with deuterium atoms occurs. Base, in this case OD^-, facilitates the reaction.



cyclohexanone — cyclohexanone-2,2,6,6-d_4

Because an enolate ion intermediate forms, only α hydrogen atoms exchange with deuterium. Although the exchange of deuterium for hydrogen occurs stepwise, deuterium atoms eventually replace all possible enolizable hydrogen atoms. The hydrogen atoms are "lost" in the solvent, which contains deuterium atoms far in excess of the hydrogen atoms transferred from the carbonyl compound. The exchange of hydrogen by deuterium also occurs under acidic conditions. In this case the enol gains a deuterium atom at the α carbon atom from the D_3O^+.

Problem 23.6

Determine whether each of the following chiral compounds may enolize to produce a racemic mixture.

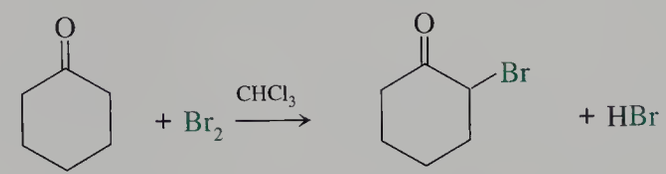
(a) (*R*)-2-ethyl-2-methylcyclopentanone
(b) (*S*)-3-ethylcyclohexanone
(c) (*S*)-3-phenyl-2-butanone

Problem 23.7

Assuming that the number of deuterium atoms incorporated in a molecule can be determined, indicate how 2-methylcyclohexanone and 3-methylcyclohexanone can be distinguished.

23.5 α Halogenation Reactions of Aldehydes and Ketones

Halogens regiospecifically replace one or more of the α hydrogen atoms of aldehydes or ketones. In the case of aldehydes, the aldehydic hydrogen atom, the hydrogen atom directly bonded to the carbonyl carbon atom, is not substituted. The number of halogen atoms incorporated depends on reaction conditions. Chlorine and bromine are most commonly used.



cyclohexanone — 2-bromocyclohexanone

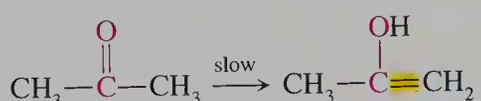
cyclopentanecarbaldehyde — 1-chlorocyclopentanecarbaldehyde

The halogenation reaction can be carried out under either acidic or basic conditions, but not with the same efficiency or experimental results. Under acidic conditions, the reaction can be used to substitute one hydrogen atom without significant complications of multiple substitutions. However, under basic conditions, the reactions occur very much more rapidly, and substitution of a single hydrogen atom is not possible.

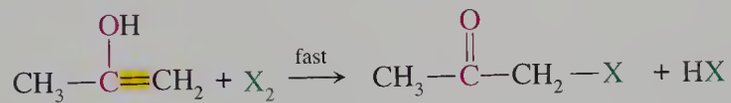
Acid-Catalyzed Halogenation

Very little acid is required for "acidic conditions" because one of the products of the halogenation reaction is an acid that catalyzes the reaction. After the halogen and the ketone are mixed, there is an induction period during which no apparent reaction occurs. However, as the hydrogen halide forms, the reaction becomes autocatalytic and proceeds faster.

Nearly a century ago, chemists determined that the rates of iodination, bromination, and chlorination of acetone are the same. They also found that the reaction is first order in acetone and independent of the concentration of the halogen. A mechanism that explains these data involves formation of an enol in the rate-determining step. The enol reacts with the halogen in a second, more rapid step to give the α-halogenated acetone.



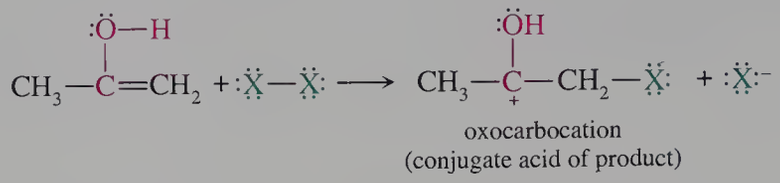
enol of acetone



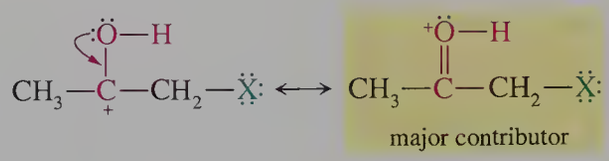
α halogen compound

By studying this mechanism, we can understand why the reaction is autocatalyzed by acid. The formation of an enol in the rate-determining step is an acid-catalyzed re-

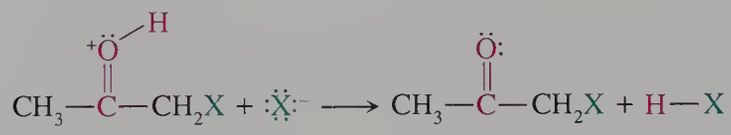
action. Because the acid-catalyzed exchange of deuterium also occurs by way of an enol, the rate of deuterium exchange is identical to the rate of the acid-catalyzed halogenation. The addition of an electrophilic halogen atom to the double bond of the enol is analogous to the addition to alkenes presented in Chapter 7. However, the double bond of an enol is more reactive because the oxygen atom releases electron density by resonance.



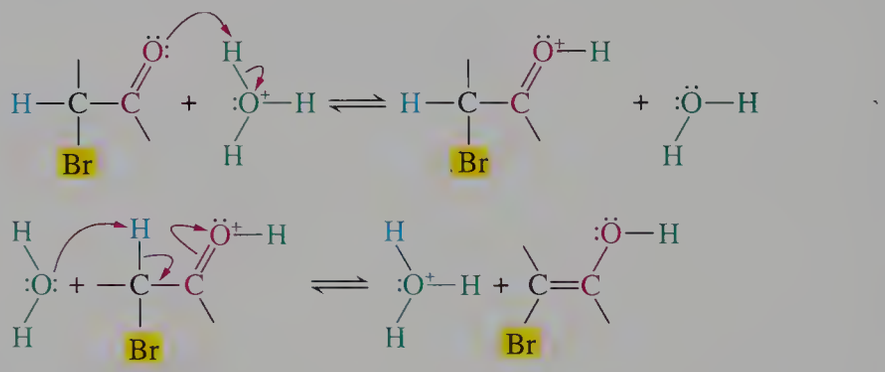
Delocalization of a lone pair of electrons of the oxygen atom resonance-stabilizes the oxocarbocation, a conjugate acid of the product. The protonated carbonyl resonance form is the more important contributor to the structure because the carbon and oxygen atoms both have octets of electrons.



The conjugate acid of the α-halogenated ketone loses a proton to give the product.

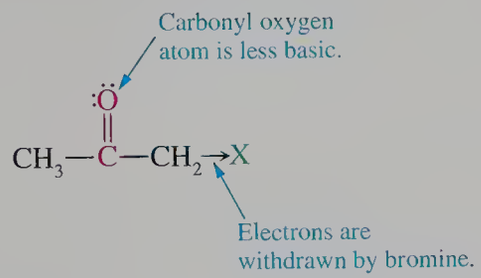


Although multiple halogen substitution for all α hydrogen atoms may occur, a single halogen atom substitution does not occur readily under acidic conditions. The proposed mechanism of the reaction accounts for this observation. Because the reaction rate depends on the rate of formation of the enol, we need only compare this mechanistic step for the monohalogenated ketone to that for the original ketone.

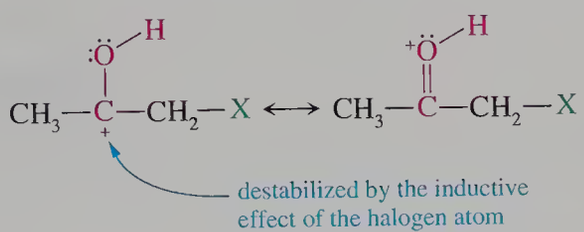


We recall that chlorine and bromine are deactivating groups in electrophilic aromatic substitution because they inductively withdraw electron density, but are ineffective in the donation of electron density by resonance. The same features are important in controlling the rate of subsequent halogenation of a ketone. The bromine

atom withdraws electron density from the carbonyl carbon atom, making the carbonyl oxygen atom less basic. As a consequence, the enol forms more slowly.

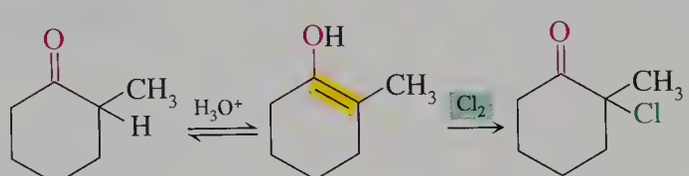


The bromine atom also destabilizes the conjugate acid of the halogenated ketone. This feature also decreases the equilibrium constant for formation of the enol.



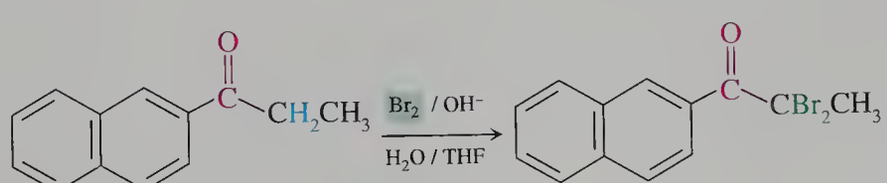
The bromine atom decreases the stability of the ketone and increases the K_a of its conjugate acid. As a result, the reaction of an α-halogenated ketone with a second halogen is retarded. Further halogenation occurs only after the original carbonyl compound has reacted completely.

When the ketone has two nonequivalent α carbon atoms, the acid-catalyzed reaction yields the α haloketone with the halogen on the more substituted atom. We can explain this observation by considering the two enols that can form. The more highly substituted site gives the more highly substituted double bond of the enol. Because halogenation under acidic conditions requires the formation of an enol, the stability of the enol controls the formation of the halogen product.



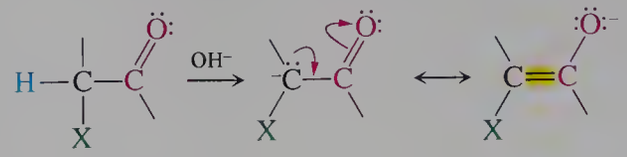
Base-Catalyzed Halogenation

Alpha halogenation of aldehydes and ketones occurs readily under basic conditions and does not stop with the replacement of a single hydrogen atom. All α hydrogen atoms are substituted. This method cannot be used to prepare monohaloketones.



Multiple substitution occurs because the initial α haloketone formed is even more reactive than the original ketone. We can explain this phenomenon by examining the

structure of the enolate formed from the α haloketone and comparing its reactivity to the enolate of the original ketone.

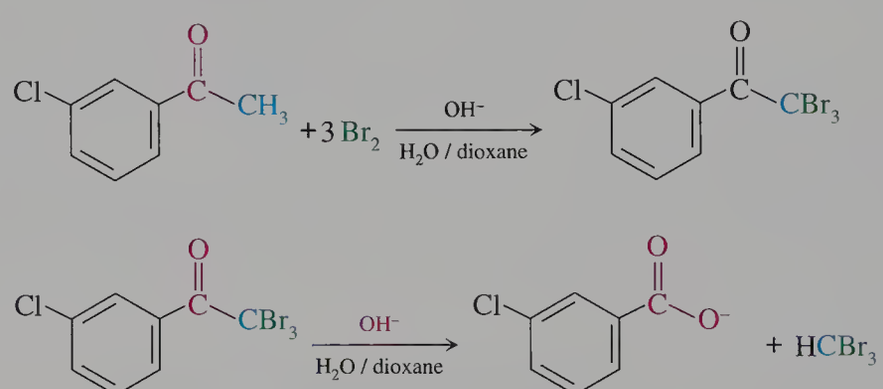


The electron-withdrawing halogen atom stabilizes the enolate ion, increasing the equilibrium constant for formation of this conjugate base of the α haloketone compared to the original ketone. We can also explain the experimental results by considering the inductive effect of the halogen on the acidity of the α hydrogen atom. The halogen draws the bonding electrons of the C—H bond toward carbon, increasing the acidity of the hydrogen atom.

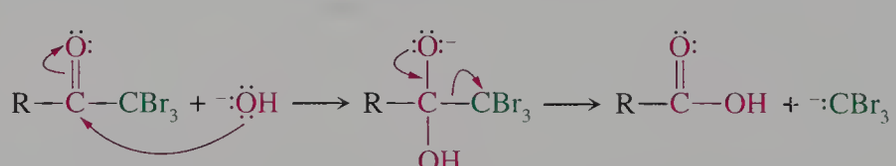
Note that the enhanced reactivity of an α carbon atom caused by the α halogen atom results in multiple substitution at that site, but not at an alternate α carbon atom, until the first site is fully halogenated. Therefore 2,2-dibromo-3-pentanone forms faster than 2,4-dibromo-3-pentanone. When the two α hydrogen atoms are nonequivalent, the more acidic hydrogen determines the site of the first halogenation. The acidity of C—H bonds decreases in the order 1° > 2° > 3°.

The Haloform Reaction

When a methyl ketone is halogenated in basic solution, the halogen replaces all three α hydrogen atoms. This trihaloketone reacts further, resulting in the cleavage of a carbon–carbon bond. After acidification, the products are a carboxylic acid and a trihalomethane known as a **haloform**. For chlorine, bromine, and iodine, the haloforms are chloroform, bromoform, and iodoform, respectively.



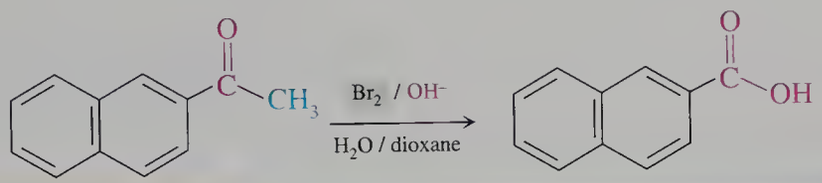
The cleavage of the carbon–carbon bond occurs by way of a two-step mechanism in which hydroxide ion attacks the carbonyl carbon atom to give a tetrahedral intermediate that subsequently releases the tribromomethyl carbanion.



Under basic conditions, the carboxylic acid product shown exists as an anion. However, after neutralization in the workup of the reaction mixture, the products are a carboxylic acid and $CHBr_3$.

The haloform reaction is used in two ways. First, it serves as a qualitative test

to identify methyl ketones. If iodine is used, iodoform forms. Because this compound is a bright yellow, insoluble solid, its appearance indicates that the carbonyl compound was a methyl ketone. The haloform reaction also can be used as a synthetic method to prepare carboxylic acids.



Problem 23.8

Which of the following compounds will give a positive iodoform test?

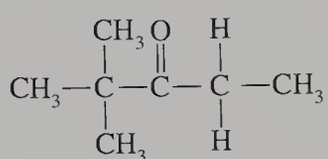
(a) 3-pentanone (b) 2-pentanone
(c) 2-methyl-3-pentanone (d) 2-methylcyclohexanone

Problem 23.9

Write the product of the reaction of bromine with 2,2-dimethyl-3-pentanone under acidic conditions as well as under basic conditions.

Sample Solution

Only one of the two α carbon atoms has hydrogen atoms that may be replaced by a halogen atom.



Under acidic conditions, one bromine atom replaces a hydrogen atom at C-4 to give 2-bromo-4,4-dimethyl-3-pentanone. Under basic conditions the reaction continues to replace the second hydrogen atom faster than the first and a dibromo compound is obtained.

Problem 23.10

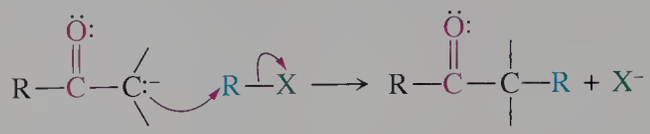
Recalling the structural factors that affect the stability of the enol, predict the product of the reaction of 3-methyl-2-butanone with bromine under acidic conditions.

23.6 Alkylation of Enolate Ions

We recall that many nucleophiles displace leaving groups from primary alkyl halides by an S_N2 mechanism (Section 10.3). A similar reaction occurs with secondary alkyl halides, but competitive elimination reactions also occur. Primary alkyl halides react with carbanions, such as the alkynide ion, by an S_N2 mechanism. (Secondary alkyl halides react in displacement reactions, but also in elimination reactions because the alkynide ion is a strong base). The reaction of a nucleophilic carbon atom with an electrophilic carbon atom of a second species is one of the most important reactions in organic chemistry because it results in formation of a carbon–carbon bond. We now extend our repertoire of these reactions by using enolates as the nucleophile and linking them to an electrophilic carbon atom.

An enolate is a nucleophile that can displace a leaving group from a primary alkyl halide. The carbon atom of an alkyl halide is electrophilic because the electronegative halogen removes electron density. Although the enolate has two sites of reactivity, we have already learned that reaction of an electrophile with an enolate

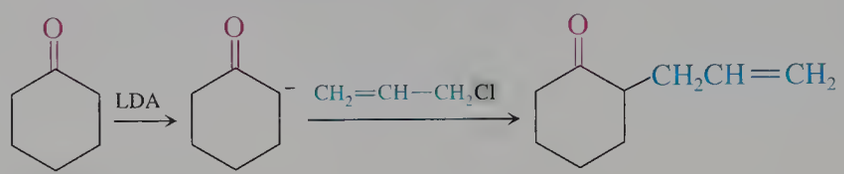
usually occurs at the α carbon atom to give a substituted keto product called the C-alkylated product. The alternate reaction at oxygen to give an O-alkylated product is much less common.



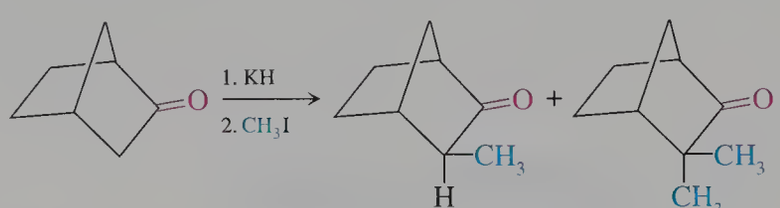
C-alkylated product

We recall that hydroxide ion is not basic enough to form an enolate ion in high concentration. The alkoxide bases also cannot provide a high concentration of the enolate ion. Because the enolate ion is not the predominant basic species in solution, the hydroxide ion or alkoxide ion would substitute for the leaving group and give an alcohol or ether, respectively.

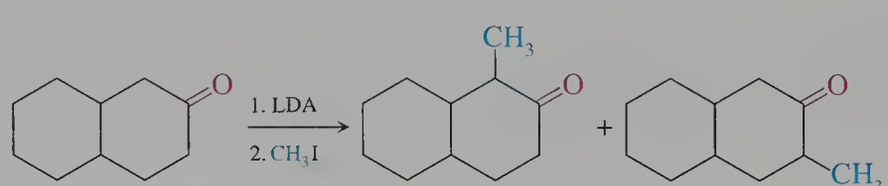
Strong bases, such as potassium hydride or LDA, are used to obtain stoichiometric quantities of enolates. Then an alkyl halide is added to the solution of the enolate.



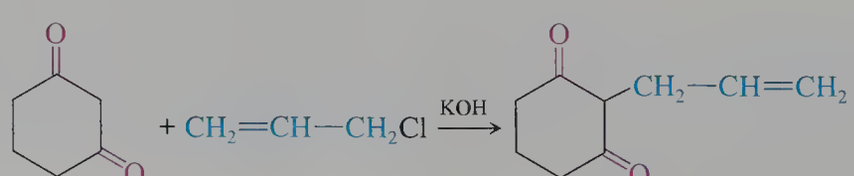
Dialkylation can occur because an enolate of the monoalkylated product can form by proton transfer from the original enolate. This enolate reacts with the alkyl halide to give the dialkylated product. For example, methylation of bicyclo[2.2.1]heptan-2-one gives a mixture of mono- and dialkylated products.



When the two α hydrogen atoms are nonequivalent, the removal of the more acidic hydrogen atom determines the alkylated product formed. The strong base abstracts the more acidic hydrogen atom. We recall that the acidity of C—H bonds decreases in the order 1° > 2° > 3°. When both α carbon atoms have the same degree of substitution, a mixture of products results.



Alkylation of 1,3-diketones gives excellent yields of product. This reaction does not require a strong base because the two carbonyl groups greatly increase the acidity of the C—H bond located between them.



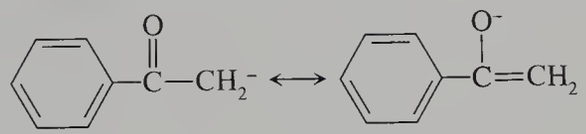
Alkylation of aldehydes is not a useful reaction because side reactions occur in which the nucleophilic enolate attacks the electrophilic carbonyl carbon atom of the aldehyde of another molecule. This reaction does not compete with the alkylation of ketones because ketones are less susceptible to nucleophilic attack at the carbonyl carbon atom.

Problem 23.11

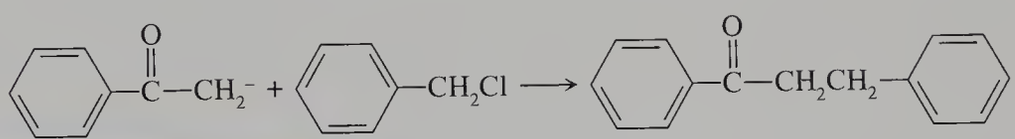
Draw the product of the reaction of acetophenone with KH followed by reaction with benzyl chloride.

Sample Solution

Only one of the two α carbon atoms has bonded hydrogen atoms. Removal of a proton from the methyl group of acetophenone by KH gives a resonance-stabilized enolate.



Benzyl chloride is very reactive in substitution reactions. Displacement of chloride ion by the enolate results in carbon–carbon bond formation.

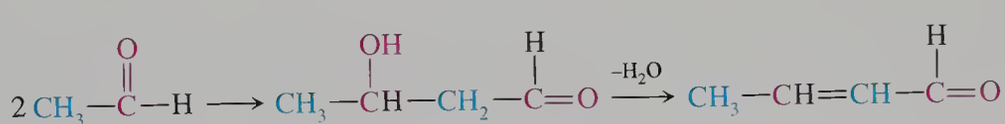


Problem 23.12

Draw the products of the reaction of 2-methylcylopentanone with LDA followed by reaction with allyl chloride.

23.7 The Aldol Condensation of Aldehydes

Two molecules of an aldehyde can join in a reaction called an **aldol condensation**. This base-catalyzed reaction gives a product that is both an aldehyde and an alcohol, called an **aldol**. The aldol can be isolated, but it can also react further to form a conjugated unsaturated carbonyl compound and water.

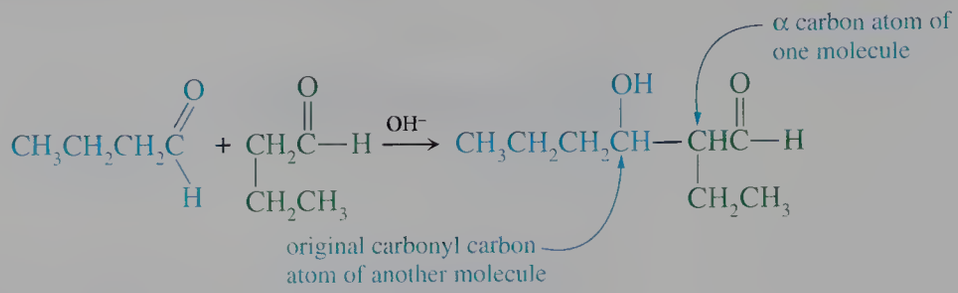


3-hydroxybutanal
(an aldol)

The combination of two molecules to give a larger molecular weight product and a smaller molecule, such as water, is called a condensation reaction. In that sense, only the final unsaturated aldehyde product qualifies as a condensation product. However, the reaction of two carbonyl compounds is often termed a condensation reaction even if the aldol is the major product. We will distinguish between these two reactions by calling the product of the first step an addition product and the product of the second step the condensation product. Specific structural features and experimental conditions favor one product over the other.

In the addition step of an aldol condensation, a new carbon–carbon bond forms between the α carbon atom of one carbonyl compound and the carbonyl carbon atom

of the other. Note that the addition product has just one carbon atom between the aldehyde and alcohol carbon atoms. The aldol product derived from butanal illustrates this relationship.



Thermodynamic Considerations

Both steps of the aldol condensation are reversible. Thus, it is often necessary to manipulate the experimental conditions to drive the reaction toward product. At equilibrium, the conversion of acetaldehyde to its aldol is less than 50%. The equilibrium concentration of the addition product is seldom above 1% for ketones. We can understand why the reaction is easily reversed and the equilibrium concentration of product is so low by analyzing the stoichiometry of the reaction and the number and types of bonds broken and formed.

The addition step is slightly exothermic: $\Delta H^\circ_{rxn} \approx -16$ kJ mole^{-1} (-4 kcal mole^{-1}). The contributions of the bonds formed and broken can be estimated using average bond energies. The addition process can be dissected into formation of C—C, H—O, and C—O bonds and the cleavage of C—H and C=O bonds. From this approximate analysis, we find that the predicted ΔH°_{rxn} is indeed only slightly negative.

	ΔH° (kJ mole^{-1})
break C=O	+745
form C—O	−380
break C—H	+410
form C—C	−360
form O—H	−425
approximate ΔH°_{rxn}	−10

An unfavorable ΔS°_{rxn} counterbalances this favorable contribution of ΔH°_{rxn} to ΔG°_{rxn}. Two molecules combine to give one, resulting in $\Delta S^\circ_{rxn} < 0$. The balance of these two thermodynamic state functions results in an equilibrium constant ≈ 1 for the addition of aldehydes. Because ketones have stronger C=O bonds than aldehydes, the ΔH°_{rxn} is less negative. As a result the ΔG°_{rxn} is positive.

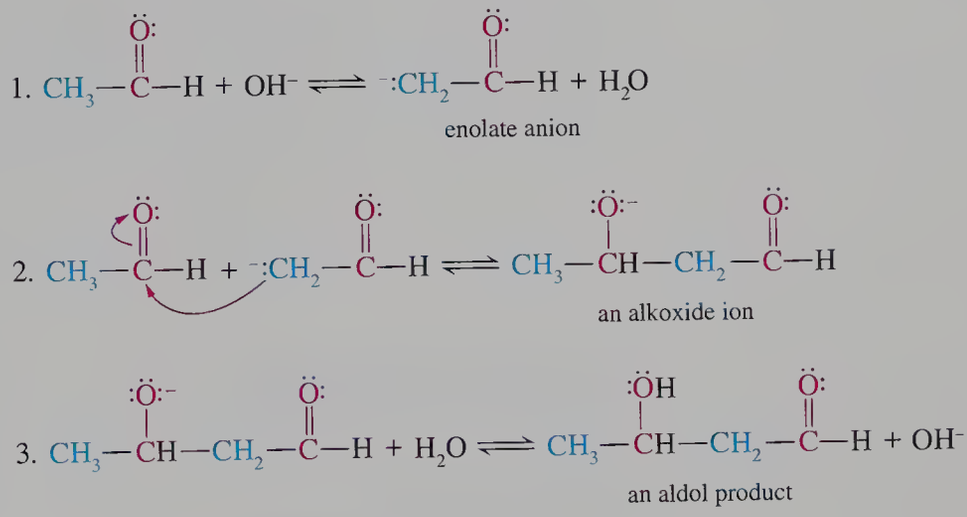
Mechanism of the Addition Reaction

The addition step of the aldol condensation occurs at room temperature when an aldehyde is treated with an aqueous solution of sodium hydroxide. The reaction occurs in a three-step mechanism.

1. One aldehyde molecule reacts with base (OH^-) at its α C—H bond to give a nucleophilic enolate anion.

2. The nucleophilic enolate anion reacts with the carbonyl carbon atom of another aldehyde molecule. The alkoxide ion product is the conjugate base of an aldol.
3. The alkoxide anion extracts a proton from the solvent, water, and regenerates a hydroxide anion.

The sequence of steps is shown for acetaldehyde, but the same reactions occur for any other aldehyde with α hydrogen atoms.



Under the conditions of the reaction, little of the carbonyl compound is converted to the enolate (Section 23.2). An equilibrium occurs between the aldehyde and the enolate so that the enolate is replaced as it reacts. The enolate is present in an excess of aldehyde, so its nucleophilic carbon atom is surrounded by many electrophilic carbon atoms. Note that the hydroxide ion is a catalyst, and its concentration does not change.

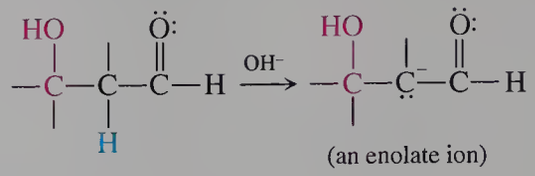
Dehydration of Aldols

If the aldol reaction mixture is heated under basic conditions, the dehydrated product forms. The dehydration of the aldol under basic reaction conditions drives the reaction to completion. Dehydration is mildly exothermic, and ΔS°_{rxn} is positive because a single aldol molecule gives two molecules of product, the unsaturated aldehyde and water. The ΔH°_{rxn} for each step is negative, so the entire reaction is exothermic. The overall ΔS°_{rxn} is approximately zero because the first step has $\Delta S^\circ < 0$, but this is counterbalanced by the second step, which has $\Delta S^\circ > 0$.

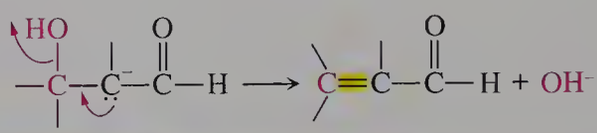
$2\ RCHO \longrightarrow$ aldol	$\Delta H^\circ_{rxn} < 0$	$\Delta S^\circ_{rxn} < 0$
aldol $\longrightarrow$ unsaturated aldehyde + H_2O	$\Delta H^\circ_{rxn} < 0$	$\Delta S^\circ_{rxn} > 0$
$2\ RCHO \longrightarrow$ unsaturated aldehyde + H_2O	$\Delta H^\circ_{rxn} < 0$	$\Delta S^\circ_{rxn} \approx 0$

The aldol may also be isolated and dehydrated like any other alcohol by using a strong acid. The mechanism of acid-catalyzed dehydration of an aldol is exactly like that of alcohols (Section 8.20) and will not be reviewed here. However, the base-catalyzed dehydration that occurs in the aldol reaction is an E2 process that does not occur for simple alcohols. Special structural features account for the dehydration of an aldol by base. First, the base removes an α hydrogen atom to give a resonance-

stabilized enolate ion. This step would not occur for an ordinary alcohol because the C—H bond is not sufficiently acidic.



The hydroxide ion leaves in the second step of this E2 mechanism. This step might be regarded as unusual because we know that the hydroxide ion is not a good leaving group. However, in this case the loss of a hydroxide ion generates a conjugated unsaturated aldehyde. The stabilization associated with the formation of conjugated multiple bonds makes this step exothermic.



Problem 23.13

Draw the product of the aldol condensation of 3-phenylpropanal.

Problem 23.14

A commercial process for the preparation of 1-butanol starts with an aldol condensation of acetaldehyde. Write the additional steps required to produce 1-butanol.

Sample Solution

Under conditions favoring dehydration, the product of the aldol condensation of acetaldehyde is 2-butenal. The desired product, 1-butanol, is more saturated than 2-butenal. Reduction of both the carbonyl group and the carbon–carbon double bond is required. Catalytic hydrogenation is a reasonable second step to simultaneously reduce both unsaturated sites.

Problem 23.15

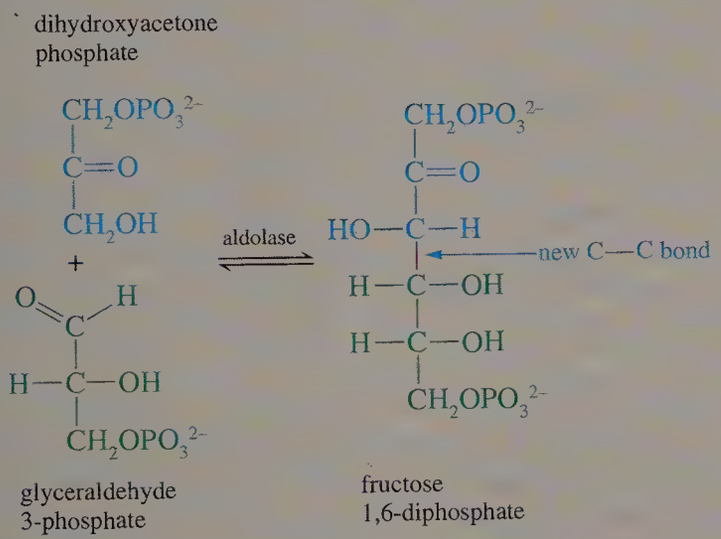
A commercial process to produce the insect repellent 2-ethyl-1,3-hexanediol starts with an aldol condensation. What starting material is used? Write equations for the reactions required to form the diol.

23.8 Mixed Aldol Condensation

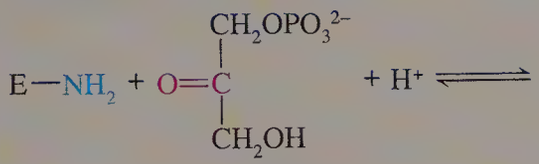
In the aldol condensation reactions we described above, the same aldehyde provided both the enolate and the substrate attacked by the enolate anion. But if two different aldehydes are mixed and heated in a basic solution, the enolate anion of one can react with the carbonyl form of the other. Mixtures of products can result because any two aldehydes can react with each other. Thus, if the aldehydes are A_1 and A_2, aldol condensation can produce A_1A_1, A_2A_2, A_1A_2, and A_2A_1—in short, a dreadful mixture. This unhappy outcome can be avoided if one of the aldehydes lacks α hydrogen atoms and the other aldehyde is less reactive. For example, an aldol condensation occurs between benzaldehyde and acetaldehyde to give a high yield of a single aldol product. Reaction between two benzaldehyde molecules cannot occur because benzaldehyde lacks α hydrogen atoms. Therefore, benzaldehyde is mixed with a base, and acetaldehyde is then slowly added. The acetaldehyde is rapidly converted to an

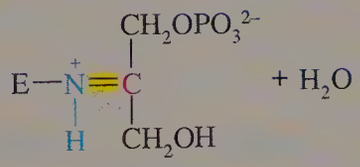
Mixed Aldol Condensations in Metabolic Reactions

When an aldol condensation occurs, a new carbon–carbon bond forms under moderate reaction conditions in the laboratory. The reactions are even faster in biological systems. However, the reactions are usually mixed aldol condensations rather than an aldol condensation of one reactant. For example, an aldol condensation occurs in the synthesis of glucose from three-carbon precursors. In this reaction, catalyzed by the enzyme aldolase, the carbon atom bearing the hydroxyl group in dihydroxyacetone phosphate reacts with the carbonyl carbon atom of glyceraldehyde 3-phosphate to give fructose 1,6-diphosphate.

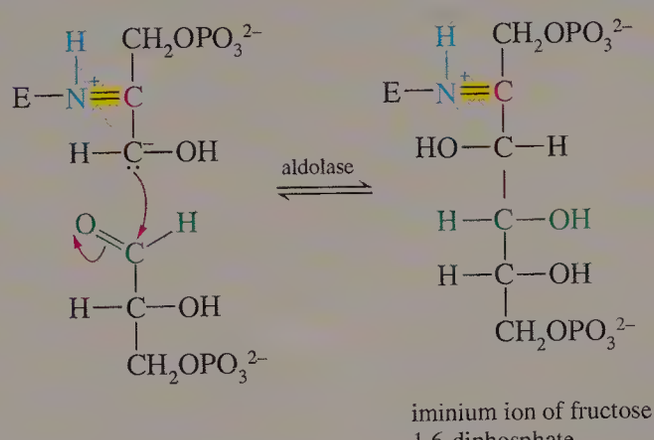


Why does only this aldol form among the four possible combinations of aldol products? The condensation of dihydroxyacetone phosphate with itself would involve nucleophilic attack at a ketone carbonyl group and is unlikely. For the same reason, the attack of the enolate of glyceraldehyde 3-phosphate on the carbonyl group of dihydroxyacetone phosphate is also unlikely. The only remaining possible competitive process is the attack of the enolate of glyceraldehyde 3-phosphate on the aldehyde carbonyl group of glyceraldehyde 3-phosphate. This process could occur in an ordinary base-catalyzed reaction. However, in the enzyme-catalyzed reaction, dihydroxyacetone phosphate serves as the enolate. The specificity of this mixed aldol reaction results from the formation of an imine between dihydroxyacetone phosphate and the amino group of the amino acid lysine at the active site of aldolase.



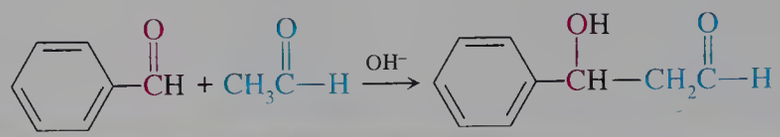


This imine of dihydroxyacetone phosphate can react with glyceraldehyde 3-phosphate. The enolate ion of the dihydroxyacetone phosphate bonded to the enzymeattacks the carbonyl carbon atom of glyceraldehyde 3-phosphate. This enolate forms more readily because of the greater acidity of the α hydrogen atom. This enhanced acidity derives from the stronger electron-withdrawing properties of the iminium group compared to a carbonyl group.



The iminium ion of fructose 1,6-diphosphate is then deprotonated, and hydrolysis of the imine yields fructose 1,6-diphosphate.

enolate anion. Because benzaldehyde is more reactive than acetaldehyde and the concentration of free acetaldehyde in the mixture is much smaller than that of benzaldehyde, the enolate of acetaldehyde reacts with benzaldehyde. Only one product results. Because the product derives from two different aldehydes, the reaction is called a **mixed aldol condensation**.



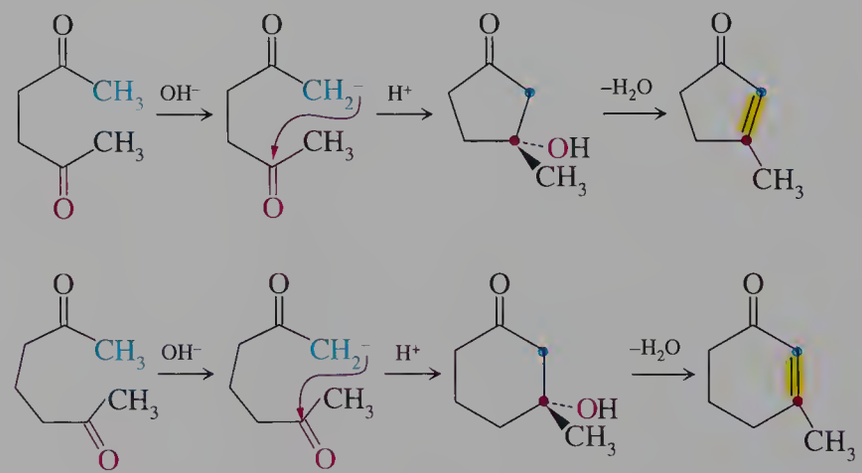
Problem 23.16

Acetophenone undergoes a condensation reaction with benzaldehyde to give a product with the molecular formula $C_{15}H_{12}O$. Draw its structure and indicate why it forms.

23.9 Intramolecular Aldol Condensations

In Section 23.7, we described the role of closely balanced enthalpy and entropy changes for the aldol condensation of aldehydes. The equilibrium constants for the condensation reactions of aldehydes are not large, and those for ketones are so small that the aldol condensation of a ketone is impractical. In Section 19.6, we learned that formation of a hemiacetal or hemiketal is also a reaction in which the enthalpy and entropy of reaction oppose each other. We learned that an intramolecular reaction of an alcohol and a carbonyl group occurs because the entropy term is less negative than for the intermolecular reaction. Intramolecular reactions convert a single molecule of reactant into a single molecule of product, and $\Delta S^\circ_{rxn} \approx 0$. The same principle applied to a dicarbonyl compound suggests that intramolecular aldol condensation would give good yields of products. Even ketones can react intramolecularly to give cyclic aldol products.

Now let's consider the type of dicarbonyl compounds that can cyclize to form an aldol product. First, the carbon atom that is α to one carbonyl group must lie near the second carbonyl carbon atom. In other words, there must be a good probability that the nucleophilic and electrophilic carbon atoms are close enough to react. In fact, we find that favorable reactions occur to give five- or six-membered ring products. For example, 1,4-dicarbonyl compounds condense and dehydrate to give cyclopentenones. Similarly, 1,5-dicarbonyl compounds give cyclohexenones.



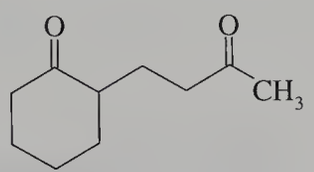
Would we expect that smaller and larger rings might form in intramolecular aldol condensations? If the reactive sites required for an intramolecular aldol reac-

tion are close, the ring closure could occur to give four- and three-membered rings, but they would be strained. Rings larger than six carbon atoms are not likely because the probability of forming such a ring is lower than the formation of an alternate smaller ring. Furthermore, all possible aldol products form in equilibrium reactions, each of which can reverse to regenerate the original dicarbonyl compound. As a consequence, the product formed at equilibrium is the more stable aldol.

Next, let's consider a problem similar to that discussed for mixed aldol condensations. Which α carbon atom will react with which carbonyl carbon atom if rings of similar size could result? Under the reaction conditions, all possible enolates can form in low concentration. Thus, we can consider the various carbonyl groups and determine which is more likely to react with the nucleophilic carbon atom of an enolate. If one carbonyl group is an aldehyde and the other a ketone, the answer to our question is easy: the aldehyde carbonyl group is more susceptible to attack by a nucleophile.

Problem 23.17

Draw the structure of the dehydrated aldol product of 2-(3-oxobutyl)cyclohexanone.

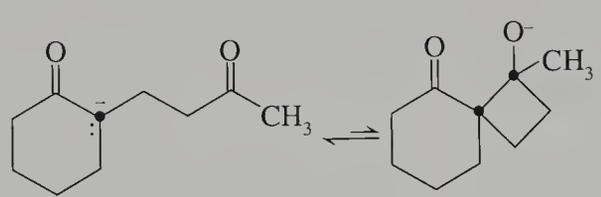


2-(3-oxobutyl)cyclohexanone

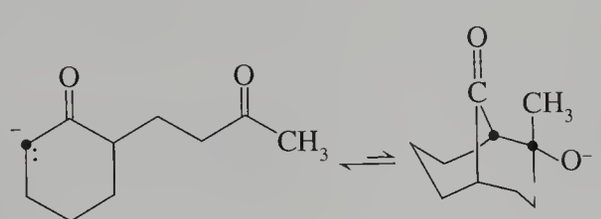
Sample Solution

There are four α carbon atoms, two for each carbonyl group. An enolate derived from the C-2 or C-6 site could react with the carbonyl group of the oxobutyl chain. An enolate derived from the C-2 or C-4 site of the oxobutyl chain could react with the carbonyl group on the cyclohexane ring.

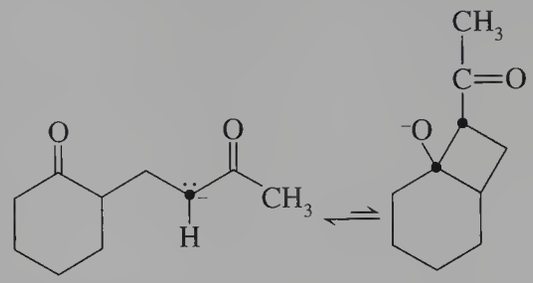
Neither of the enolates derived from the C-2 or C-6 site of the cyclohexanone ring should lead to a significant amount of product in an equilibrium reaction in competition with other possible products. The enolate derived from C-2 would produce a four-membered ring when it attacks the C-3 carbonyl carbon atom of the oxobutyl chain. Futhermore, the resulting aldol product cannot dehydrate to give a conjugated ketone.



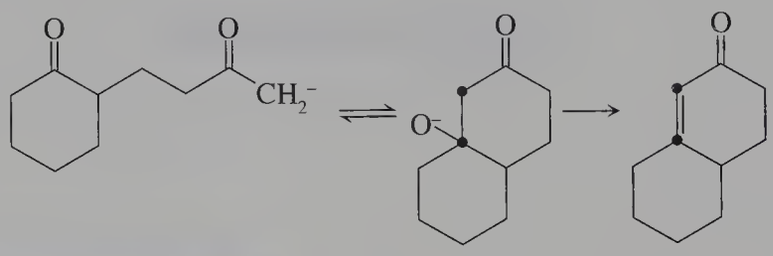
The enolate derived from the C-6 site could give a six-membered ring in a reaction with the C-3 carbonyl carbon atom. However, this reaction can occur only by reaction with the oxobutyl chain in an axial conformation. The resulting aldol cannot dehydrate to give a conjugated carbonyl compound because a double bond at the bridgehead carbon atom would be very strained.



Attack of the enolate of the C-2 site of the oxobutyl chain on the carbonyl carbon atom of the cyclohexanone ring would give a four-membered ring, which would be strained.

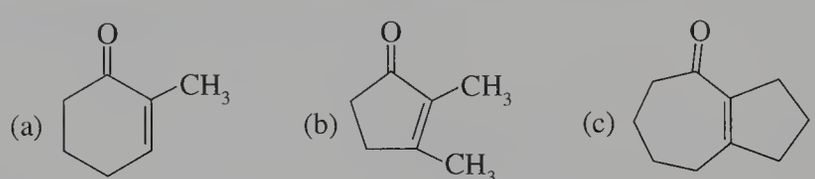


Attack of the enolate of the C-4 site of the oxobutyl chain on the carbonyl carbon atom of the cyclohexane ring gives a six-membered ring. This process is the most likely of the four processes outlined because the product is the most stable. Dehydration of the aldol occurs to give a carbon–carbon double bond in conjugation with the carbonyl group.



Problem 23.18

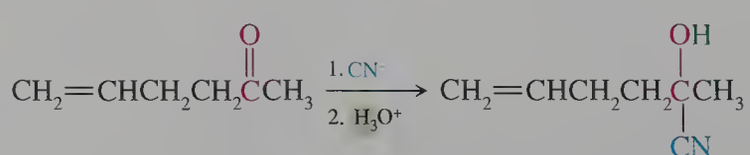
Draw the structure of the dicarbonyl compound required to form each of the following compounds by an aldol condensation.



23.10 Conjugation in α,β-Unsaturated Aldehydes and Ketones

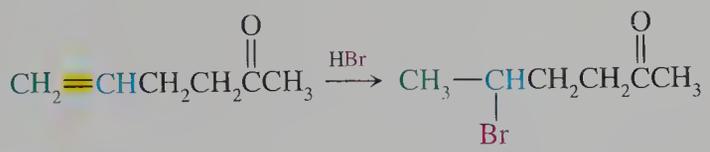
We recall that nonconjugated dienes have more than one single bond between the two double-bonded units and that these compounds are chemically similar to alkenes. However, with one single bond located between two double-bonded units, the diene is conjugated, and its chemical reactivity differs from that of simple alkenes. In this section the same phenomenon is illustrated for α,β-unsaturated aldehydes and ketones.

First, let's compare the chemical reactivities of a carbon–carbon double bond and a carbon–oxygen double bond in a nonconjugated molecule. The carbonyl group reacts at the carbonyl carbon atom with nucleophiles such as cyanide ion. Carbon–carbon double bonds do not react directly with nucleophiles. Thus, cyanide ion reacts with 5-penten-2-one to give an addition product of the carbonyl group and does not react with the carbon–carbon double bond.



(a cyanohydrin)

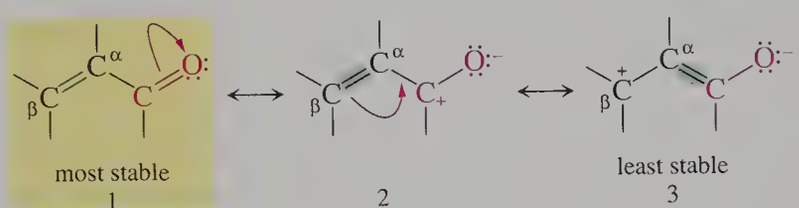
The carbon–carbon double bond of this nonconjugated compound reacts with electrophilic reagents such as HBr. The carbon–oxygen double bond does not react with HBr (Section 19.1).



Markovnikov addition product

α,β-Unsaturated aldehydes and ketones are more stable than nonconjugated unsaturated carbonyl compounds because the two π bonds interact. This "extra" stability is called the resonance energy. In Chapter 12, we showed that the resonance energy of dienes results from the distribution of electrons in molecular orbitals extended over more than two atoms. However, many of the physical and chemical properties of these dienes can also be explained using Lewis structures. We will use this technique to consider the physical and chemical properties of α,β-unsaturated aldehydes and ketones.

An α,β-unsaturated carbonyl compound can be represented by one uncharged and two dipolar resonance forms.



most stable
1

2

least stable
3

Of the three resonance forms, structure 3 is the least stable. However, we shall see shortly that its contribution is important in explaining the special reactivity of α,β-unsaturated carbonyl compounds. In structures 2 and 3, the carbonyl carbon atom and the β carbon atom are positively charged, respectively. We used the partial positive charge of the carbonyl carbon atom to explain the addition reaction of carbonyl groups (Chapter 19). The partial positive charge of a carbon atom of the carbon–carbon double bond alters its characteristic reactivity. The diminished electron density makes the carbon–carbon π bond less reactive toward an electrophile. But for the same reason, the β carbon atom is electrophilic and can react with nucleophiles. Reactions that reflect this polarity for a double bond are the subject of the following section.

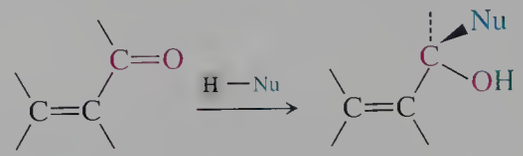
23.11 Conjugate Addition Reactions

We recall that many addition reactions of a nucleophile to a carbonyl compound are reversible because the carbon–nucleophile bond of the addition product is weak and the nucleophile is a good leaving group. The addition of cyanide ion is one such example. However, strong bases, such as hydride ion or an alkyl carbanion, add irreversibly to the carbonyl group.

To understand the product distribution in addition reactions of carbonyl groups, we have to know whether the product results from kinetic control or thermodynamic control. If a reaction is irreversible, the product is "trapped" and results from kinetic control. However, the product distribution in reversible addition reactions depends on the relative stabilities of the products. We call this feature thermodynamic control.

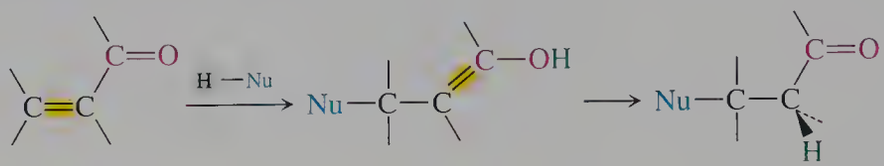
1,2- and 1,4-Additions

Like conjugated dienes, conjugated unsaturated carbonyl compounds can add reagents in two ways, termed 1,2 and 1,4-additions. In these compounds, the C=C—C=O unit is described using the number 1 for the carbonyl oxygen atom and the number 4 for the β carbon atom. The 1,2-addition product of a reagent H—Nu is simply the addition reaction to the carbonyl group studied in Chapter 19.



1,2-addition product

It is not immediately obvious that a 1,4-addition reaction has occurred with α,β-unsaturated carbonyl compounds because the initial product is an enol.

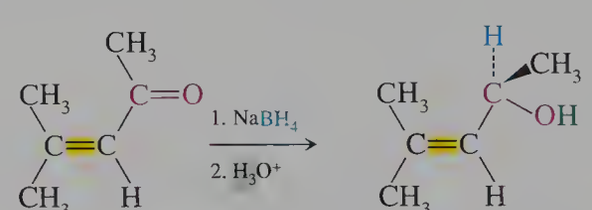


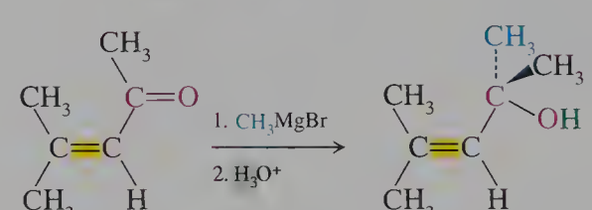
enol from 1,4-addition

1,4-addition product

Thus, the nucleophile is bonded to the β carbon atom called number 4 in the description of conjugated carbonyl compounds, but the electrophile is bonded to the α carbon atom designated number 3. From the structure of the isolated product, the reaction appears to be simply the addition of H—Nu to a carbon–carbon double bond. However, we know that this could not have occurred. The atoms added are not in the places predicted by Markovnikov's rule. Furthermore, the presence of the electron-withdrawing carbonyl group should make the α carbon susceptible to attack by the nucleophile, not the electrophile.

We already know that metal hydride reagents reduce carbonyl groups and not carbon–carbon double bonds. This reaction is an example of a 1,2-addition. Similarly, a Grignard reagent adds to a carbonyl group, but not to a carbon–carbon double bond. We conclude that strong nucleophiles such as hydride ion and carbanions undergo 1,2-addition. Neither reaction is reversible, and the products result from kinetic control.





1,4-Addition reactions occur with weak nucleophiles such as CN^-. 1,2-Addition usually still occurs because this kinetic product results from attack at the carbonyl car-

bon atom, which is more electrophilic than the carbon atom. However, the reaction is reversible. Meanwhile, although the 1,4-addition product forms more slowly, it accumulates because it is thermodynamically more stable than the 1,2-addition product. The 1,4-addition product retains the carbon–oxygen double bond, which is more stable than the carbon–carbon double bond of the 1,2–addition product (Figure 23.1).

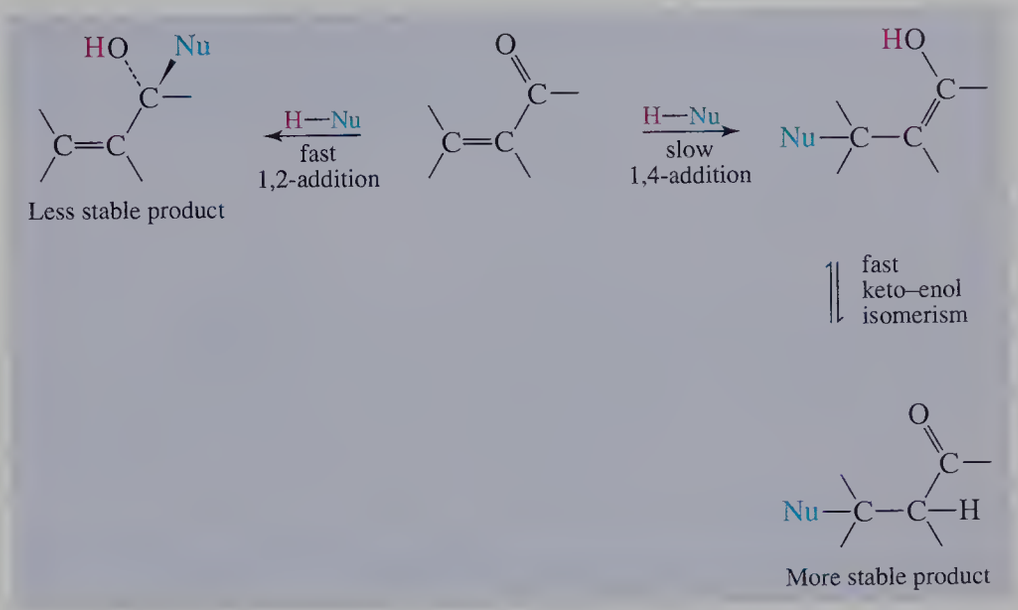
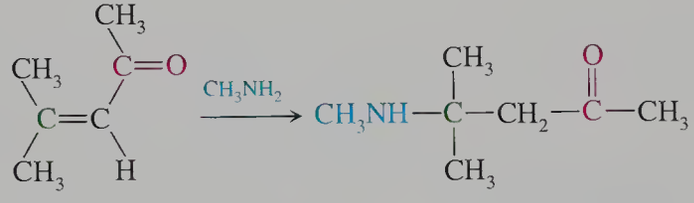
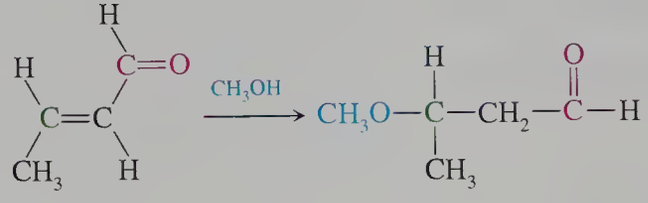
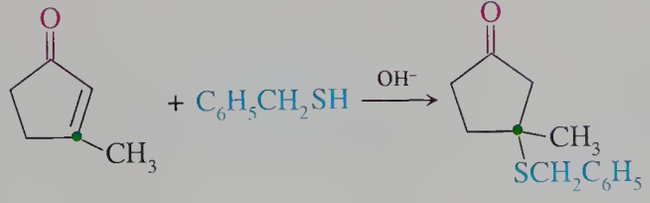


FIGURE 23.1 Kinetic vs. Thermodynamic Control of 1,2- and 1,4-Additions
Direct 1,2-addition occurs faster than 1,4-conjugate addition, but gives a less stable product. The 1,4-addition product isomerizes to give a more stable product that retains the carbonyl group.

In Chapter 19, we considered the addition of weak nucleophiles such as methylamine, methanol, and thiols to the carbonyl group. Now, let's look at the 1,4-addition reactions of these compounds with an α,β-unsaturated carbonyl compound. We have seen that methylamine adds to a carbonyl group to give an imine. But we know that an imine is less stable than a carbonyl compound, so the equilibrium constant for the reaction is less than 1. Similarly, alcohols react with carbonyl compounds to give hemiacetals. Again, the equilibrium constant for the reaction is less than 1 unless the reaction is intramolecular. Thiols react with carbonyl compounds to give thioacetals or thioketals, but the reaction requires an acid catalyst. Each of these reagents reacts with α,β-unsaturated carbonyl compounds to give 1,4-addition products. As in the case of cyanide ion, described above, these reactions lead to an accumulation of 1,4-addition product.



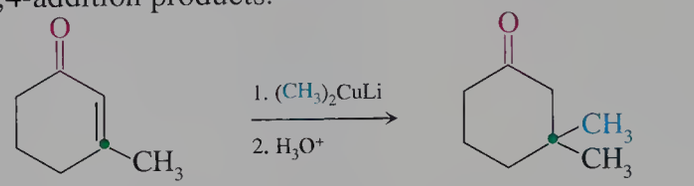




Conjugate Addition of Organometallics

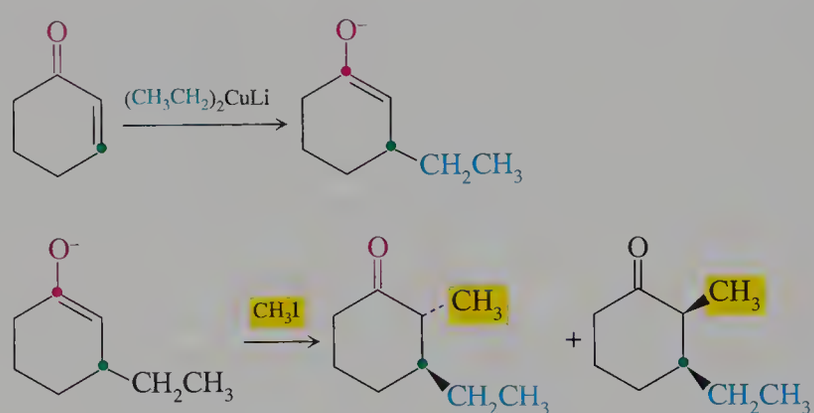
We noted earlier that the Grignard reagent undergoes 1,2-addition reactions with α,β-unsaturated carbonyl compounds with few exceptions. Those exceptions occur when the carbonyl carbon atom of a ketone is sterically hindered compared to the β-carbon atom. Aldehydes always give 1,2-addition products. Organolithium reagents are more reactive than Grignard reagents and always give 1,2-addition products.

Organo cuprates (Gilman reagents) react with α,β-unsaturated carbonyl compounds to form 1,4-addition products.



3-methyl-2-cyclohexenone 3,3-dimethylcyclohexenone

The mechanism of this reaction is not simple nucleophilic attack of a carbanion at the β- carbon atom. The details of the mechanism are not well understood. It seems that radical intermediates bonded to the copper species form during the reaction. Ultimately, a resonance-stabilized enolate forms, which explains why 1,4-addition occurs. The enolate can be trapped by adding an alkyl halide after the first step is complete, but before the reaction is worked up. This sequence of two reactions is synthetically useful because it results in alkylation at both the α and β- carbon atoms.

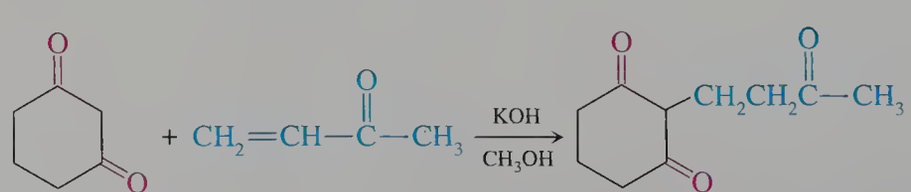


major product minor product

23.12 The Michael Reaction and Robinson Annulation

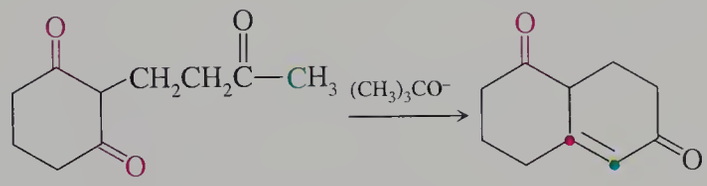
To synthesize a complex structure, we have to combine two (or more) pieces of smaller molecules in a way that leaves functional groups that can be further modified in subsequent steps. In this section we will discuss two reactions, the Michael reaction and the Robinson annulation, to illustrate this principle.

In the **Michael reaction**, an enolate acts as a nucleophile and adds 1,4 to an α,β-unsaturated carbonyl compound. 1,3-Dicarbonyl (β dicarbonyl) compounds are most frequently used to provide the enolate because they are quite acidic, and alkoxide bases can abstract the hydrogen atom that is α to both carbonyl carbon atoms.



The reactants in the Michael reaction are called donors and acceptors. The enolate derived by abstraction of an α hydrogen atom is the donor. The α,β-unsaturated carbonyl compound is the acceptor.

The Michael addition product has a reactive α carbon atom located at an appropriate distance to undergo an intramolecular aldol condensation with a carbonyl carbon atom.



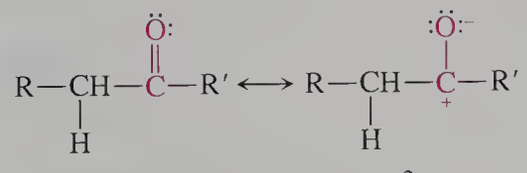
The Michael addition followed by an intramolecular aldol condensation is collectively known as the **Robinson annulation**. **Annulation** means the formation of a ring onto a reactant. In the above case, a second six-membered ring forms on the original six-membered ring of the β dicarbonyl compound.

23.13 α Hydrogen Atoms of Acid Derivatives

In Section 23.2, we saw that an enolate formed by deprotonation of the α carbon atom of aldehydes or ketones is a nucleophile and therefore a useful synthetic intermediate. The enolate reacts with the electrophilic carbon atom of an alkyl halide to give an alkylated product. The enolate reacts with the electrophilic carbon atom of a carbonyl group to yield an aldol product. Both of these processes generate carbon–carbon bonds.

The electron-withdrawing effect of the positively charged carbonyl carbon atom also increases the acidity of the α hydrogen atoms of acid derivatives. In addition, their acidity is affected by resonance and inductive effects of the attached substituents (Table 23.1). Therefore, derivatives of carboxylic acids can form enolates that undergo some reactions resembling the condensation reactions of aldehydes and ketones.

In the following sections, we focus on condensation reactions at the α carbon atom of esters. Reactions of these derivatives form carbon–carbon bonds and are useful in synthesis. Alkylation reactions using alkyl halides and reactions at carbonyl carbon atoms both occur with ester enolates. However, the reactions of enolates of acid derivatives differ somewhat from the reactions of enolates of aldehydes and ketones. For one thing, the α hydrogen atoms of esters (pK_a = 25) are less acidic than those of aldehydes and ketones (pK_a = 20). Two resonance forms are written for aldehydes and ketones. The dipolar resonance form of a ketone has a positive charge on an electron-deficient carbonyl carbon atom. The contribution of this resonance form (2) to the resonance hybrid increases the acidity of the α hydrogen atom as the result of inductive electron withdrawal.



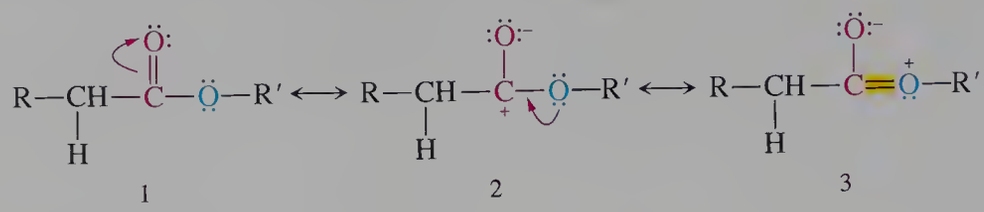
1 2

Three resonance forms are written for esters, two of which are dipolar. Donation of electron density by the bridging oxygen atom yields a dipolar resonance form (3)

Table 23.1
Acidity of α Hydrogen Atoms

Compound	pK_a
$CH_3—\overset{\overset{O}{\|}}{C}—Cl$	16
$CH_3—\overset{\overset{O}{\|}}{C}—CH_3$	19
$CH_3—\overset{\overset{O}{\|}}{C}—OCH_3$	25
$CH_3—C{\equiv}N$	25
$CH_3—\overset{\overset{O}{\|}}{C}—N(CH_3)_2$	30

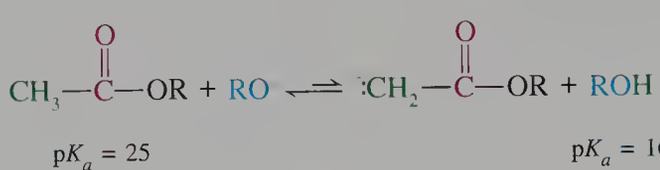
with Lewis octets at all atoms. In this resonance form the positive charge is located on the oxygen atom rather than the carbonyl carbon atom.



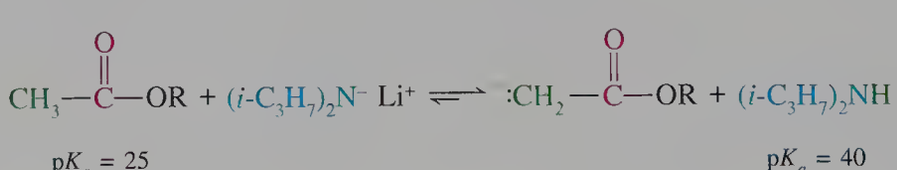
As a result, the carbonyl carbon atom has a smaller partial positive charge in esters than in ketones. Resonance donation of electron density to the carbonyl carbon atom by the bridging oxygen atom thus decreases the acidity of the α hydrogen atom of esters compared to aldehydes and ketones.

Formation of Ester Enolates

We considered the types of bases required to generate an enolate of aldehydes and ketones in Section 23.2. We recall that relatively weak bases, such as alkoxide ions, give only low concentrations of the enolates of ketones. Because esters are weaker acids than ketones, even lower concentrations of ester enolates form in reactions with alkoxide ions. Note that the alkoxide base must be the same as the alkoxy group contained in the ester to avoid exchange of alkoxy groups.



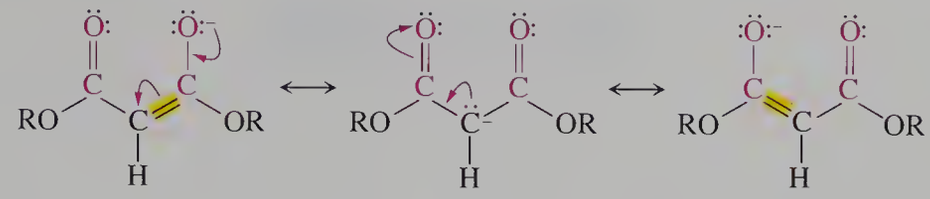
We recall that the conjugate base of an aldehyde must react with the aldehyde, which is present in a significantly greater concentration, to make an aldol condensation possible. A similar condensation reaction, called the Claisen condensation, occurs when low concentrations of ester enolates react with esters (Section 23.15). If an ester were treated with a very strong base, such as lithium diisopropylamide (LDA), high concentrations of the ester enolate would form, and no ester would remain for a bimolecular self-condensation reaction. The ester enolate yield is stoichiometric when LDA is used as the base because diisopropylamine is a much weaker acid than an ester. Furthermore, LDA is a sterically hindered nucleophile, so it does not react with the electrophilic carbon atom of the ester.



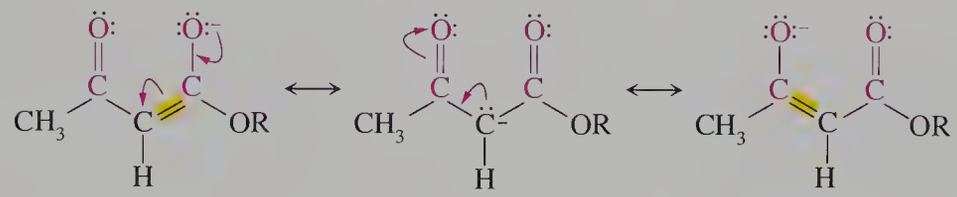
Dicarbonyl Compounds

Compounds with a carbonyl group β to the carbonyl carbon atom of an ester are stronger acids (Table 23.2) than simple esters. When the α hydrogen atom of a β-keto ester is removed, the negative charge of the conjugate base is delocalized from

the α carbon atom to two oxygen atoms. In an ester, the negative charge of the conjugate base is delocalized from the α carbon atom to just one oxygen atom. Malonate esters and esters of acetoacetic acid form such resonance-stabilized enolate ions.



resonance forms of enolate ion of a malonate ester



resonance forms of enolate ion of an acetoacetate ester

Table 23.2
pK_a Values of ß Dicarbonyl Compounds

Compound	pK_a	*Common name*
$CH_3-C(=O)-CH_2-C(=O)-CH_3$	9	acetylacetone
$CH_3-C(=O)-CH_2-C(=O)-O-C_2H_5$	11	ethyl acetoacetate
$N\equiv C-CH_2-C(=O)-O-C_2H_5$	9	ethyl cyanoacetate
$C_2H_5-O-C(=O)-CH_2-C(=O)-O-C_2H_5$	13	diethyl malonate

Malonate esters and acetoacetate esters are more acidic than water or alcohols (Table 23.2). Thus, the hydroxide ion or an alkoxide ion is sufficiently basic to produce the conjugate base of either of these β-dicarbonyl compounds. The enolates of simple esters and β-keto esters are nucleophiles, and they undergo the condensation reactions we will discuss below.

Problem 23.19

Rank the three resonance forms of the malonate ester in order of their stability. Are any two of the resonance forms equivalent?

Problem 23.20

Why are malonate esters weaker acids than acetoacetate esters?

Sample Solution

The α carbon atom of a malonate ester is bonded to the carbonyl carbon atoms of two ester functional groups, whereas the α carbon atom of an acetoacetate ester is bonded to the carbonyl carbon atoms of an ester and a ketone. The α carbon atom of esters are weaker acids than those of ketones because the alkoxy group donates electrons by resonance to the

carbonyl carbon atom, thus decreasing its partial positive charge. The "replacement" of a ketone by an ester in acetoacetate esters to give malonate esters decreases the positive charge on the carbonyl carbon atom and the adjacent α hydrogen atoms are less acidic.

Problem 23.21

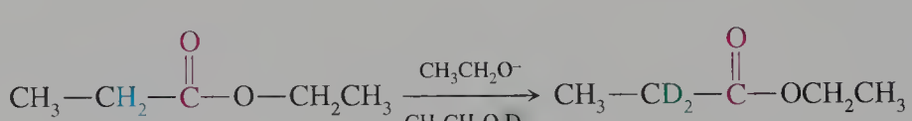
Calculate the equilibrium constant for the reaction of ethoxide ion with diethyl malonate.

23.14 Reactions at the α Carbon Atom of Acid Derivatives

The enolates of aldehydes and ketones undergo deuterium exchange, bromination, and alkylation reactions (Section 23.4, 23.5, and 23.6). Carboxylic acid derivatives react similarly. However, the added possibility of a competing nucleophilic acyl substitution reaction limits some of the substitution reactions at the α carbon atom of acid derivatives. For example, acyl halides react with most bases in substitution reactions at the carbonyl carbon atom rather than by abstraction of the α hydrogen atom. On the other hand, the pK_a of the α hydrogen atoms of amides is very large, and these derivatives would require a very strong base for formation of enolates for synthetic reactions. Esters are the most convenient acyl derivatives for enolate formation and subsequent substitution at the α carbon atom. The substituted ester can subsequently be converted into other acyl derivatives.

Deuterium Exchange

We recall that a hydrogen atom located on an α carbon atom of an aldehyde or ketone can be lost to a solvent molecule and then regained in equilibrium reactions that occur by formation of an enol intermediate (Section 23.4). This hydrogen atom is called an enolizable hydrogen atom. The proton transfer equilibrium between a carbonyl compound and its enol is useful in the synthesis of isotopically labeled aldehydes or ketones using deuterium oxide (heavy water) and NaOD as a base. The same hydrogen–deuterium exchange occurs with esters. However, the exchange requires an alkoxide and its corresponding deuterated alcohol as solvent to avoid saponification of the ester.



Only α hydrogen atoms are exchanged because the reaction occurs through an enolate ion intermediate. All possible enolizable hydrogen atoms are eventually replaced. The hydrogen atoms are "lost" in the solvent, which contains many more deuterium atoms than the number of hydrogen atoms transferred from the carbonyl compound.

The rate of exchange of hydrogen by deuterium in esters is much slower than in ketones. Ketone exchange occurs at room temperature in a few minutes. Exchange reactions of esters require weeks at the same temperature. The exchange reaction is therefore usually carried out at the boiling point of the alcohol solvent.

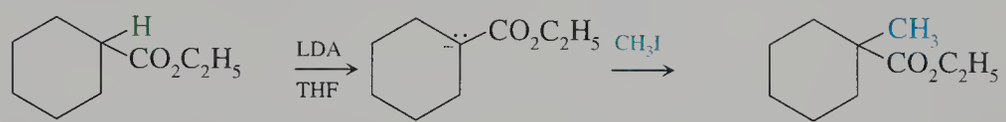
Alkylation of Esters

We recall that an enolate of a ketone is a nucleophile that can displace a leaving group from a primary alkyl halide. Although the enolate has two reactive sites, we

have already learned that reaction of an electrophile with an enolate occurs at the α carbon atom to give a substituted keto product called the C-alkylated product. The alternate reaction at the oxygen atom to give an O-alkylated product occurs much less commonly.

We also recall that the hydroxide ion or alkoxide ion is not basic enough to form the enolate ion in high concentration. Hence, the hydroxide ion or alkoxide ion would substitute for the halide ion of the alkyl halide to give an alcohol or ether, respectively. However, strong bases, such as potassium hydride or LDA, yield stoichiometric quantities of the enolate. An alkyl halide is then added to the solution of the enolate to give the α-alkylated product.

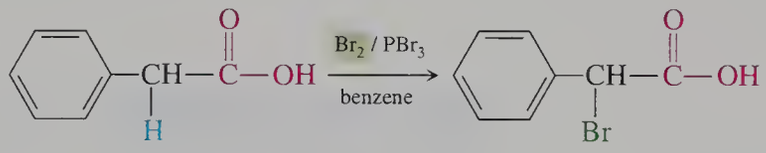
The α hydrogen atoms of esters are less acidic than those of ketones. However, as in the case of ketones, LDA quantitatively deprotonates α hydrogen atoms of esters. Subsequent addition of an alkyl halide to the solution of the ester enolate yields an alkylated ester. Because the ester enolate is an even stronger base than enolates of ketones, only primary alkyl halides can be used as alkylating agents. Both secondary and tertiary alkyl halides undergo elimination reactions.



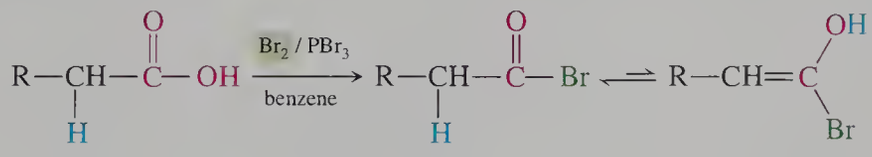
ethyl cyclohexanecarboxylate — ethyl 1-methylcyclohexanecarboxylate

α Bromination

Because the enol content of carboxylic acids is much lower than that of aldehydes and ketones, carboxylic acids do not react with halogens to give α-halo carboxylic acids. However, bromination does occur in the presence of a catalytic amount of PBr_3. The reaction also occurs in the presence of a small amount of phosphorus, which reacts with the bromine to generate PBr_3 under the reaction conditions. Either variation of the method is called the **Hell–Volhard–Zelinsky** reaction.



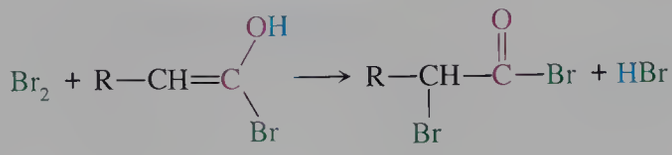
The carboxylic acid itself is not brominated in the Hell–Volhard–Zelinsky reaction. Rather, a small amount of the carboxylic acid is converted into an acid bromide, which has a substantially higher concentration of the enol tautomer than does the carboxylic acid.

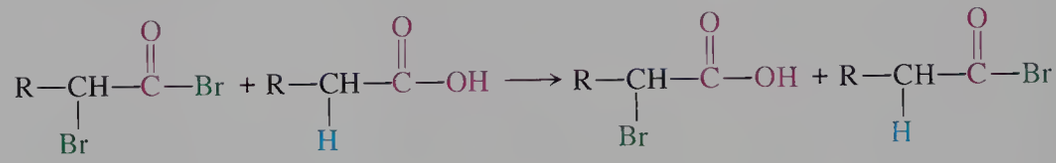


enol tautomer of an acid bromide

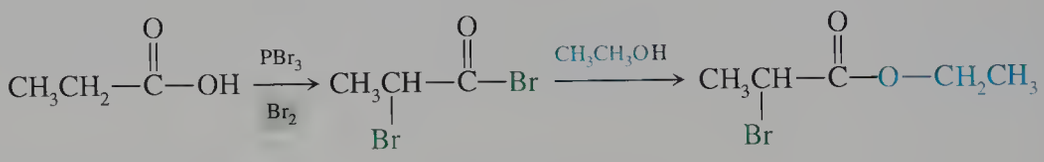
Reaction of the enol tautomer with bromine gives an α-bromo acyl bromide. An exchange reaction between the α-bromo acyl bromide and the unreacted carboxylic acid then occurs giving an α-bromo carboxylic acid. The second product, an acyl bromide,

then reacts with bromine to form additional α-bromo acyl bromide. That is why only a catalytic amount of PBr_3 is required to convert all the carboxylic acid to an α-bromo derivative.

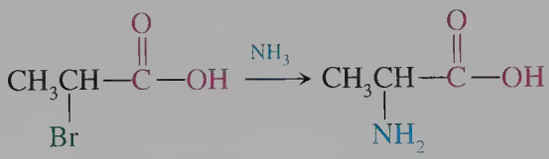




If one equivalent of PBr_3 is used in the Hell–Volhard–Zelinsky reaction, an α-bromo acid bromide results. This acid halide can be used in the typical reactions of acid halides discussed in Chapter 22. For example, if an alcohol is added after completion of the reaction, an α-bromo ester results.



α-Bromo acids or esters undergo typical S_N2 substitution reactions. For example, bromide can be displaced by ammonia in aqueous solution to give an α-amino acid (Chapter 26).



alanine
(an α-amino acid)

Problem 23.22

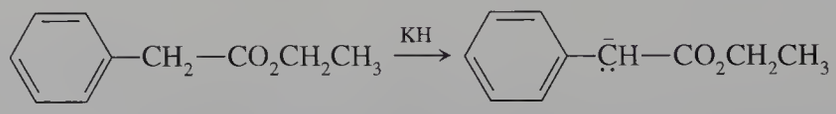
Predict the product of the reaction of 2-bromobutanoic acid with an aqueous sodium carbonate solution.

Problem 23.23

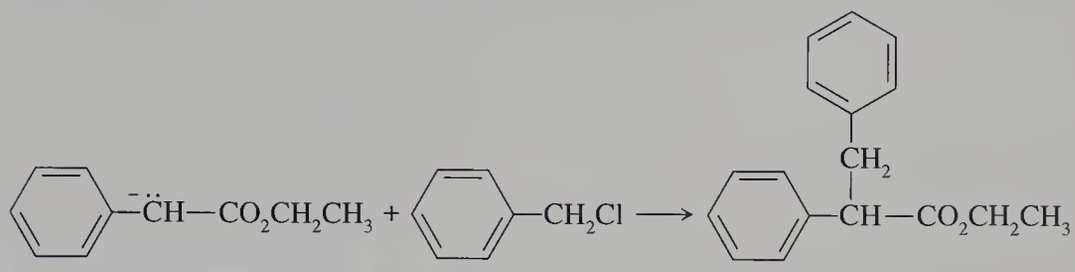
Draw the product of the reaction of ethyl 2-phenylacetate with KH followed by reaction with benzyl chloride.

Sample Solution

Potassium hydride is a sufficiently strong base to remove the α hydrogen atom and generate a resonance-stabilized carbanion.



Benzyl chloride is very reactive in S_N2 reactions and cannot undergo competitive elimination reactions because it has no β hydrogen atoms. Displacement of the chloride ion by the carbanion derived from ethyl 2-phenylacetate gives an alkylated product.

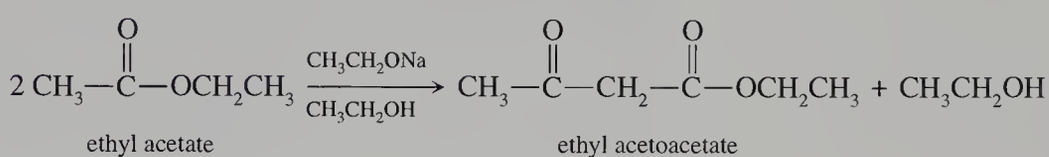


Problem 23.24

Suggest two methods to prepare 2-isopropylpentanenitrile using an α alkylation reaction. Which would give the better yield?

23.15 The Claisen Condensation

Two molecules of an ester react in the presence of an alkoxide base to produce a condensation product. The reaction, which produces a β-keto ester, is called the **Claisen condensation**.



ethyl acetate — ethyl acetoacetate

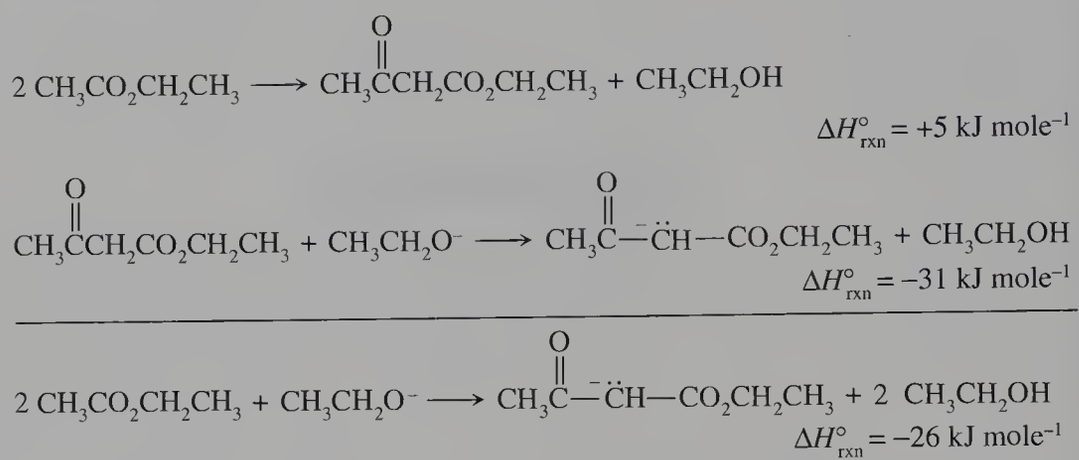
The ester must have two α hydrogen atoms, for reasons we will present in our discussion of the mechanism. A full equivalent of base is required for the Claisen condensation, whereas only a catalytic amount is required for the aldol condensation. The base promotes the reaction, but does not act as a catalyst. That is, the base is consumed in the reaction.

Thermodynamic Considerations

Let's first analyze the Claisen condensation reaction from a thermodynamic point of view. Because two molecules condense to give one molecule of the Claisen product and an alcohol, the ΔS°_{rxn} is expected to be close to zero. We can estimate ΔH°_{rxn} by considering the bond energies of the bonds broken and formed. A C—O and a C—H bond break during the reaction, and a C—C and an O—H bond form. When we summarize these events using approximate bond energies, we find that the reaction is slightly endothermic.

	ΔH° (kJ mole^{-1})
break C—O	+380
break C—H	+410
form C—C	−360
form O—H	−425
ΔH°_{rxn}	+5

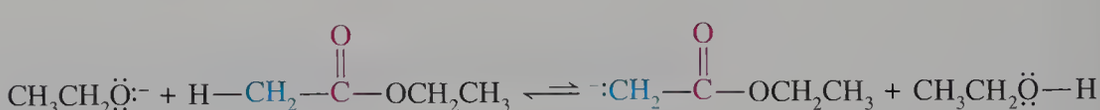
How can we obtain a good yield of the Claisen product if the ΔH°_{rxn} is positive? The answer is that we haven't really calculated ΔH°_{rxn} for the reaction as it occurs under the reaction conditions. The Claisen product itself is not formed in the basic solution. Rather, its conjugate base forms because the Claisen product loses a proton to the alkoxide ion. So, we have to add the ΔH°_{rxn} for an acid–base reaction. Because the heat of reaction of the keto ester with ethoxide ion is negative, the overall heat of reaction to form the conjugate base of the Claisen product is negative.



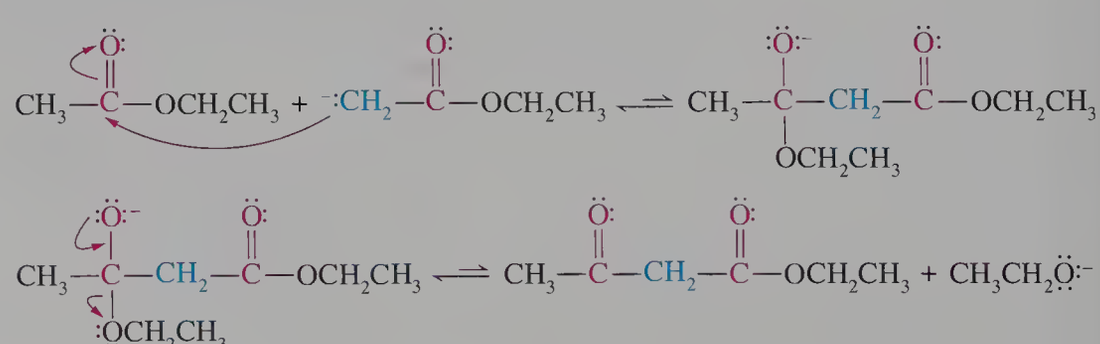
Mechanism of the Claisen Condensation

Some of the steps in the mechanism of the Claisen condensation resemble those of the aldol condensation. Both mechanisms have several reversible steps, but there are important differences. Several equilibria in the Claisen condensation are not favorable. The entire sequence becomes favorable only when we drive the final step to completion using an acid–base reaction that requires a molar equivalent of base.

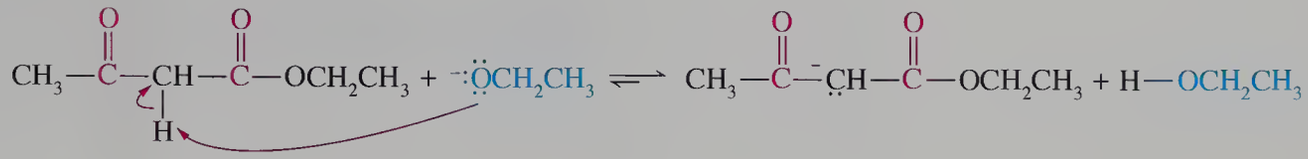
The acid dissociation constants of esters ($pK_a = 25$) are about 10^9 times smaller than that of ethanol ($pK_a = 16$). Thus, the reaction of sodium ethoxide with an ester to produce an ester enolate and ethanol has an equilibrium constant of 10^{-9}, and only a minuscule amount of the enolate exists at equilibrium.



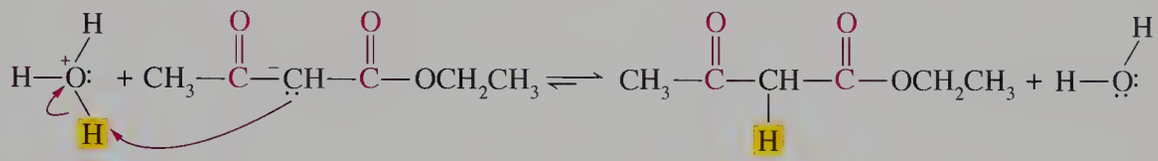
The ester enolate reacts with another molecule of ester to form a carbon–carbon bond. The addition product is the conjugate base of a hemiketal, which loses an alkoxide to give a β-keto ester.



β-Keto esters have pK_a values around 11 because the negative charge of the conjugate base can be delocalized over both carbonyl groups. Ethanol is a weaker acid than β-keto esters. Therefore, ethoxide ion completely removes a proton from the product of the Claisen condensation. This final step drives the overall sequence of reactions to completion.

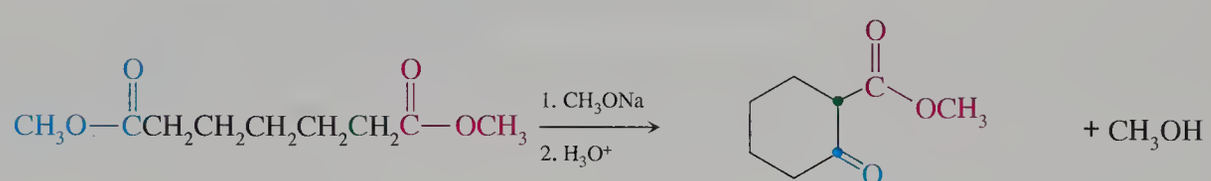


Finally, dilute acid added at the end of the reaction converts the conjugate base of the β-keto ester to the product.



Dieckmann Condensation

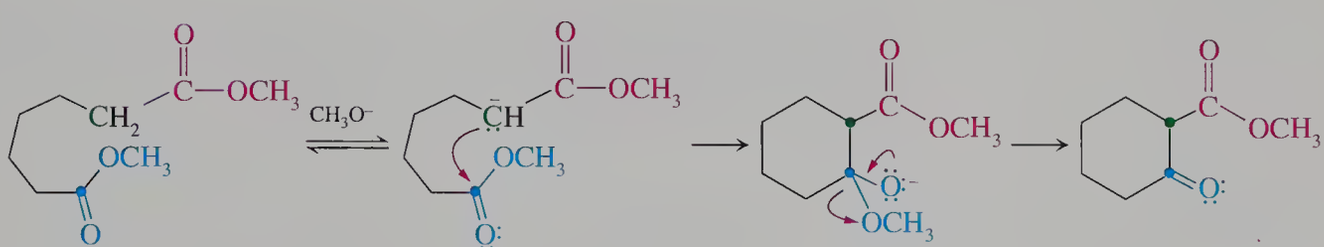
We recall that intramolecular aldol condensation reactions can occur (Section 23.9) to give five- or six-membered ring compounds. An intramolecular Claisen condensation, known as the **Dieckmann** reaction, can also occur. The Dieckmann reaction is more favorable than the bimolecular Claisen condensation because it converts a single molecule of reactant into two molecules of product. As a result, the $\Delta S^\circ_{rxn} > 0$.



dimethyl heptanedioate

methyl 2-oxocyclohexanecarboxylate

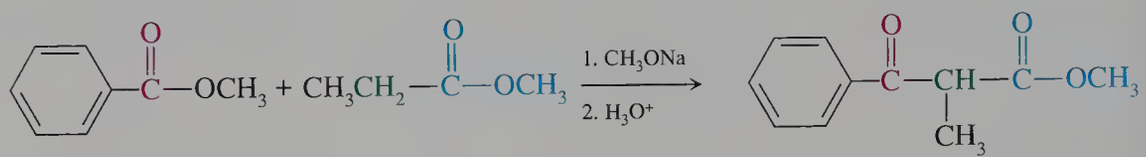
The mechanism of this intramolecular reaction is parallel to the mechanism for the intermolecular Claisen reaction. An anion forms by abstracting an α hydrogen atom next to one carbonyl group. This carbanion attacks the other carbonyl carbon atom, and an alkoxide group is subsequently eliminated.



Again, note that the Dieckmann product must have a remaining α hydrogen atom to react with base and drive the reaction to completion. Thus the original α carbon atom must have two α hydrogen atoms.

Mixed Claisen Condensations

We recall that mixed aldol condensation reactions between two different aldehydes are successful only in limited cases (Section 23.8). Similar circumstances are required for the reaction of two different esters in a mixed Claisen condensation. One of the esters must be nonenolizable. That is, it must not have any α hydrogen atoms. One ester must also be more susceptible to attack of a nucleophile at the carbonyl carbon atom than the second ester used in the mixed Claisen condensation. Only then can the reaction give a good yield. For example, a mixed Claisen condensation occurs between methyl benzoate and methyl propanoate.

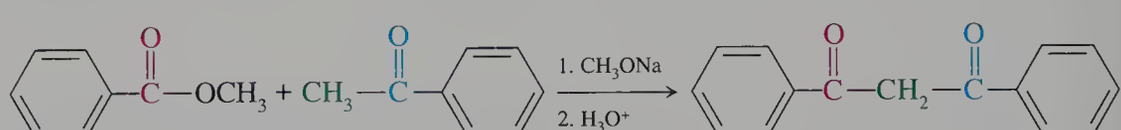


methyl benzoate methyl propanoate methyl 2-methyl-3-phenyl-3-oxopropanoate

Reaction between two methyl benzoate molecules cannot occur because there are no α hydrogen atoms. Therefore, methyl benzoate is mixed with a base, and methyl propanoate is then slowly added. The reaction converts methyl propanoate to an ester enolate anion. Because methyl benzoate is more reactive than methyl propanoate, and the concentration of methyl propanoate in the mixture is much smaller than that of methyl benzoate, the enolate of methyl propanoate reacts preferentially with methyl benzoate.

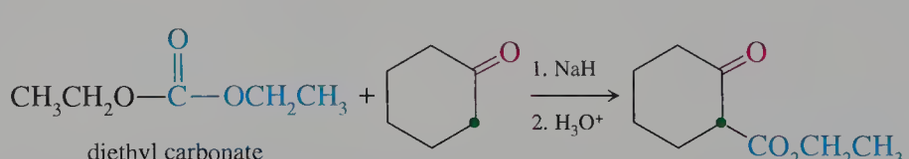
Acylation of Ketones with Esters

Nonenolizable esters can be used to acylate a ketone, yielding a β diketone. For example, methyl benzoate can serve as a benzoylation agent for the methyl group of acetophenone.



methyl benzoate acetophenone 1,3-diphenyl-1,3-propanedione

A useful variation of the acylation of a ketone with an ester uses diethyl carbonate. The enolate of a ketone serves as the nucleophile to attack the carbonyl carbon atom of the carbonate and displace one of the two alkoxy groups. The product of this Claisen-type condensation is a β-keto ester.



diethyl carbonate

Problem 23.25

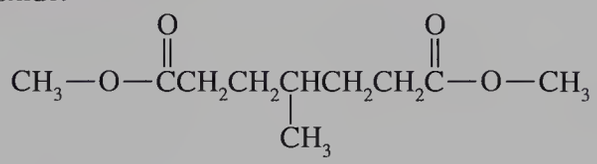
Which of the following esters cannot undergo a Claisen condensation?

(a) $CH_3CH_2CH_2CO_2CH_3$ (b) $CH_3CH_2CH_2CO_2CH_3$

(c) $(CH_3)_2CHCO_2CH_2CH_3$ (d) $C_6H_5CO_2CH_3$

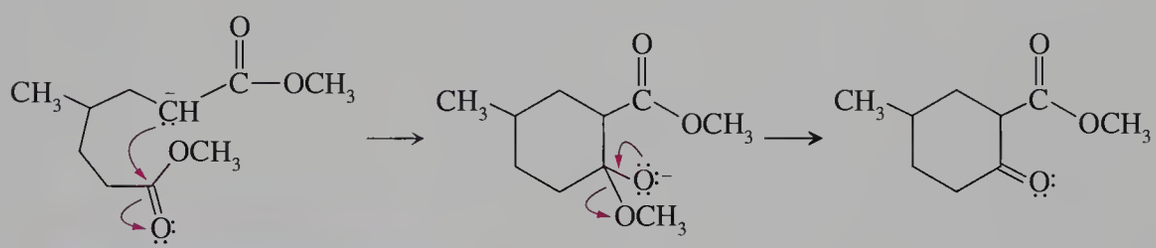
Problem 23.26

Draw the structure of the product formed by a Dieckmann reaction of the following diester with sodium methoxide.



Sample Solution

The diester is symmetrical. Abstraction of a hydrogen ion from either of the two equivalent α-methylene groups gives a carbanion that can attack a carbonyl carbon atom. There are four carbon atoms between the carbanionic atom and the carbonyl carbon atom. Thus a six-membered ring forms in the Dieckmann condensation.

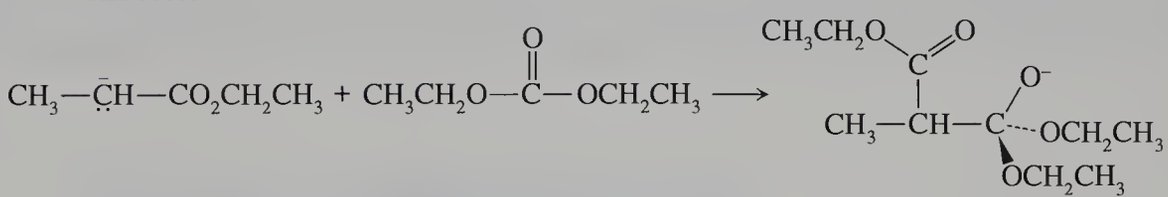


Problem 23.27

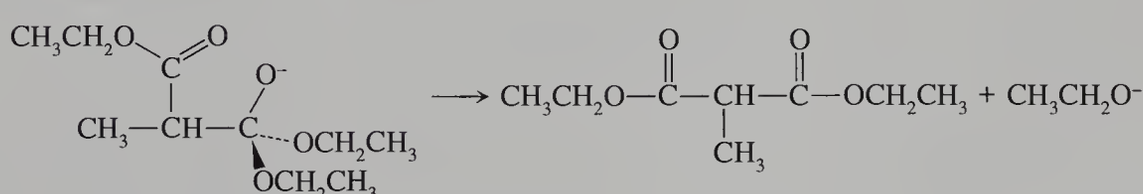
Write the structure of the product of a mixed Claisen reaction using ethyl propanoate and diethyl carbonate.

Sample Solution

Ethyl propanoate can form an enolate, but diethyl carbonate cannot. Thus nucleophilic attack of the enolate of ethyl propanoate on the carbonyl carbon atom of diethyl carbonate can occur.



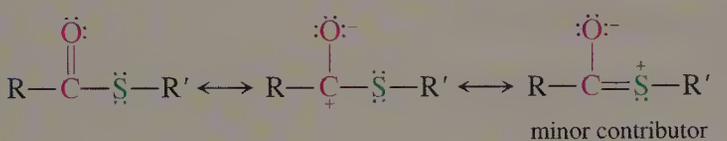
Loss of an ethoxide ion from the tetrahedral intermediate gives a methyl-substituted malonate ester.



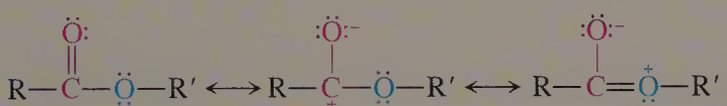
Claisen Condensation of Thioesters

A variation on the Claisen condensation is an important biochemical reaction responsible for carbon–carbon bond formation in the biosynthesis of fatty acids (Section 24.10). Also, a reverse Claisen condensation occurs in the catabolism of fatty acids (Section 24.8). We have seen that the base-catalyzed condensation of two carboxylate esters occurs because the proton α to the carbonyl group is slightly acidic. The α hydrogen atom in β-keto esters has a pK_a of about 10.5. This pK_a value is too high for β-keto esters to be of much use in biochemical reactions; at pH 7, the ratio of the conjugate base to the keto ester is less than 0.001. Claisen condensations in cells result from the condensation of thioesters. The sulfur atom of the thioester is part of a relatively large molecule called coenzyme A.

An α hydrogen atom of a β-keto thioester has a pK_a of about 8.5, so it is a hundred times more acidic than the α hydrogen atom of a β-keto ester. The increased acidity of thioesters results from the ineffective resonance stabilization of the positive charge of the carbonyl carbon atom by sulfur as compared to oxygen.

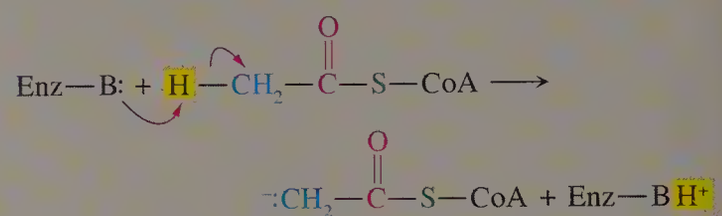


minor contributor

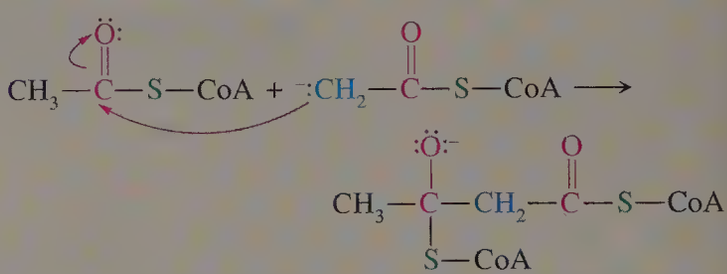


Because the 3*p* orbitals of sulfur do not effectively overlap with 2*p* orbitals of carbon, the positive charge of the dipolar resonance form of a carbonyl group cannot be further delocalized. The higher positive charge of the carbonyl carbon atom of the thioester more strongly polarizes the α C—H bond compared to the same bond of carboxylate esters and increases the acidity of thioesters.

Enzymes called acyl CoA ligases catalyze the Claisen condensation of thioesters. The first step in the reaction is abstraction of the acidic α hydrogen atom to form a resonance-stabilized thioenolate anion.

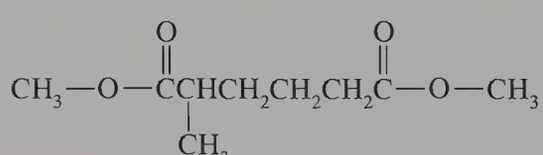


This anion is a nucleophile that attacks the electrophilic carbonyl carbon atom of a second acetyl CoA molecule to give a tetrahedral intermediate.



Problem 23.28

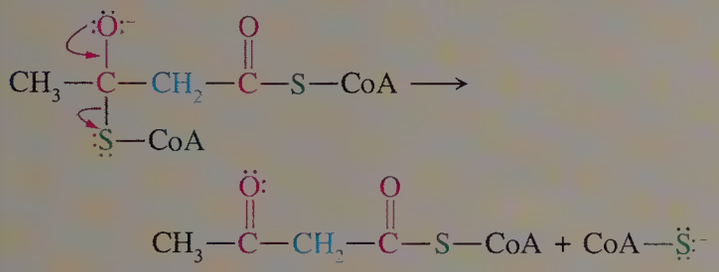
Although the diethyl ester of 2-methyladipic acid is not symmetrical, nevertheless a good yield of a single Dieckmann condensation product is possible. Explain why. Write the structure of the product.



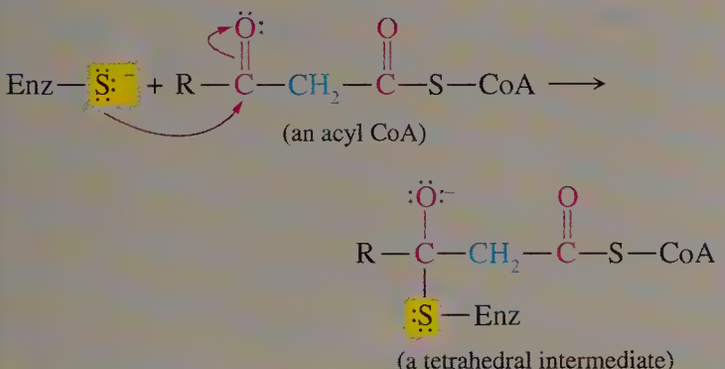
Problem 23.29

Draw the structure of the major product formed in the reaction of methyl formate and dimethyl succinate using a molar equivalent of sodium methoxide.

Because thiolates are weaker bases than alkoxides, the thiolate anion is a better leaving group. The tetrahedral intermediate breaks down with loss of CoA—SH to give the Claisen product, acetoacetyl CoA.

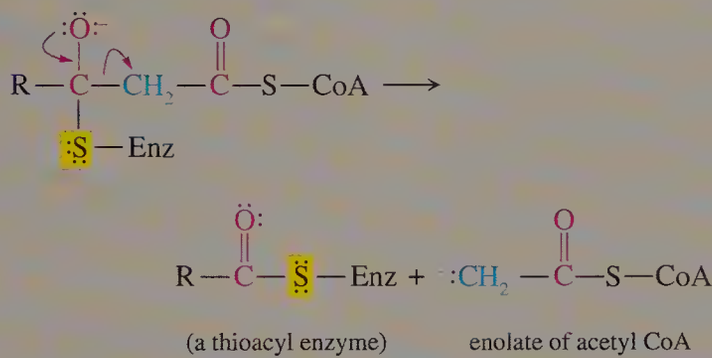


This product is a precursor of long-chain fatty acids. It is also the starting material in the biosynthesis of isoprenoid molecules such as terpenes and steroids.

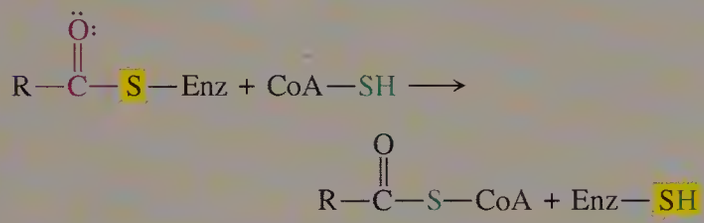


The Claisen condensation runs in reverse in the catabolism of fatty acids. The retro-Claisen reaction is initiated by attack of a sulfhydryl group of an enzyme at the electrophilic carbon atom of the β-keto group of an acyl CoA to give a tetrahedral intermediate.

This intermediate then decomposes to give the enolate form of acetyl CoA and a thioacyl enzyme intermediate.



The enolate of acetyl CoA is then protonated. A thioester exchange reaction with CoA—SH then generates an acyl CoA molecule with two fewer carbon atoms than the original acyl CoA.



Problem 23.30

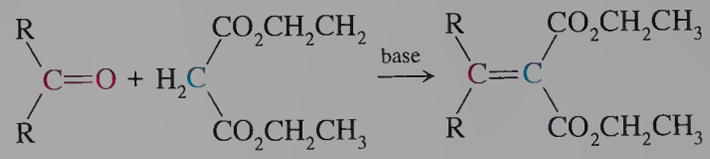
Ethyl 4-oxohexanoate intramolecularly cyclizes when treated with a molar equivalent of sodium methoxide. Draw the structure of the product.

23.16 Aldol-Type Condensations of Acid Derivatives

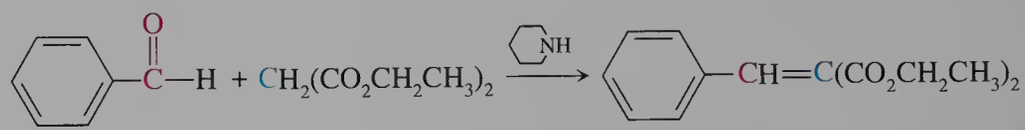
We recall that an aldol condensation occurs by attack of a carbanion derived from an aldehyde or ketone on the carbonyl carbon atom of a second molecule of an aldehyde or ketone. The product is a β-hydroxy carbonyl compound, or an α,β-unsaturated carbonyl dehydration product. Aldol-type condensations also occur when the carbanion is derived from a compound other than an aldehyde or ketones.

Knoevenagel Condensation

The **Knoevenagel condensation** reaction resembles a mixed aldol reaction. The enolate is derived from an ester and attacks the electrophilic carbon atom of an aldehyde or ketone. Dehydration occurs under the reaction conditions to give an α,β-unsaturated carbonyl compound.



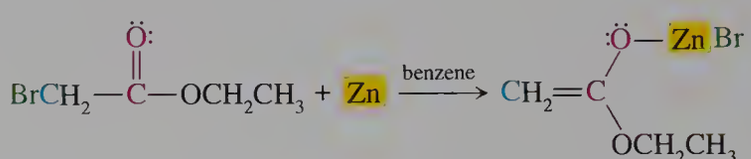
The Knoevenagel condensation is restricted to compounds with α hydrogen atoms that are relatively acidic, such as malonate esters or esters of acetoacetic acid. Piperidine is a common base used for the reaction.



benzaldehyde diethyl malonate diethyl benzylidinemalonate

Reformatskii Reaction

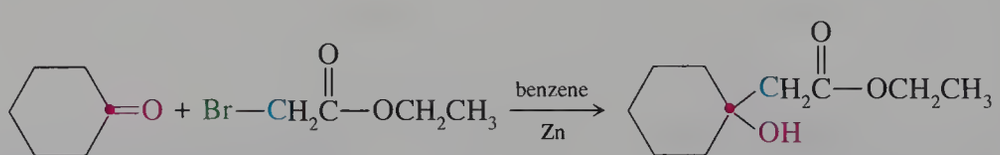
The reaction of an α-halo ester with zinc gives an intermediate ester enolate coordinated to a zinc ion. This ester enolate is the same as formed by deprotonation of an ester. Although the charge on an enolate is delocalized, the zinc is probably bonded to the oxygen atom, the site of most of the negative charge.



ethyl 2-bromoacetate zinc enolate

Subsequent reaction of the zinc enolate with an electrophilic carbon atom could occur at either the carbon atom or the oxygen atom of the enolate. However, we recall that similar reactions of enolates of aldehydes and ketones occur at carbon, retaining the very stable carbonyl group. The same considerations are important for the reactions of ester enolates.

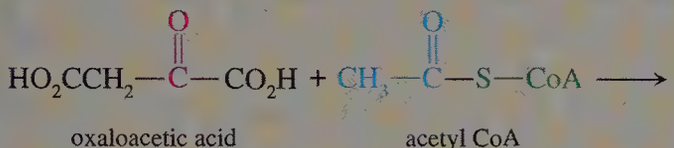
The reaction of a zinc enolate of an ester derived from an α-halo ester with a carbonyl group of an aldehyde or ketone is known as the **Reformatskii reaction**. The nucleophilic α carbon atom of the ester enolate attacks the carbonyl carbon atom.



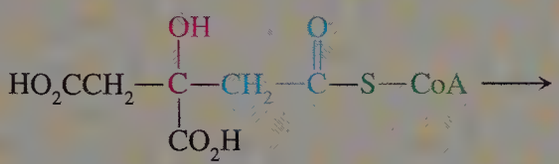
cyclohexanone ethyl 2-(1-hydroxycyclohexyl)acetate

Biochemical Condensation Reactions

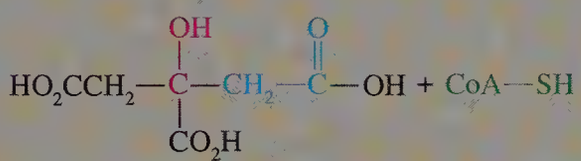
A condensation of acetyl CoA and oxaloacetic acid occurs in the first step of the citric acid cycle. This reaction occurs between a thioester and a ketone. The α carbon atom of acetyl CoA bonds to the carbonyl carbon of oxaloacetic acid in a reaction resembling the aldol condensation. In this reaction, an acetyl group is transferred to oxaloacetic acid to form a compound, citryl CoA, which is subsequently hydrolyzed to citric acid.



oxaloacetic acid acetyl CoA

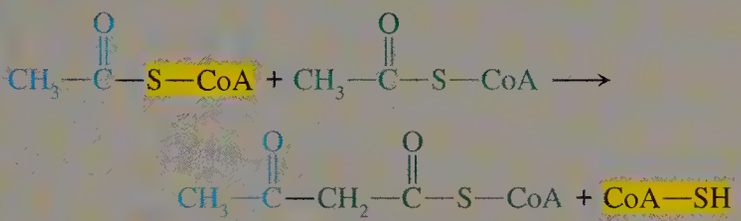


citryl CoA

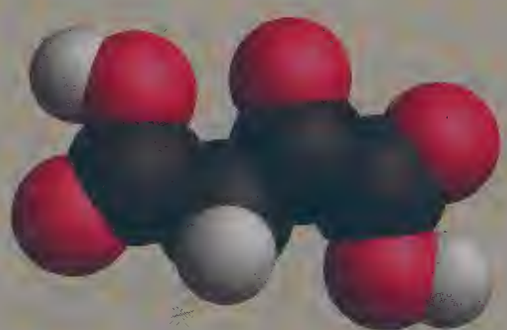


citric acid

Acetyl CoA is produced by the catabolism of carbohydrates, fatty acids, and certain amino acids. The catabolism of fatty acids predominates over the degradation of carbohydrates in certain illnesses, such as diabetes. When there is not enough oxaloacetic acid to react with all the acetyl CoA being produced by fatty acid degradation, acetyl CoA reacts with itself in a Claisen condensation.



Hydrolysis of the resulting β-keto thioester yields acetoacetic acid (3-ketobutanoic acid). Subsequent reactions produce 3-hydroxybutanoic acid by reduction and acetone by decarboxylation. These compounds, collectively called ketone bodies, occur in the urine of individuals with diabetes.



oxaloacetic acid

This reaction resembles an aldol reaction because a carbanion attacks a carbonyl group to give a α-hydroxy carbonyl compound. In an aldol reaction, the enolate comes from an aldehyde or ketone. In the Reformatskii reaction, the enolate comes from an ester.

Problem 23.31

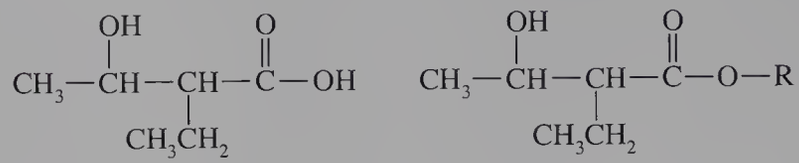
Draw the structure of the product formed in the reaction of ethyl acetoacetate and benzaldehyde catalyzed by piperidine.

Problem 23.32

Outline a synthesis of 2-ethyl-2-butenoic acid using the Reformatskii reaction as one of the steps in the reaction sequence. Will a single product result from this reaction?

Sample Solution

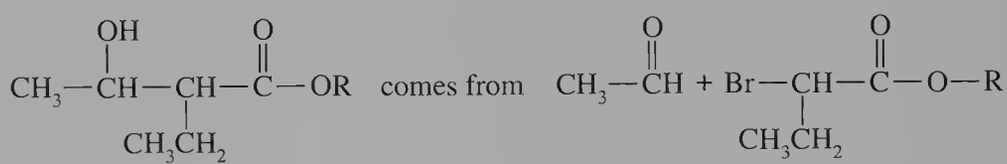
The desired product is an α, β-unsaturated carboxylic acid, which can be obtained by dehydration of a β-hydroxy acid or its related β-hydroxy ester.



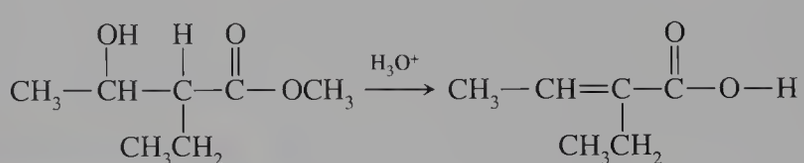
proposed β-hydroxy acid

its related β-hydroxy ester

The β-hydroxy ester is a typical product of the Reformatskii reaction, which forms a carbon–carbon bond between the a carbon atom of an α-halo ester and the carbonyl carbon atom of an aldehyde or ketone. Mentally separate the compound into the two required components.



Thus reaction of the methyl ester of 2-bromobutanoic acid and acetaldehyde gives the required methyl ester of 2-ethyl-3-hydroxybutanoic acid. Heating the product with aqueous acid will simultaneously dehydrate the alcohol and hydrolyze the ester. The unsaturated acid formed can be either (*E*) or (*Z*).



Problem 23.33

Outline a synthesis of 3-phenyl-2-butenoic acid using the Reformatskii reaction as one of the steps in the reaction sequence.

23.17 β-Dicarbonyl Compounds in Synthesis

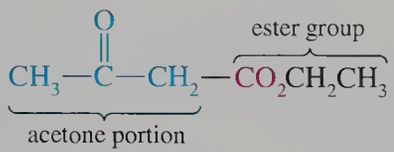
The alkylation of simple aldehydes, ketones, or esters is limited as a synthetic procedure. When an alkoxide is used as the base to form an enolate, a competing aldol condensation occurs in the case of aldehydes and ketones, and a Claisen condensation occurs for esters. Stronger bases, such as LDA, can be used to yield alkylated products, but special experimental techniques are required to preserve these very reactive reagents.

Alkylation at the α position of a carbonyl compound can be carried out indirectly by using a β-dicarbonyl compound such as ethyl malonate or ethyl acetoacetate. Both compounds are readily deprotonated using an alkoxide as base, and the resulting enolate is easily alkylated. β-Keto esters are valuable synthetic intermediates because they readily undergo decarboxylation. At the end of the synthesis, the β-keto ester is hydrolyzed to yield a β-keto acid. We recall that β-keto acids readily decarboxylate when heated (Section 21.8). Therefore the final product is the same as that obtained by direct alkylation of a simpler carbonyl compound. However, the yields are high even though more steps are required. Furthermore, it is more convenient to use common bases such as alkoxides than the stronger bases required for

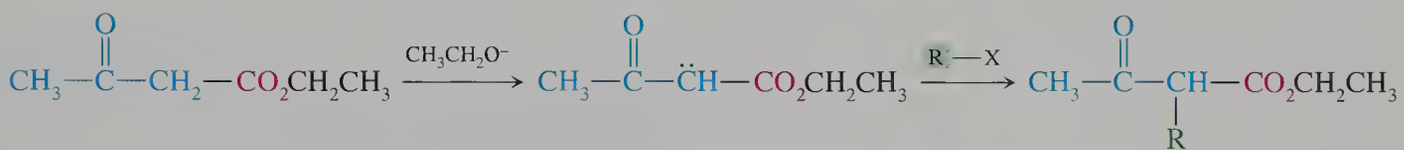
direct alkylation of an ester. Finally, because the ester enolate of a β-dicarbonyl compound is a weaker base, both primary and secondary alkyl halides can be used as alkylating agents without competing elimination reactions.

Acetoacetate Ester Synthesis

The Claisen condensation of ethyl acetate yields ethyl acetoacetate. This readily available material and other β-keto esters formed by Claisen condensations are used as intermediates in the synthesis of alkyl derivatives of ketones. For example, ethyl acetoacetic acid is like a molecule of acetone with an appended ester group.

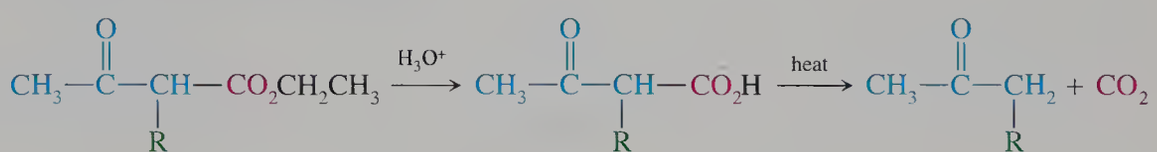


Sodium ethoxide is a sufficiently strong base to deprotonate ethyl acetoacetate. The resulting enolate is alkylated by the alkyl halides.



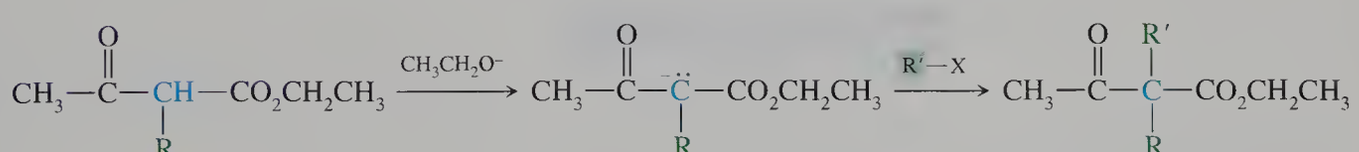
ethyl acetoacetate — enolate ion — alkylated acetoacetate ester

Acidic hydrolysis of the alkylated product yields a β-keto acid, which readily decarboxylates when heated.



In summary, acetone has been alkylated by taking advantage of a "temporary" ester group that enhances the acidity of the α hydrogen atom and allows alkylation of the α carbon atom. After it has served its purpose, the ester group is removed.

More complicated structures can be prepared by the acetoacetic acid synthetic method. Acetoacetate esters with one or more groups bonded to the γ carbon atom are available. It is also possible to dialkylate the α carbon atom by repeating the outlined steps using either the same alkyl group or a different one.

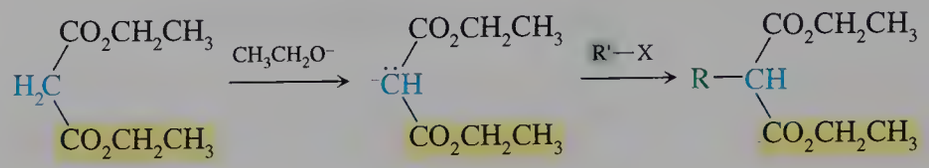


alkylated acetoacetate ester — enolate ion — dialkylated acetoacetate ester

Malonate Ester Condensations

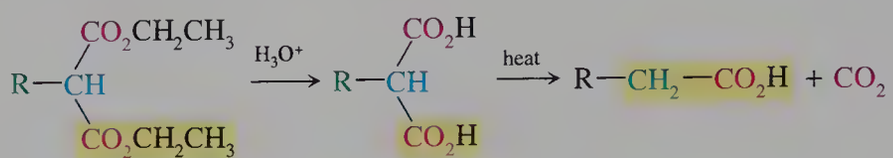
The malonate ester synthesis resembles the acetoacetate ester synthesis. It is used to prepare alkylated derivatives of acetic acid and other carboxylic acids, rather than

derivatives of acetone or other ketones prepared by the acetoacetic ester synthesis. The α hydrogen atom of diethyl malonate is sufficiently acidic to be deprotonated by ethoxide ion. Subsequent alkylation with a primary or secondary alkyl halide yields an alkylated malonate ester.



diethyl malonate — enolate ion — alkylated malonate ester

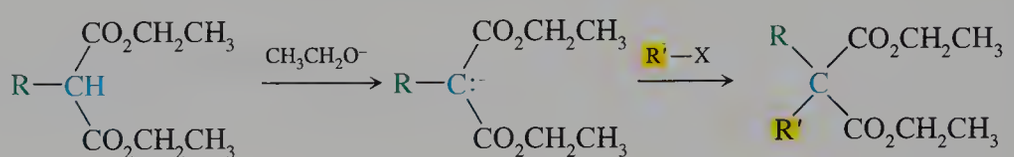
Acidic hydrolysis of the alkylated product yields a malonic acid that decarboxylates when heated.



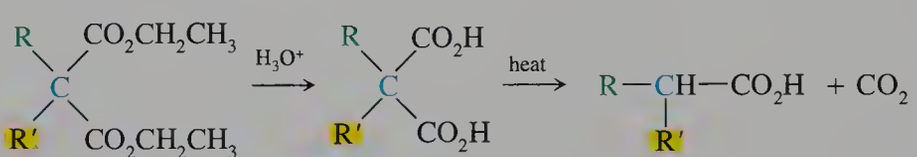
alkylated acetic acid

In summary, acetic acid has been alkylated by taking advantage of a "temporary" ester group, which enhances the acidity of the α hydrogen atom and allows the alkylation of the α carbon atom. Then the ester group is removed.

More complicated structures can be prepared by the malonate ester synthetic method. Malonate esters with one group bonded to the α carbon atom are available. Therefore, it is possible to introduce a second alkyl group by repeating the steps outlined above using either the same alkyl group or a different one.



alkylated malonate ester — enolate ion — dialkylated malonate ester



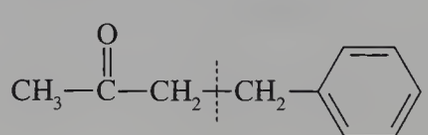
dialkylated acetic acid

Problem 23.34

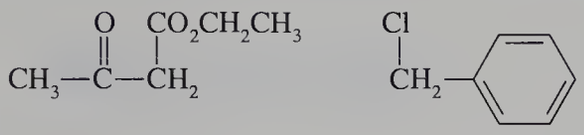
What reactants are required to prepare 4-phenyl-2-butanone using the acetoacetic ester method.

Sample Solution

Mentally disconnect the carbon–carbon bond that forms in the acetoacetic ester condensation. It is located between the α carbon atom of an acetone unit and the alkylating group.

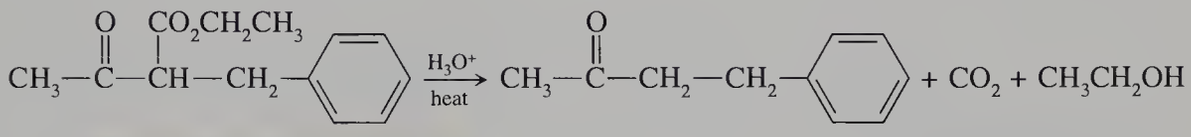


The acetone unit is derived from an acetoacetic ester such as ethyl acetoacetate. The alkylating group is available in the form of a halogen derivative such as benzyl chloride.



ethyl acetoacetate benzyl chloride

Reaction of ethyl acetoacetate with sodium ethoxide followed by addition of benzyl chloride gives an alkylated acetoacetate ester. Subsequent hydrolysis with heat leads to decarboxylation of the keto acid.



Problem 23.35

What alkylating agent is required to prepare 1-phenyl-1,4-pentanedione using ethyl acetoacetate as the other reactant?

Problem 23.36

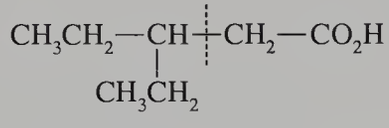
Ethyl acetoacetate can be doubly alkylated. Outline a multistep synthetic sequence to produce 3-propyl-5-hexen-2-one from ethyl acetoacetate as one of the starting materials.

Problem 23.37

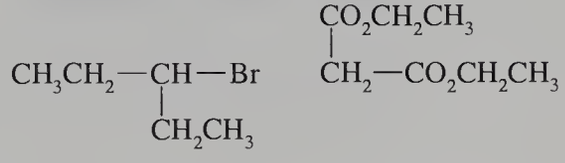
What reactants are required to prepare 3-ethylpentanoic acid by the malonate ester synthesis?

Sample Solution

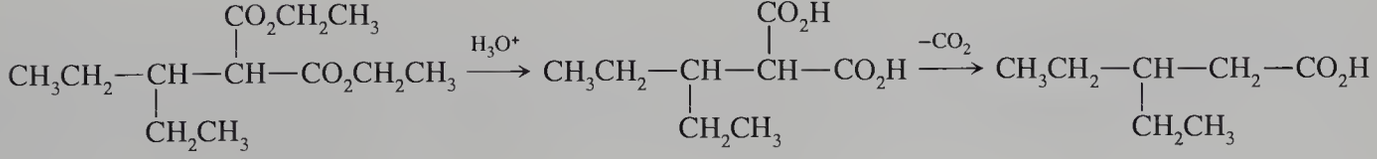
Mentally disconnect the bond between the α and β carbon atoms.



The acetic acid portion is derived from a malonate ester. The alkyl group is available as a haloalkane, which in this case could be 3-bromopentane.



Reaction of diethyl malonate with sodium ethoxide followed by addition of 3-bromopentane gives an alkylated malonate ester. Subsequent hydrolysis with heat leads to decarboxylation of the dicarboxylic acid.



Problem 23.38

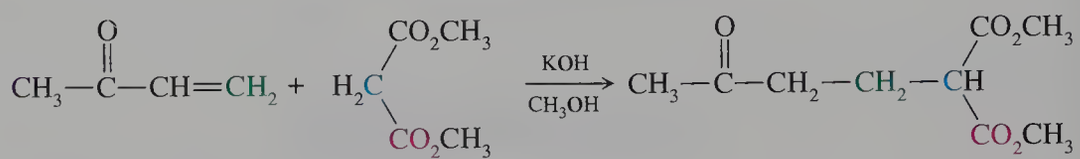
Explain why 3,3-dimethylpentanoic acid cannot be prepared by the malonate ester synthesis.

Problem 23.39

The reaction of diethyl malonate and 1,4-dibromobutane in the presence of two moles of sodium ethoxide followed by acidification and heat gives a compound $C_6H_{10}O_2$. What is the structure of the product?

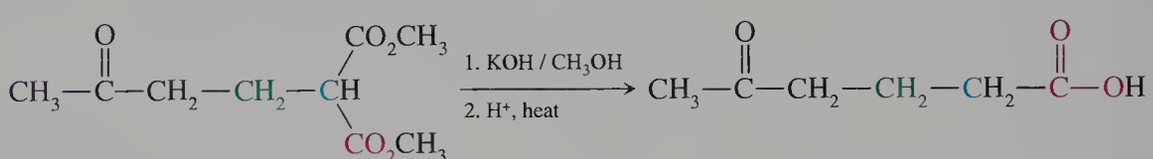
23.18 Michael Condensations of Acid Derivatives

In the **Michael reaction**, an enolate acts as a nucleophile and adds 1,4 to an α,β-unsaturated carbonyl compound (Section 23.12). 1,3-Dicarbonyl compounds frequently provide the enolate, called the Michael donor. Three α,β-unsaturated carbonyl compounds are commonly used as Michael acceptors: 3-buten-2-one (methyl vinyl ketone), 2-propenal (acrolein), and methyl 2-propenoate (methyl acrylate). For example, dimethyl malonate reacts with 3-buten-2-one in a base-catalyzed reaction.



3-buten-2-one (methyl vinyl ketone) | dimethyl malonate | methyl 2-carbomethoxy-5-oxohexanoate

Hydrolysis of the ester functional groups of this Michael product followed by decarboxylation yields a 5-keto acid.



5-oxohexanoic acid

In general, the Michael addition of 1,3-dicarbonyl donors to typical α,β-unsaturated carbonyl compounds (Michael acceptors) yields 1,5-dicarbonyl compounds.

Problem 23.40

Draw the product of the Michael addition of methyl acetoacetate to 2-cyclohexenone. Draw the product obtained by hydrolyzing the adduct followed by heating to decarboxylate the intermediate acid.

EXERCISES

Acidity of α Hydrogen Atoms

23.1 The pK_a of 2,4-pentanedione is 9. Calculate the equilibrium constant for the acid–base reaction of 2,4-pentanedione with sodium ethoxide. The pK_a of ethanol is 15.9.

23.2 The pK_a of acetonitrile, CH_3CN, is 25. Calculate the equilibrium constant for the acid–base reaction of acetonitrile with LDA.

23.3 The pK_a of acetophenone is 16. Calculate the equilibrium constant for the acid–base reaction of acetophenone with LDA.

23.4 The pK_a of nitromethane is 10.2. Calculate the equilibrium constant for the acid–base reaction of nitromethane with sodium ethoxide. The pK_a of ethanol is 15.9.

23.5 The pK_a values of acetone and 3-pentanone as measured in DMSO are 26.5 and 27.1, respectively. Explain this order of values.

23.6 The pK_a values of acetone and 1-phenyl-2-propanone as measured in DMSO are 26.5 and 19.8, respectively. Explain this order of values.

Stability of Enols

23.7 Which ketone has the larger percent enol at equilibrium, cyclohexanone or cyclobutanone?

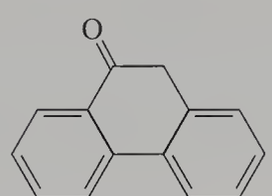
23.8 Which ketone has the larger percent enol at equilibrium, 1,3-cyclohexanedione or 1,4-cyclohexanedione?

23.9 Write the structures of the isomeric enols of 2,2-dimethyl-3-pentanone and rank them in order of their stability.

23.10 Write the structures of the isomeric enols of 2-methylcyclopentanone and rank them in order of relative stability.

23.11 Which ketone has the larger percent enol at equilibrium, 1,2-diphenylethanone or 1,3-diphenyl-3-propanone?

23.12 Write the structure for the enol tautomer of the following molecule. What structural features contribute to the stability of each tautomer?



Enolates

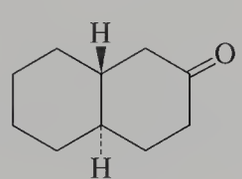
23.13 Write the resonance form with a negative charge on the oxygen atom for the enolates derived from each of the following compounds.
(**a**) 3,3-dimethyl-2-butanone (**b**) acetophenone (**c**) 2,2-dimethylcyclohexanone

23.14 Write the resonance form with a negative charge on the oxygen atom for all possible enolates derived from each of the following compounds. Which enolate is the most stable in each case?
(**a**) 2-pentanone (**b**) 1-phenyl-2-propanone (**c**) 1,3-cyclohexanedione

23.15 Write the contributing resonance forms of the conjugate base of acetonitrile (CH_3CN) and nitromethane (CH_3NO_2).

23.16 Write the contributing resonance forms for all possible conjugate bases of 3,6,6-trimethyl-2-cyclohexenone.

23.17 The following ketone gives a mixture of two enolates in approximately equal amounts (53:47). Write the structures of the enolates and explain why they are of comparable stability.

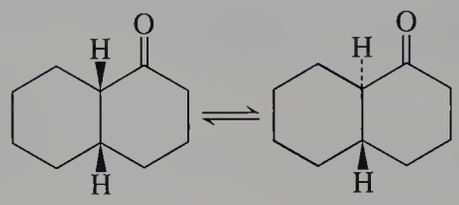


23.18 2-Methylcyclopentanone gives a mixture of two enolates in a 94:6 ratio. Write the structures and assign their relative stabilities.

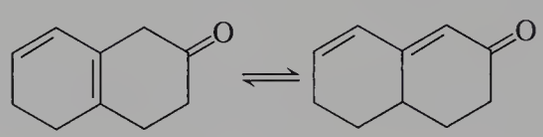
23.19 3-Pentanone gives a mixture of two enolates in a 84:16 ratio. Write the structures and assign their relative stabilities.

23.20 2,2-Dimethyl-3-pentanone gives a mixture of two enolates. Based on the data in Exercise 23.19, predict how the ratio of the amounts of the two enolates would differ from the ratio for 3-pentanone.

23.21 Write the mechanism for the following isomerization reaction, which occurs using sodium ethoxide in ethanol. Predict which isomer is more stable.



23.22 Write the mechanism for the following isomerization reaction, which occurs using sodium ethoxide in ethanol. Predict which isomer is the more stable.



23.23 Write a mechanism for the base-catalyzed isomerization of 3-cyclohexenone to 2-cyclohexenone.

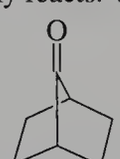
23.24 Write a mechanism for the base-catalyzed isomerization of 5-methyl-2-cyclopentenone to 2-methyl-2-cyclopentenone. (*Hint:* A third isomeric unsaturated ketone is a required intermediate.)

23.25 Write a mechanism that explains why a solution of (*R*)-2-methyl-1-phenyl-1-pentanone in ethanol containing sodium ethoxide gradually loses optical activity but a solution of (*R*)-3-methyl-1-phenyl-1-pentanone does not.

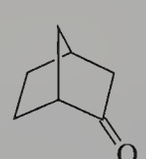
23.26 Predict the change in the optical activity of each of the following in a solution of sodium ethoxide in ethanol.
(**a**) (*R*)-2-methylcyclohexanone (**b**) (*R*)-3-methylcyclohexanone (**c**) (*R*)-2-methyl-2-ethylcyclohexanone

Deuterium Exchange

23.27 Explain why 7-bicyclo[2.2.1]heptanone does not undergo an exchange reaction using sodium hydroxide in D_2O but 2-bicyclo[2.2.1]heptanone readily reacts. Which hydrogen atoms are exchanged?

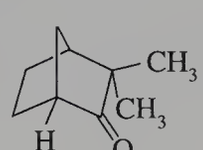


7-bicyclo[2.2.1]heptanone



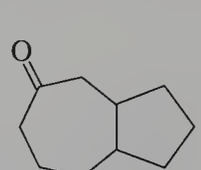
2-bicyclo[2.2.1]heptanone

23.28 Explain why 3,3-dimethyl-2-bicyclo[2.2.1]heptanone does not undergo an exchange reaction using sodium hydroxide in D_2O.



3,3-dimethyl-2-bicyclo[2.2.1]heptanone

23.29 Explain how the following isomeric ketones could be distinguished using the base-catalyzed exchange reaction with deuterium.



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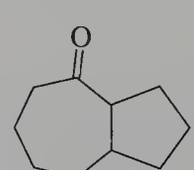


II

23.30 Explain how 2-pentanone and 3-pentanone could be distinguished using the base-catalyzed exchange reaction with deuterium.

23.31 3-Methyl-2,4-pentanedione rapidly exchanges one hydrogen using sodium hydroxide and D_2O. After a long period of time, a total of seven hydrogen atoms are eventually exchanged. Explain the reason for these observations.

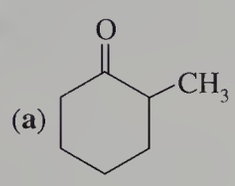
23.32 After a long period of time, 3-methyl-2-cyclohexenone exchanges a total of eight hydrogen atoms. Identify the hydrogen atoms exchanged and write a step showing the transfer of deuterium to an enolate that gives exchange at each of the required sites.

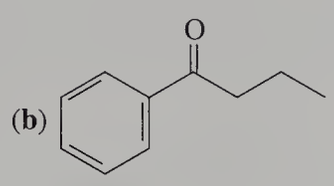
Halogenation Reactions

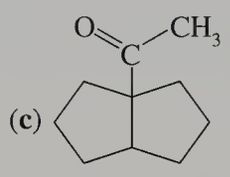
23.33 Reaction of 3-methyl-2,4-pentanedione with bromine under acidic conditions rapidly yields a monobromo derivative. Write the structure of the product and explain how it forms.

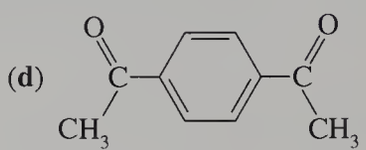
23.34 Reaction of 3-methyl-2-butanone with bromine under acidic conditions yields a mixture of two monobromo derivatives in a 95:5 ratio. Write the structure of the products and explain why the observed ratio occurs.

23.35 Which of the following compounds will give a positive iodoform test when treated with iodine in an alkaline solution?



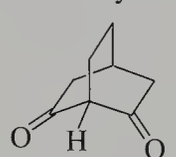




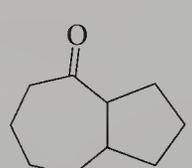


23.36 Write the structure of a compound with molecular formula $C_8H_{14}O_2$ that gives adipic acid when reacted with excess bromine in an alkaline solution.

23.37 Explain why the indicated hydrogen atom at the bridgehead carbon of the following compound is not replaced by bromine in alkaline solution. What competing reactions may occur?

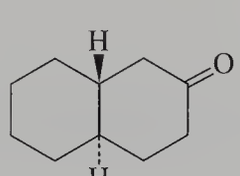


23.38 Predict the structure of the dibromo derivative obtained from the following ketone in alkaline solution.



23.39 Bromination of 4-*tert*-butylcyclohexanone under acidic conditions yields a mixture of two isomeric monobromo derivatives in approximately equal amounts. Write the structures of the products and explain why the ratio of the two compounds is approximately one.

23.40 Write the structures of the four isomeric monobromo derivatives that could result from bromination of the following ketone in acidic solution.



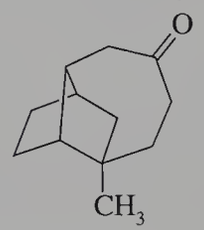
Reactions at the α Carbon Atom

23.41 Write the structure of the product obtained by the reaction of 2,2-dimethyl-3-pentanone with sodium hydride followed by addition of 1-iodobutane.

23.42 Explain why reaction of cyclohexanone with LDA followed by the addition of 2-bromopropane gives only the original ketone upon aqueous workup.

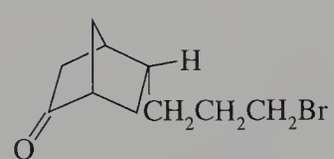
23.43 The enolate derived from reaction of LDA with 4-*tert*-butylcyclohexanone reacts with ethyl iodide to give a mixture of two monoalkylated products in approximately equal amounts. Write the structures of the products and explain why the ratio of the two compounds is approximately one.

23.44 A mixture of enolates forms from reaction of the following ketone with LDA. Write the structure of all possible monoalkylated products from reaction of the enolates with methyl iodide.

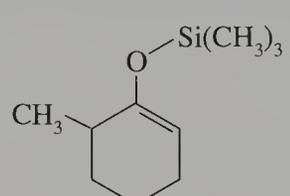


23.45 Reaction of 6-bromo-3,3-dimethyl-2-hexanone with LDA give a product with the molecular formula $C_8H_{14}O$. Write its structure.

23.46 Reaction of the following ketone with a sterically hindered strong base gives a product with the molecular formula $C_{10}H_{14}O$. Write its structure.



23.47 Trimethylchlorosilane, $(CH_3)_3SiCl$, reacts with enolates exclusively at the oxygen atom to give trimethylsilyl enol ethers. When heated with triethylamine and trimethylchlorosilane, the silyl ethers I and II derived from 2-methylcyclohexanone occur in a 1:3 ratio. Which is more stable? Explain why the indicated ratio occurs.



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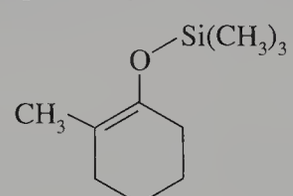
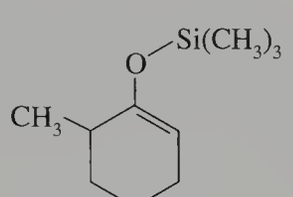


II

23.48 Using the data in Exercise 23.47, predict the structure of the major product of the reaction of 2-pentanone with triethylamine and trimethylchlorosilane.

23.49 The reaction of 2-methylcyclohexanone with LDA in 1,2-dimethoxyethane at 0 °C yields a solution that, when subsequently reacted with trimethylchlorosilane and triethylamine, yields I and II in a 99:1 ratio. Explain why the indicated ratio occurs.



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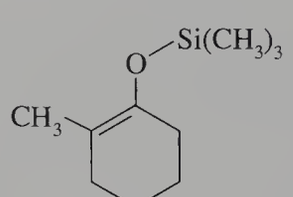


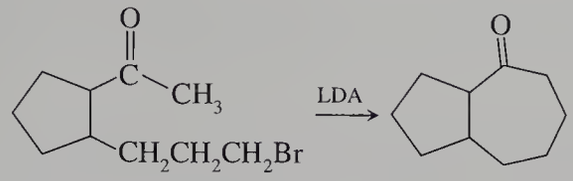
II

23.50 Based on the data in Exercise 23.49, predict the structure of the major product of the reaction of 2-pentanone with LDA in 1,2-dimethoxyethane at 0 °C followed by trimethylchlorosilane and triethylamine.

23.51 The reaction of 2-methylcyclohexanone with LDA in 1,2-dimethoxyethane at 0°C yields a solution that when subsequently reacted with benzyl bromide yields 2-benzyl-6-methylcyclohexanone and 2-benzyl-2-methylcyclohexanone in a 12:1 ratio. Explain why the indicated ratio occurs.

23.52 What experimental conditions would favor formation of 2-benzyl-2-methylcyclohexanone by alkylation of 2-methylcyclohexanone with benzyl bromide?

23.53 Explain why the reaction of the following ketone with LDA in THF at -60 °C yields the indicated bicyclic ketone.

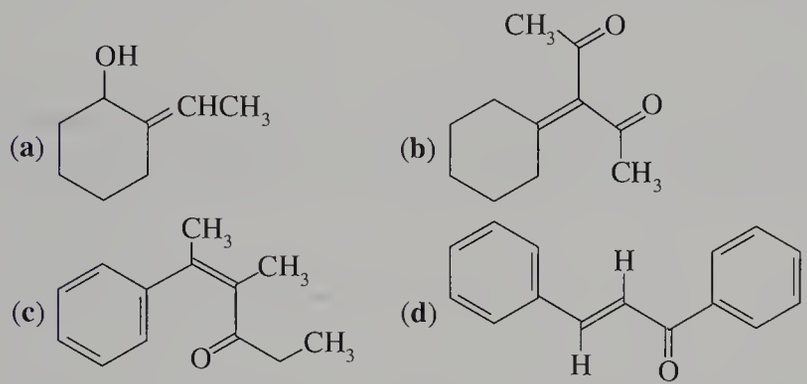


23.54 The ketone shown in Exercise 23.53 reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to give a constitutional isomer of the bicyclic ketone shown there. Write its structure and explain its origin.

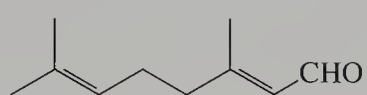
Aldol Condensations

23.55 Draw the structure of the product of the self-condensation of each of the following aldehydes in the presence of a catalytic amount of sodium hydroxide.
(**a**) 2-methylpropanal (**b**) phenylethanal (**c**) octanal

23.56 What reactants are required to give the following compounds by a crossed aldol reaction?



23.57 Pseudoionone, a component of some perfumes, has the molecular formula $C_{13}H_{20}O$. It can be prepared by a crossed aldol reaction of citral and acetone. Write the structure of pseudoionone.

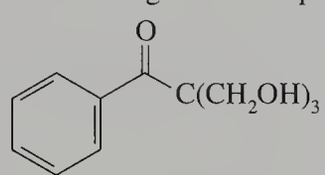


citral

23.58 A crossed aldol reaction between citral and 2-butanone yields two isomeric compounds. Write their structures.

23.59 2,2-Dimethyl-1,3-propanediol can be synthesized by reduction of a crossed aldol product using sodium borohydride. What is the aldol and what two carbonyl compounds are required to produce it?

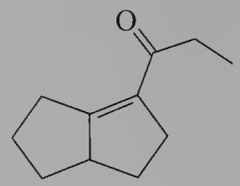
23.60 Suggest a synthesis of the following compound starting from acetophenone.



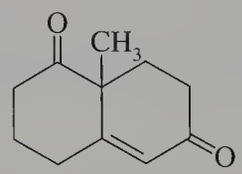
23.61 The favored products of the intramolecular aldol condensation of 2,5-hexanedione and 2,6-heptanedione are given in Section 23.9. Write an alternative isomeric structure for each product and explain why it is not formed.

23.62 The intramolecular aldol condensation of 2,6-octanedione could yield two possible six-membered unsaturated products. Write their structures and predict which isomer would be the major product.

23.63 What diketone will yield the following as a product of an intramolecular aldol condensation? What isomeric bicyclic compound could also form but in smaller amount?



23.64 What reactant could yield the following product from an intramolecular aldol condensation?



Conjugate Addition Reactions

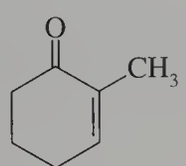
23.65 Amines will give a conjugate addition products with α,β-unsaturated ketones. Write the structure of the product for each of the following combinations of reactants.

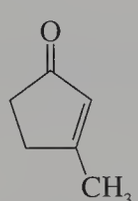
(**a**) 2-cyclohexenone and $CH_3CH_2NH_2$

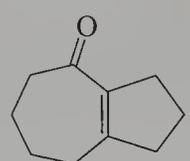
(**b**) 3-butenone and $(CH_3)_2NH$

(**c**) 4-methyl-3-penten-2-one and CH_3NH_2

23.66 The conjugate addition of HCN to α,β-unsaturated ketones can be done using diethylaluminum cyanide, $(C_2H_5)_2Al—CN$, followed by acidic workup. Write the structure of the addition product for each of the following reactants.

(**a**) 

(**b**) 

(**c**) 

23.67 Write the structure of the addition product of 2-cyclohexenone with ethylmagnesium bromide after hydrolysis. Do the same for the addition product of 2-cyclohexenone with lithium diethylcuprate.

23.68 What combination of an α,β-unsaturated ketone and a Gilman reagent is required to synthesize each of the following compounds?

(**a**) 3-phenylcycloheptanone

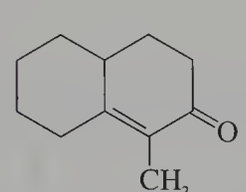
(**b**) 2-hexanone

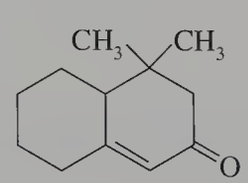
(**c**) 3-vinylcyclohexanone

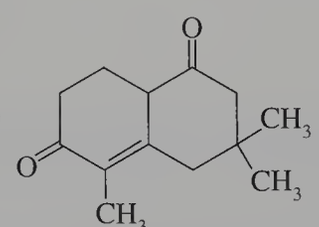
Michael Addition and Robinson Annulation Reactions

23.69 Write the product of the Michael addition reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one followed by Robinson annulation.

23.70 What combination of α,β-unsaturated ketone and a ketone is required to synthesize each of the following compounds by a Michael addition followed by Robinson annulation?

(**a**) 

(**b**) 

(**c**) 

Acidity of α Hydrogen Atom of Acid Derivatives

23.71 The cyano group is more deactivating in electrophilic aromatic substitution than a carboethoxy group. Which compound is more acidic, ethyl β-cyanoacetate or diethyl malonate?

23.72 The pK_a of nitromethane is 11. Which compound is more acidic, nitroacetone or ethyl acetoacetate?

23.73 The pK_a of malonitrile, $CH_2(CN)_2$, is 11. Calculate the equilibrium constant for the acid–base reaction of malonitrile with sodium ethoxide.

23.74 The equilibrium constant for the reaction of ethyl 2-cyanoacetate with sodium ethoxide is approximately 10^7. What is the pK_a of ethyl 2-cyanoacetate?

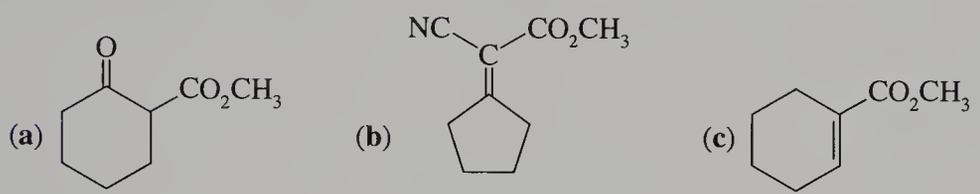
Enolate of Acid Derivatives

23.75 Write the resonance forms of the conjugate base of malonitrile, $CH_2(CN)_2$, and dinitromethane, $CH_2(NO_2)_2$.

23.76 Write the resonance forms of the conjugate base of ethyl 2-cyanoacetate.

23.77 Ethyl acetoacetate reacts with two equivalents of LDA to give a dianion. Draw the structure of the dianion.

23.78 Draw the resonance contributors of the anion formed by deprotonation of the most acidic hydrogen atom of each of the following compounds.

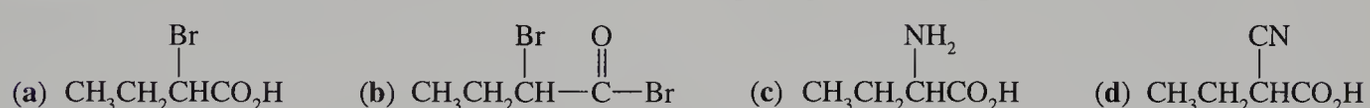


Reactions at the α Carbon Atom

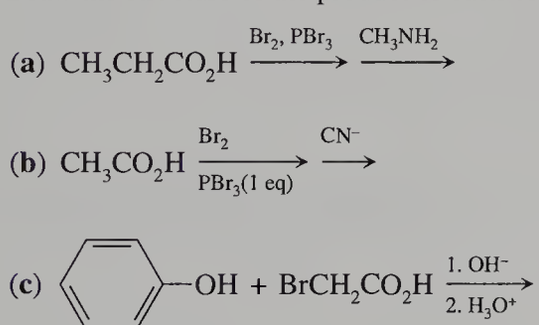
23.79 What products result from the reaction of each of the following isomeric esters with sodium ethoxide in CH_3CH_2OD?
(**a**) ethyl pentanoate
(**b**) ethyl 2-methylbutanoate
(**c**) ethyl 3-methylbutanoate

23.80 Ethyl acetoacetate reacts rapidly with sodium ethoxide in CH_3CH_2OD to give a product incorporating two deuterium atoms. After a longer period of time, an additional three deuterium atoms are incorporated. Explain why.

23.81 Write the equations for the synthesis of each of the following compounds starting from butanoic acid.



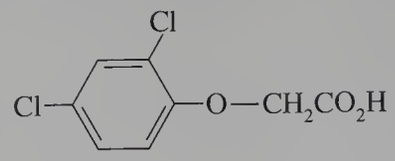
23.82 Draw the structure of the product of each of the following reactions.



23.83 Draw the structure of the product resulting from reaction of each of the following esters with LDA followed by reaction of the enolate with the second reactant.
(**a**) *tert*-butyl-2-methylpropanoate and benzoyl chloride
(**b**) ethyl 2-methylpropanoate and ethyl iodide
(**c**) *tert*-butyl-2-methylpropanoate and one equivalent of 1-bromo-3-chloropropane

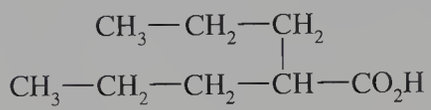
23.84 Explain why diethyl 2-phenylmalonate cannot be prepared by arylation of diethyl malonate. Suggest a method of synthesis starting from ethyl 2-phenylacetate.

23.85 Outline a synthesis of the herbicide 2,4-D using acetic acid as one of the reactants.



2,4-dichlorophenoxyacetic acid (2,4-D)

23.86 Outline a synthesis of valproic acid, a compound used in treatment of epilepsy, using ethyl acetate as one of the reactants.



Claisen Condensations

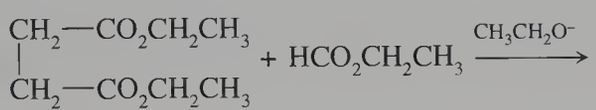
23.87 Draw the structure of the product of the self-condensation of each of the following esters in the presence of a molar equivalent of sodium methoxide.

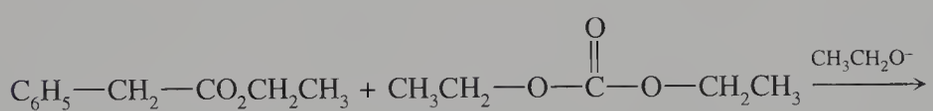
(**a**) methyl propanoate

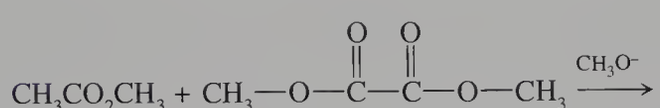
(**b**) methyl 3-phenylbutanoate

(**c**) methyl 2-cyclohexylethanoate

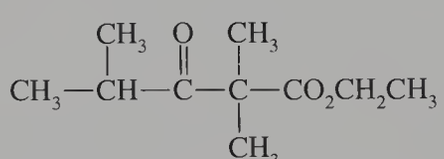
23.88 Draw the structure of the product of each of the following reactions.

(**a**) 

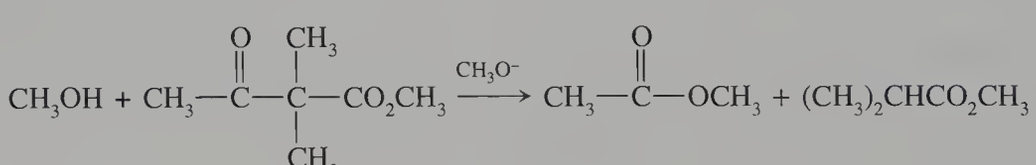
(**b**) 

(**c**) 

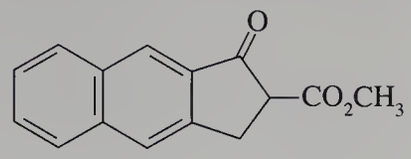
23.89 Explain why the following keto ester reacts with sodium ethoxide in ethanol to yield ethyl 2-methylpropanoate.

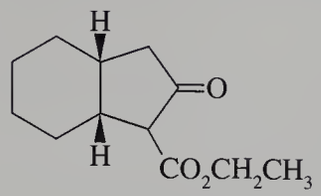


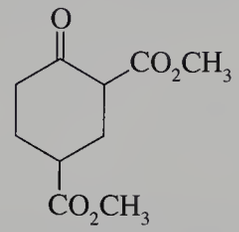
23.90 Explain why the equilibrium constant for the following reaction is greater than one.



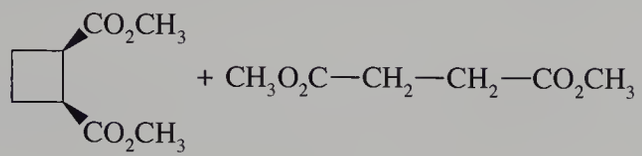
23.91 What reactant is required to synthesize each of the following structures using a Dieckmann condensation?

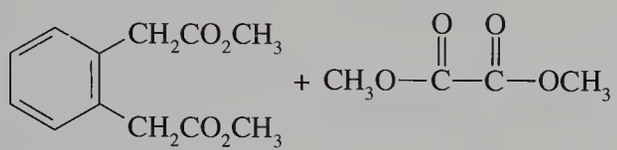
(a) 

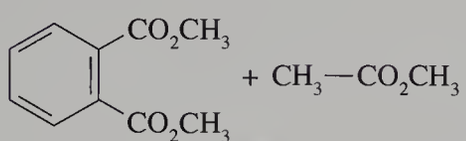
(b) 

(c) 

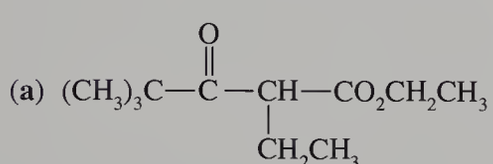
23.92 Each of the following pairs of compounds undergoes a "double" Claisen condensation in methanol and sodium methoxide to form a structure containing an additional ring. Draw the structure of the product of each reaction.

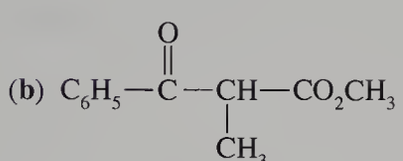
(a) 

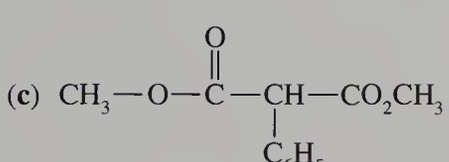
(b) 

(c) 

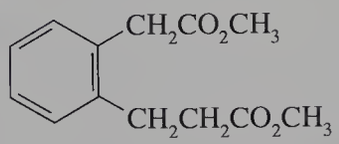
23.93 What esters are required to give the following mixed Claisen products?

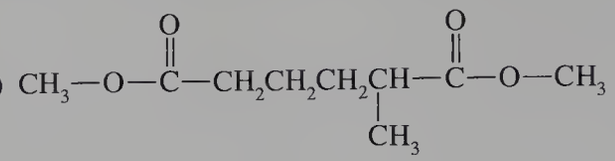
(a) 

(b) 

(c) 

23.94 There are two possible Dieckmann condensation products for each of the following compounds. Which product forms in each case?

(a) 

(b) 

23.95 2-Methylcyclohexanone is treated with one molar equivalent of LDA to form an enolate. Draw the structure of the product of the reaction of the enolate with diethyl oxalate.

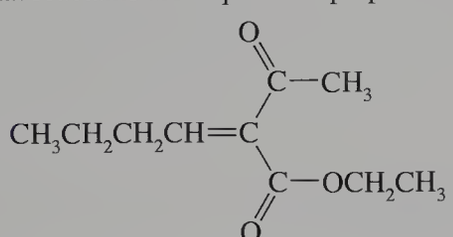
23.96 A mixture of cyclohexanone and diethyl carbonate is allowed to react in a solution of ethanol containing sodium ethoxide. Write the structure of the product.

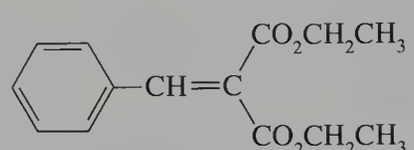
Aldol-Type Condensations

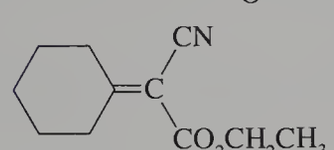
23.97 Draw the structure of the product of each of the following combinations of reagents in a reaction using one equivalent of sodium ethoxide.
(a) *p*-nitrobenzaldehyde and diethyl malonate
(b) cyclopentanone and ethyl acetoacetate
(c) cyclooctanone and diethyl succinate

23.98 The reaction of ethyl 2-bromopropanoate with zinc and acetophenone gives two isomeric compounds. Explain why.

23.99 What reactants are required to prepare the following compounds using the Knoevenagel condensation?

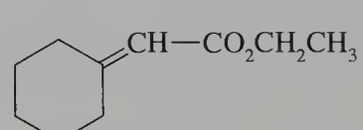
(a) 

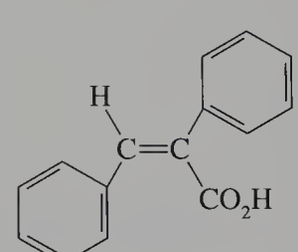
(b) 

(c) 

23.100 The product of a Reformatskii reaction can be dehydrated to give an α,β-unsaturated acid or ester. What reactants are required to synthesize each of the following products using the Reformatskii reaction as one of the steps?

(a) 

(b) 

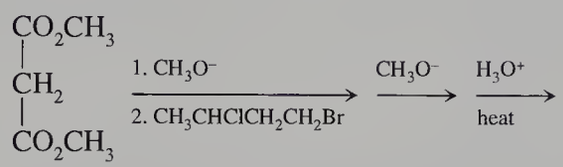
(c) 

Synthesis Using β Dicarbonyl Compounds

23.101 Outline the synthesis of each of the following compounds using diethyl malonate as one of the reactants.
(a) 2-methyl-4-pentenoic acid (b) 3-propylpentanoic acid (c) 2-benzylbutanoic acid
(d) 3-phenylpropanoic acid (e) 2-ethyl-4-pentynoic acid

23.102 Outline the synthesis of each of the following compounds using ethyl acetoacetate as one of the reactants.
(**a**) 4-phenyl-2-butanone
(**b**) 5-hexene-2-one
(**c**) 5-methyl-2-hexanone
(**d**) 3-propyl-5-hexene-2-one
(**e**) 4-cyclopentyl-3-methyl-2-butanone

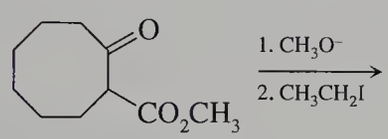
23.103 The malonic acid synthesis can be used to prepare cycloalkanecarboxylic acids by a double alkylation using a dihalide. Write the structure of the product of each of the steps in the following sequence.

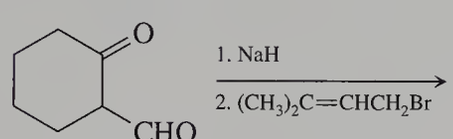


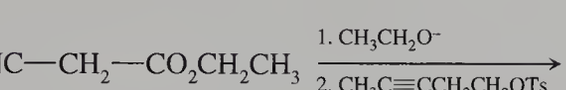
23.104 What is the product of a malonic acid synthesis if the final step uses aqueous hydroxide ion in a saponification reaction followed by careful neutralization with HCl rather than an acid-catalyzed hydrolysis reaction?

23.105 Ethyl acetoacetate reacts with one molar equivalent of sodium ethoxide followed by the addition of 2,2-dimethyloxirane to give a cyclic compound of molecular formula $C_8H_{12}O_3$. Draw its structure.

23.106 Draw the structure of the product of each of the following reactions.

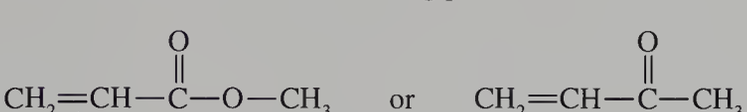
(**a**) 

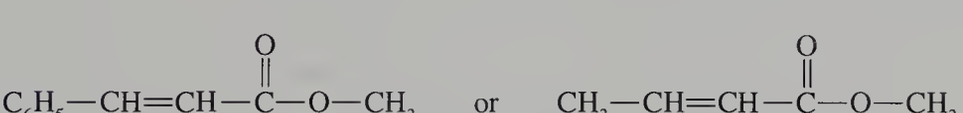
(**b**) 

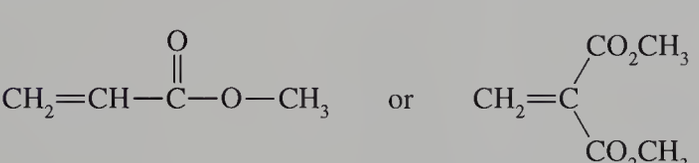
(**c**) 

Michael Addition Reactions

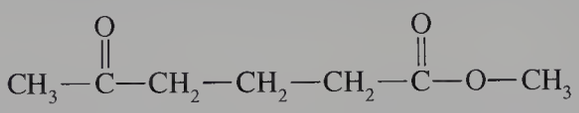
23.107 Which member of each of the following pairs is more reactive as an acceptor in the Michael addition reaction?

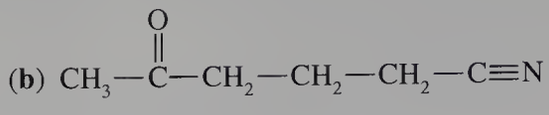
(**a**) 

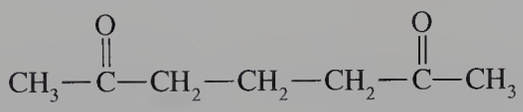
(**b**) 

(**c**) 

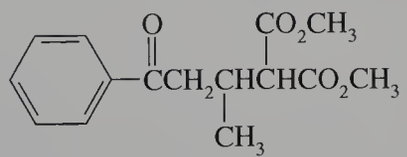
23.108 What reactants are required to synthesize each of the following compounds by a Michael addition reaction?

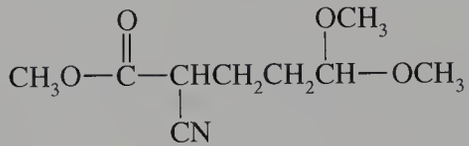
(a) 

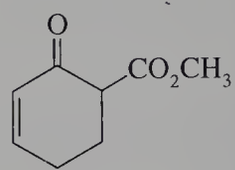
(b) 

(c) 

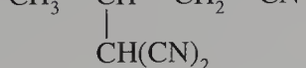
23.109 What reactants are required to synthesize each of the following compounds using a Michael addition reaction as one of the steps?

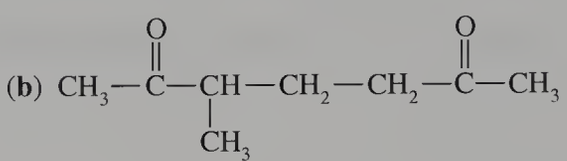
(a) 

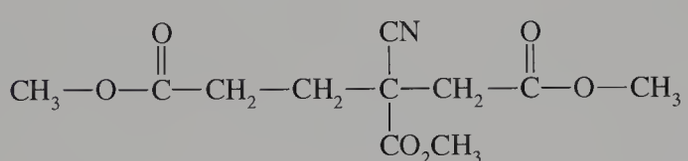
(b) 

(c) 

23.110 Write the steps required to synthesize the following structures using a Michael addition reaction as one of the steps.

(a) 

(b) 

(c) 

24

Lipids

24.1 Classification of Lipids

The name lipid encompasses a wide range of molecular structures and an extraordinary range of biochemical functions. As the molecules making up dietary fat, certain lipids provide a major source of metabolic energy. As components of biological membranes, lipids provide an insoluble partition between a cell and its watery environment. Lastly, as hormones, lipids regulate a wide spectrum of cellular activities.

Lipids are relatively nonpolar compounds, and they can be separated from more polar cellular substances by their solubility in nonpolar organic solvents. In fact, lipids were historically classified as compounds of biological origin that are soluble in organic solvents. The term lipid is sometimes used as a synonym for fat (Greek *lipos*, fat). However, fat is only one of the various types of lipids. Lipids are divided into groups based on their hydrolysis reactions. **Simple lipids** are not hydrolyzed by aqueous basic solution. These include terpenes (Chapter 12), produced in plants; and steroids (Chapter 4), important hormones in animals. **Complex lipids** are hydrolyzed by aqueous basic solution. The major hydrolysis products of complex lipids are the long-chain carboxylic acids called fatty acids. The fatty acids in complex lipids usually have an even number of carbon atoms. The other components resulting from the hydrolysis of a complex lipid determine its subclass.

Figure 24.1 shows only the major classes of lipids. This chapter will deal with the general structures of only the following types of lipids.

1. **Waxes** are esters of long-chain alcohols and fatty acids.
2. **Triacylglycerols**, also known as triglycerides, are esters of glycerol and long-chain fatty acids.
3. **Glycerophospholipids** are composed of glycerophosphate (an ester of glycerol and phosphoric acid), long-chain fatty acids, and certain low molecular weight alcohols.
4. **Sphingophospholipids** are composed of a phosphate ester of sphingosine, long-chain fatty acids, and choline.
5. **Glycosphingolipids** are composed of sphingosine, fatty acids, and a carbohydrate, either a monosaccharide or an oligosaccharide.

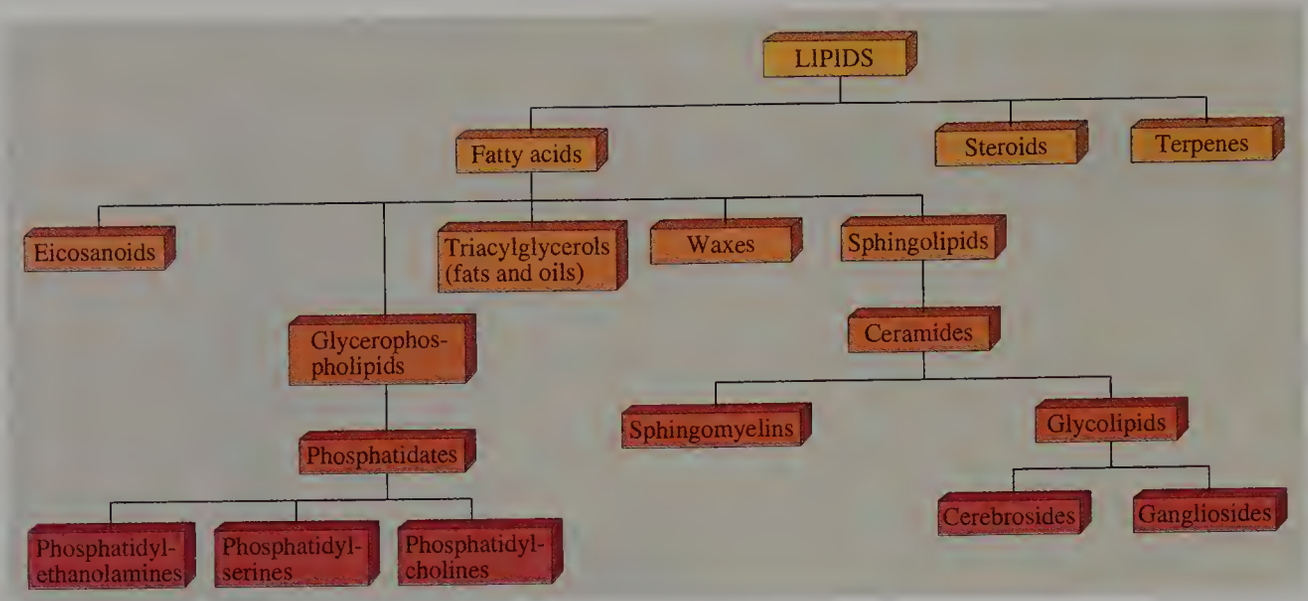


FIGURE 24.1 Major Classes of Lipids

24.2 Fatty Acids

Fatty acids are long-chain carboxylic acids that usually contain an even number of carbon atoms. More than 100 fatty acids have been found in the lipids of animals, plants, and microorganisms. They differ in the length of the chain, the number of carbon–carbon double bonds, and the location of those double bonds in the carbon chain. The fatty acids found in mammals range from 12 to 22 carbon atoms, but 16- and 18-carbon acids are the most abundant. Fatty acids without a carbon–carbon double bond are *saturated*, and all of those containing one or more carbon–carbon double bonds are *unsaturated*. Those with one carbon–carbon double bond are *monounsaturated*, and those with two or more carbon-carbon double bonds are *polyunsaturated*.

Nomenclature

Common names of fatty acids are more often used than the IUPAC names (Table 24.1). The most common saturated fatty acids, palmitic and stearic acids, contain 16 and 18 carbon atoms, respectively. Their IUPAC names are hexadecanoic acid and octadecanoic acid, respectively.

The most common unsaturated fatty acids also have either 16 or 18 carbon atoms, and the double bonds in these molecules are generally cis. The double bonds of polyunsaturated fatty acids are separated by a methylene group, so they are not conjugated. The position of the double bond is indicated in IUPAC names by the Greek letter delta (Δ), followed by a superscript to indicate the position of the double bond. For example, the 16-carbon fatty acid with a cis double bond between the C-9 and C-10 atoms is called *cis*-Δ^9-hexadecenoic acid. Its common name is palmitoleic acid. The 18-carbon fatty acid with a cis double bond between the C-9 and C-10 atoms is called *cis*-Δ^9-octadecenoic acid. Its common name is oleic acid. Polyunsaturated fatty acid names have multiple superscript numbers separated by commas. The most common polyunsaturated fatty acids are *cis*,*cis*-$\Delta^{9,12}$-octadecadienoic acid (linoleic acid) and *cis*,*cis*,*cis*-$\Delta^{9,12,15}$-octadecatrienoic acid (linolenic acid).

Table 24.1
Nomenclature of Fatty Acids

Common name	*IUPAC name*	*Molecular formula*
lauric	dodecanoic	$CH_3(CH_2)_{10}CO_2H$
myristic	tetradecanoic	$CH_3(CH_2)_{12}CO_2H$
palmitic	hexadecanoic	$CH_3(CH_2)_{14}CO_2H$
stearic	octadecanoic	$CH_3(CH_2)_{16}CO_2H$
arachidic	eicosanoic	$CH_3(CH_2)_{18}CO_2H$
behenic	docosanoic	$CH_3(CH_2)_{20}CO_2H$
lignoceric	tetracosanoic	$CH_3(CH_2)_{22}CO_2H$
palmitoleic	*cis*-Δ^9-hexadecenoic	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$
oleic	*cis*-Δ^9-octadecenoic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$
linoleic	*cis,cis*-$\Delta^{9,12}$-octadecadienoic	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH_2)_6CO_2H$
linolenic	*cis,cis,cis*-$\Delta^{9,12,15}$-octadecatrienoic	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6CO_2H$

Table 24.2
Melting Points of Fatty Acids

Common name	*Melting point (°C)*
lauric	43
myristic	54
palmitic	63
stearic	70
arachidic	75
behenic	80
lignoceric	84
palmitoleic	–0.5
coleic	13
linoleic	–5
linolenic	–16
arachidoic	–49

Physical Properties

Table 24.2 lists the melting points of several fatty acids. The melting points of the saturated fatty acids rise with increasing chain length, as expected, because London forces increase with increasing chain length. The hydrocarbon chains of saturated acids pack together tightly in the solid.

Cis unsaturated fatty acids are "bent" molecules because of the geometry around the double bonds. These "bends" hinder efficient molecular packing, and London forces are weaker than those in saturated fatty acids. As a result, unsaturated fatty acids have lower melting points than saturated fatty acids. The melting point of stearic acid (saturated) is 69.6 °C. In contrast, the melting points of unsaturated fatty acids oleic, linoleic, and linolenic acid are 13, –5, and –16 °C, respectively. Figure 24.2 shows space-filling models of oleic, linoleic, and stearic acids.

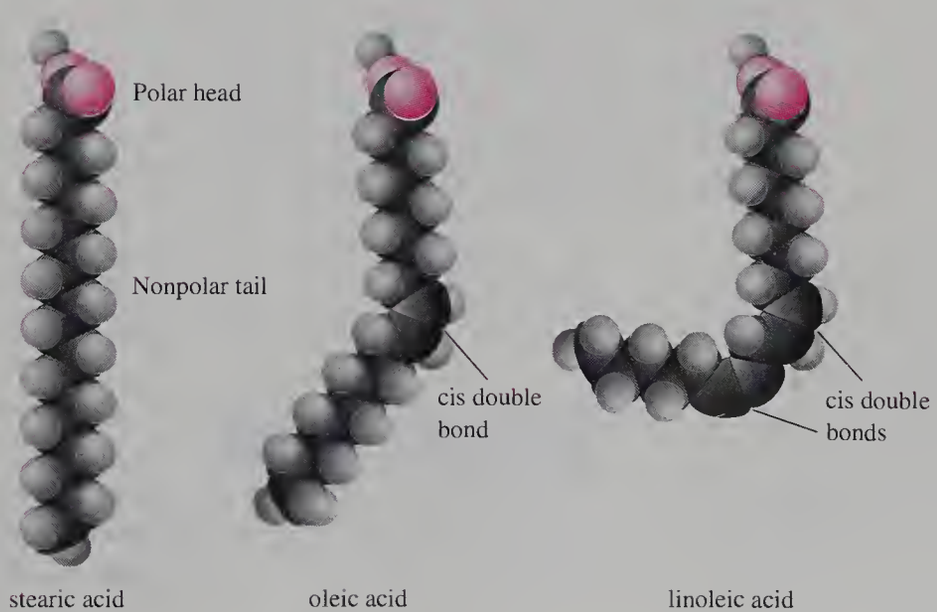
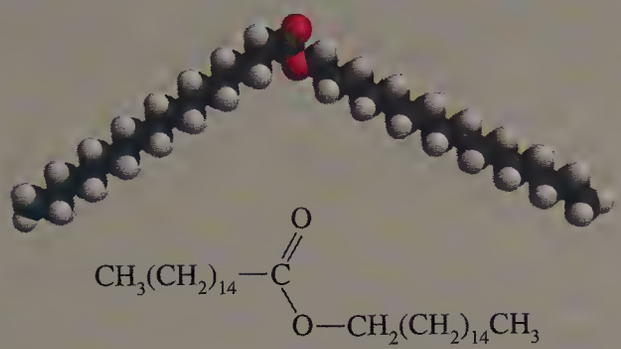


FIGURE 24.2 Molecular Models of Saturated and Unsaturated Fatty Acids

Whale Oil

Whale oil isn't an oil—that is, it isn't a triacylglycerol. It is actually a mixture of waxes. The head of a sperm whale contains as much as 4 tons of whale "oil". The whale uses this mixture to control its buoyancy. One of the compounds is an ester of a 16-carbon acid and a 16-carbon alcohol. Because this compound has fewer carbon atoms than carnauba wax and beeswax, it has a lower melting point.



one component of whale oil

Most compounds have a greater density in the solid phase than in the liquid phase. Therefore, the volume of a substance generally decreases when it changes from a liquid to a solid. Whales take advantage of this property of liquids and solids. Whale oil tends to freeze at the cooler water temperature in the depths of the ocean where the whales feed. When the whale oil freezes, the overall density of the whale increases, allowing it to stay submerged without expending energy. The whale controls the amount of liquid and solid whale oil, and therefore its average density, by passing cold seawater through chambers in its head or by increasing the circulation of warm blood in the same area.

Essential Fatty Acids

Free fatty acids occur in only trace amounts in cells. Most are present as esters in complex lipids. The most abundant fatty acids in the esters of animals are palmitic, stearic, and oleic acids. (Plants, on the other hand, have a high percentage of unsaturated fatty acids.) Animals produce unsaturated fatty acids by the dehydrogenation of saturated fatty acids. Mammalian fatty acid desaturases are effective only with carbon chains of 18 or fewer carbon atoms. In addition, the enzymes can introduce double bonds only between the C-4 and C-5 atoms and the C-9 and C-10 atoms. Mammals cannot, therefore, produce linoleic and linolenic acids. They are termed **essential fatty acids** because mammals must obtain them in the diet. For example, linoleic acid is abundant in plant oils and in fish.

Mammals produce arachidonic acid (Section 21.2) from linoleic acid. Recall that arachidonic acid is the source of prostaglandins. Therefore, without linoleic acid in the diet, mammals could not make prostaglandins.

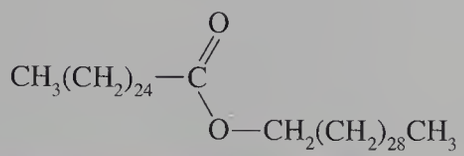
Problem 24.1

The melting point of palmitoleic acid (*cis*-9-hexadecenoic acid) is −1 °C. Compare this melting point to that of palmitic acid and explain the difference.

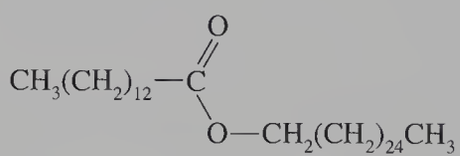
24.3 Waxes

Waxes are esters of fatty acids and of long-chain alcohols, both of which contain an even number of carbon atoms. Waxes are low-melting solids that cover the surface of plant leaves and fruits. Waxes also coat the hair of some mammals, the feathers of some birds, and the exoskeletons of insects to provide a water barrier. If an aquatic bird comes into contact with hydrocarbons—as a result of an oil spill, for example—the wax dissolves, the feathers become wet, and the bird cannot maintain its buoyancy.

We often encounter waxes in our daily lives. For example, carnauba wax, which coats the leaves of palm trees, is widely used in floor polish and car wax. Beeswax is secreted by bees and is the structural material for the beehive.



carnauba wax



beeswax

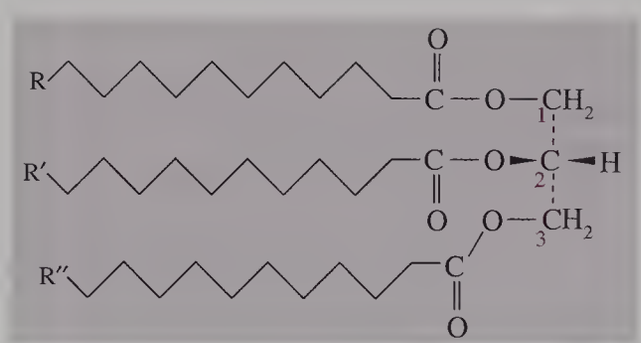
Problem 24.2

Half of the dry weight of a copepod that lives in the waters of British Columbia is the compound $C_{36}H_{62}O_2$. Hydrolysis of this compound yields an unbranched acid, $C_{20}H_{30}O_2$, and an unbranched alcohol, $C_{16}H_{34}O$. Hydrogenation of the acid yields $C_{20}H_{40}O_2$. Describe the structure of the $C_{36}H_{62}O_2$ compound.

24.4 Triacylglycerols

Triacylglycerols are triesters of glycerol and fatty acids also known as fats and oils. Figure 24.3 shows a generalized triacylglycerol representation. Fats and oils are mixtures of compounds. The fatty acid components of these mixtures vary in chain length and degree of unsaturation. A single molecule of a fat or oil may contain two or three different acid residues. In those cases where the acid residues at C-1 and C-3 of glycerol differ, the C-2 atom is a stereogenic center.

FIGURE 24.3
Triacylglycerol Structure

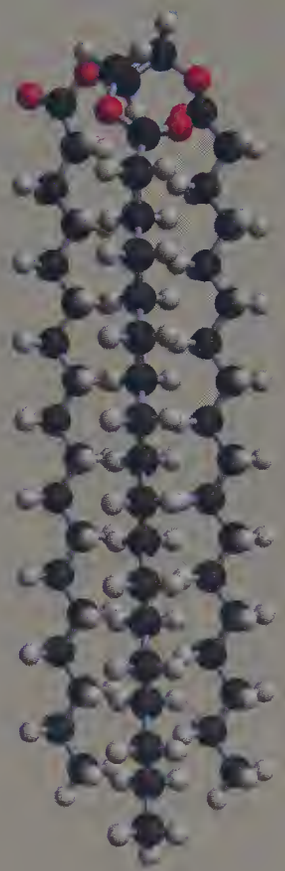


Animal fats have a high percentage of saturated acids, whereas plant oils have a high percentage of unsaturated acids. Fats are solids or semisolids at room temperature usually obtained from animals, for example "lard", the fat of pigs. The important acids in these sources are myristic, palmitic, and stearic acids (Table 24.3). The unsaturated acids found in oils are oleic, linoleic, and linolenic acid; all contain 18 carbon atoms, but they differ in their degree of unsaturation. Cooking oils are typically derived from vegetable sources such as olives, peanuts, corn, and soybeans. These oils contain a high proportion of unsaturated acid residues (Table 24.3).

Triacylglycerols Store Energy

Mammals have several sources of metabolic energy. Two are blood glucose and liver glycogen. This chemical energy is readily available during strenuous exercise, but in limited quantity. Blood sugar can sustain metabolic activity for only a few minutes. Glycogen, a readily available storage form of glucose, would be expended in a few hours of moderate activity. Therefore, larger reserves of chemical energy are needed for survival. Unabsorbed food in the digestive tract is one reserve that can be converted into blood sugar and glycogen. However, the most important energy reserves are triacylglycerols in adipose tissue, which constitutes about 15% of body weight in an average individual. The lipid reserve is sufficient to maintain life for about 40 days, provided that water is available. A person weighing 150 lb and with average body fat has chemical energy available in the following amounts from these three sources.

blood sugar	40 kcal
glycogen	600 kcal
triacylglycerols	80,000 kcal



A triacylglycerol

Triacylglycerols are more reduced than carbohydrates. Therefore, the metabolic oxidation of fatty acids releases more energy than the metabolic oxidation of carbohydrates. Oxidation of fatty acids yields about 39 kJ g^{-1} (9.3 kcal g^{-1}), whereas oxidation of carbohydrates yields about 15.5 kJ g^{-1} (3.7 kcal g^{-1}).

Triacylglycerols are a more concentrated store of metabolic energy than carbohydrates. Because triacylglycerols are nonpolar, they are stored in a nearly anhydrous form in adipose tissue. Glycogen, which contains many hydroxyl groups, is very polar and binds about 2 g of water per gram of compound. Thus, 1 g of anhydrous fat stores about six times as much energy as a gram of hydrated glycogen.

Migratory birds store energy efficiently in triacylglycerols. These birds sometimes travel for several days over water. If they used glycogen to supply the energy required for flight, a bird would have to carry six times as much weight in fuel.

Table 24.3
Composition of Fats and Oils

	Melting point (°C)	*Saturated fatty acids (%)*				*Unsaturated fatty acids (%)*		
		Myristic	*Palmitic*	*Stearic*	*Arachidic*	*Oleic*	*Linoleic*	*Linolenic*
Animal Fats								
butter	32	11	29	9	2	27	4	—
lard	30	1	28	12	—	48	6	—
human fat	15	3	24	8	—	47	10	—
Plant Oils								
corn	−20	1	10	3	—	50	34	—
cottonseed	−1	1	23	1	1	23	48	—
linseed	−24	—	6	2	1	19	24	47
olive	−6	—	7	2	—	84	5	—
peanut	3	—	8	3	2	56	26	—
soybean	−16	—	10	2	—	29	51	6

Triacylglycerols are nonpolar and hydrophobic. Thus, in animals they tend to coalesce as fat droplets in cells called adipocytes found in adipose tissue. Animals accumulate fat (adipose tissue) when their intake of food exceeds their demand for energy. Adipose tissue surrounds vital organs such as the kidneys and forms a protective cushion. A subcutaneous layer of fat helps insulate the animal against heat loss. Although plants do not generally store fats and oils for energy requirements, some (such as peanuts and olives) produce triacylglycerols in abundance.

The relationship between consumption of saturated fats and arterial disease has been the object of extensive medical research. Unsaturated fats do not tend to accumulate in arterial deposits. Safflower oil, because of its high content of unsaturated material, is now a popular product.

Problem 24.3

Soybean oil is 51% linoleic acid. Draw a structure for one of the possible triacylglycerol components of soybean oil.

24.5 Glycerophospholipids

A thin membrane separates all cells from their environment. This cell membrane, also called the plasma membrane, contains a high proportion of lipids called glycerophospholipids. The "backbone" of glycerophospholipids is L-3-phosphoglycerate (Figure 24.4). The C-1 and C-2 hydroxyl groups of L-3-phosphoglycerate are esterified with fatty acids to give molecules called phosphatidic acids. At physiological pH, a phosphatidic acid exists in an ionized form called a phosphatidate. The composition of the fatty acids in phosphatidates varies even within a single cell. Red blood cell membranes contain more than 20 different phosphatidates. In general, saturated fatty acids are located at C-1 and unsaturated fatty acids at C-2.

A phosphatidate molecule is esterified with various alcohols, including choline, ethanolamine, and serine, through its phosphoryl group (Figure 24.4). The phosphatidates exist as anions at physiological pH (~7). When the phosphoryl group of a phosphatidate is linked to the hydroxyl group of ethanolamine in a phosphate ester, the resulting molecule is a phosphatidylethanolamine, also called a cephalin. Its amine nitrogen atom is protonated at pH 7.0. Phosphatidylethanolamine is a major component of cell membranes in the heart, liver, and brain. When the phosphoryl group of a phosphatidate is linked to the hydroxyl group of choline in a phosphate ester, the resulting molecule is a phosphatidylcholine, also known as a lecithin. Lecithins are particularly abundant in eggs and are present in most cell membranes. Phosphatidylcholine has a positive charge at the nitrogen atom, a quaternary ammonium ion. Both phosphatidylcholine and phosphatidylethanolamine are dipolar, but have no net charge. Phosphatidylserine has three charged sites at pH 7.0. The phosphate oxygen atom bears a negative charge because the proton is dissociated at pH 7.0. Also, the carboxyl group of serine exists as the carboxylate ion, and the amine group of serine is protonated. In total, phosphatidylserine bears a net negative charge.

Figure 24.5 shows a molecular model of a phosphatidylcholine containing one unsaturated and one saturated acid. All phospholipids have polar sites, represented by a circle in the simplified model. The two nonpolar hydrocarbon chains of the fatty acids are represented as wavy lines or "tails" attached to the polar "head". These structural features constitute a "head-and-tail" model used in representing the structure of cell membranes.

FIGURE 24.4 Glycerophospholipids
L-3-Phosphoglycertae (a) is esterified with two fatty acid residues in a phosphatidate (b). Esterification of the phosphate with ethanolamine, choline, or serine gives the glycerophospholipids (c).

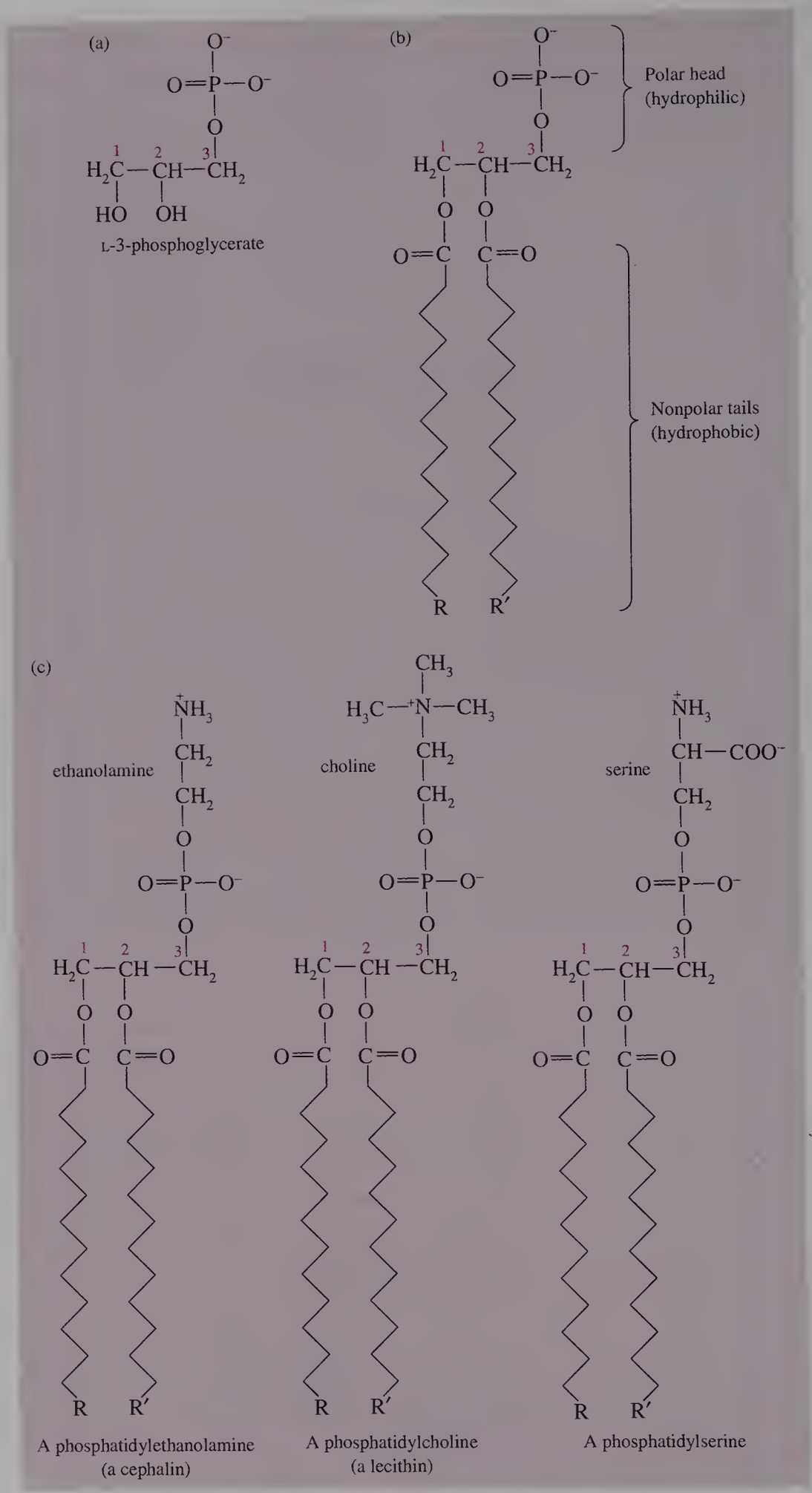
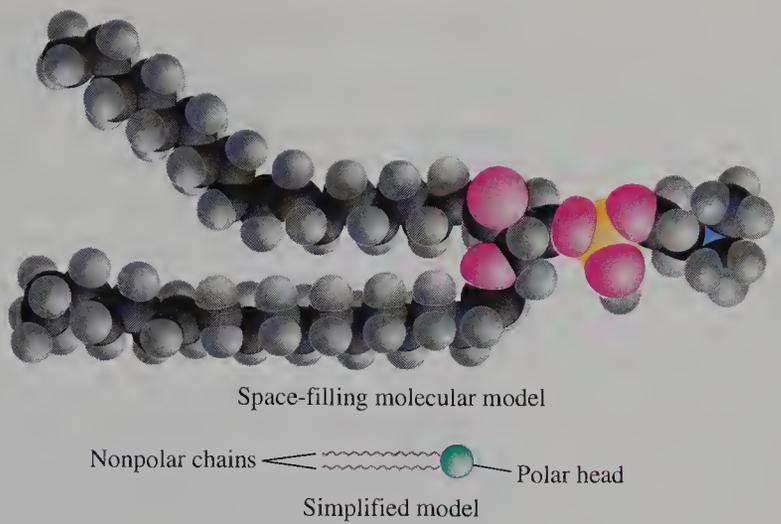


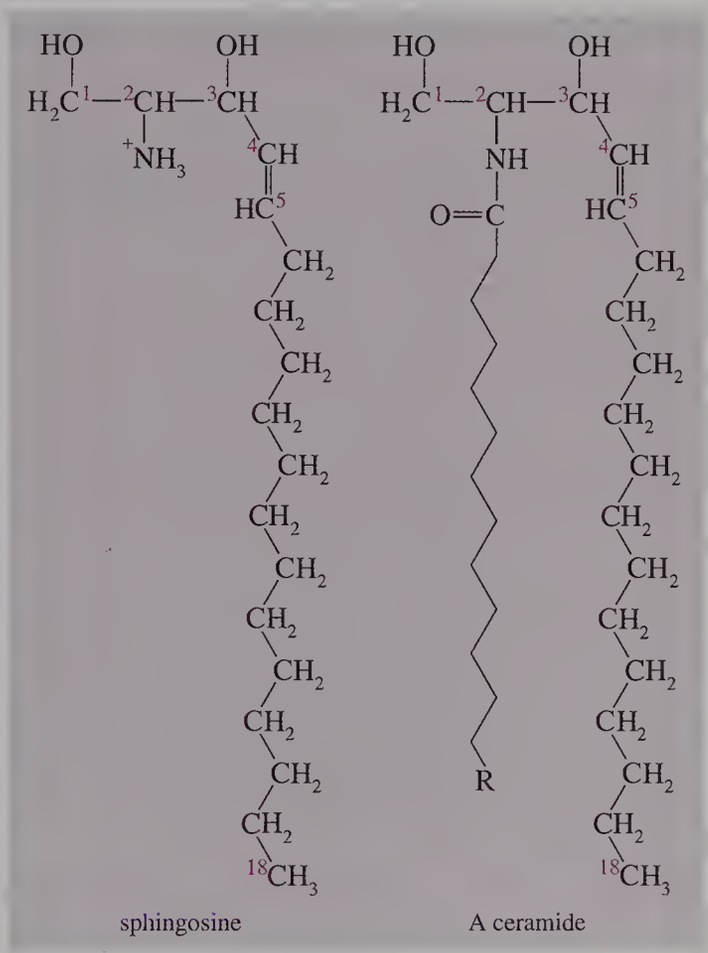
FIGURE 24.5 Molecular Model of a Glycerophospholipid



24.6 Sphingolipids

Although glycerophospholipids are the major lipid in most membranes, a second class of lipids, called sphingolipids, is a major component in the specialized cell membranes of the central nervous system. These lipids include a backbone molecule called sphingosine (Figure 24.6). The conversion of the amino group of sphingosine into an amide with a fatty acid yields a **ceramide**.

FIGURE 24.6 Structures of Sphinogosine and a Ceramide

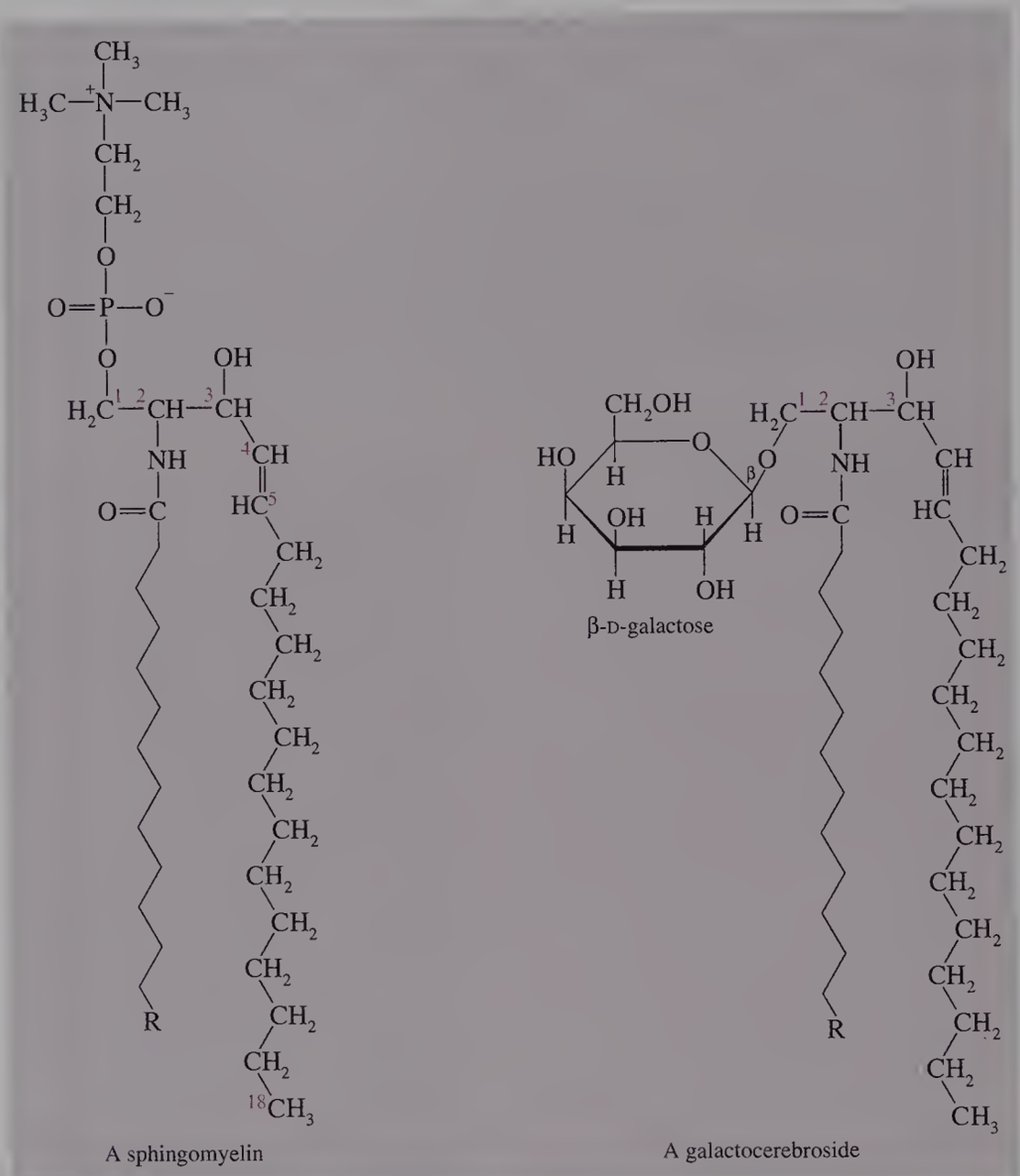


Ceramides are the common unit of three major families of sphingolipids called sphingomyelins, cerebrosides, and gangliosides. Of these, only the sphingomyelins contain phosphate, and they are therefore called **sphingophospholipids**. Cerebrosides and gangliosides contain carbohydrate residues and are called **glycosphingolipids**.

Sphingophospholipids

A ceramide has both a primary and a secondary alcohol. When the primary alcohol is linked to phosphorylcholine, the product is called sphingomyelin (Figure 24.7). Compare the structures of a sphingophospholipid and a glycerophospholipid (Figure 24.4). Although the components differ, their overall structures are similar. Both compounds have a polar head and two nonpolar tails. However, there are significant chemical differences. Sphingophospholipids have a single amide group, and are stable to hydrolysis. Glycerophospholipids have two carboxylic esters that are more easily hydrolyzed.

FIGURE 24.7 Sphingomyelin and a Cerebroside



Sphingomyelins have fatty acid residues that are 20 to 26 carbon atoms long. These long chains interact by London forces, stabilizing cell membranes in specialized cells called myelin cells. These cells wrap around nerve fibers, providing the protective myelin sheath. In individuals with some genetic diseases, the carbon chains of sphingomyelins are shorter, resulting in defects in the myelin sheath. Gaucher's disease, Niemann–Pick disease, multiple sclerosis, and leukodystrophy all result from unstable myelin membranes.

Glycosphingolipids

Glycosphingolipids contain sphingosine and a fatty acid residue bonded as an amide in a ceramide. However, glycosphingolipids contain no phosphate. Instead, a carbohydrate bonds through a β-glycosidic linkage to the primary alcohol oxygen atom of the ceramide (Figure 24.7).

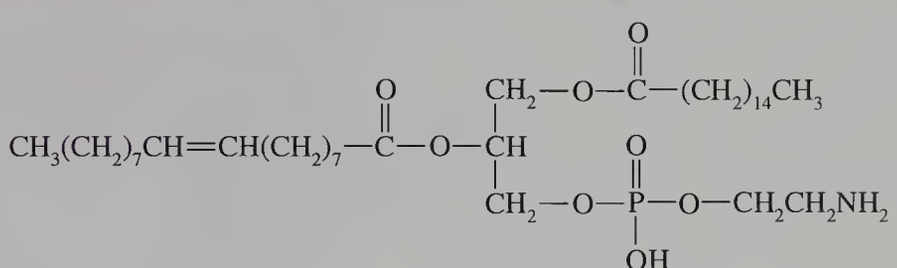
Cerebrosides and gangliosides differ in their carbohydrate components. Cerebrosides contain only galactose, whereas gangliosides contain an oligosaccharide composed of several monosaccharides, including both glucose and galactose. Cerebrosides account for about 15% of the lipids of the myelin sheath, and they also occur in the white matter of the central nervous system. Gangliosides occur in the gray matter of the brain.

Gangliosides are synthesized or degraded by the sequential addition or removal of monosaccharide units. The degradation of a ganglioside occurs inside subcellular organelles called lysosomes, which contain the necessary enzymes for the reaction. In a genetic disease called Tay–Sachs disease, gangliosides accumulate abnormally in the brain because of a deficiency of the enzymes necessary for their degradation. The consequences of this enzyme deficiency include retarded development, blindness, and death at an early age.

The carbohydrate portions of gangliosides are also found on cell surfaces with the two hydrocarbon chains embedded in the membrane. The outside "coat" of oligosaccharides provides a cellular "flag", allowing the immune system to distinguish between "self" and intruders. The blood group antigens that determine blood type differ in the composition of their oligosaccharides. However, all the oligosaccharides of the blood group antigens (Section 20.12) are linked to the C-1 atom of the ceramide by a β-glucopyranosyl residue.

Problem 24.4

Identify the components of the following compound and classify it.



24.7 Biological Membranes

Biological membranes separate cells from their environment and separate organelles from each other within the cytoplasm of a eukaryotic cell. However, membranes are more than just sacks to contain the cells and organelles. They contain proteins that regulate the flow of molecules and ions into and out of the cell.

Composition

Cell membranes are about 75 mm thick and consist of phospholipids—glycerophospholipids and sphingophospholipids—and proteins. The fraction of each component relates to the function of the membrane. The myelin sheath is about 80%

lipid by weight. This covering is nonpolar and serves a protective function. Most other cell membranes must regulate the passage of certain ions and polar molecules into and out of cells, and their lipid content is about 50% by weight. Proteins mediate the transport function of these membranes. The inner membrane of the energy-converting organelles called mitochondria contains only about 20% lipid by weight. The proteins making up most of this inner membrane regulate the transport of molecules into and out of the organelle.

Structure

Each lipid in a membrane has a polar or ionic "head" and two nonpolar "tails" (Figure 24.8). Phospholipids spontaneously form bilayered membranes in aqueous solutions. Each side of this membrane has polar heads toward the aqueous exterior and nonpolar tails toward the nonaqueous interior. The polar heads, which are hydrophilic, are exposed to the fluid surrounding and contained in cells. The hydrophobic tails stay away from water molecules and meet within the bilayer. The type of fatty acid and the kind of polar group in the phospholipids determine specific properties of the membrane. Cell membranes differ on the inner and outer surfaces. For example, phosphatidylcholine and sphingomyelin tend to be located on the outer surface of a membrane, whereas phosphatidylethanolamine and phosphatidylserine are usually on the inner surface.

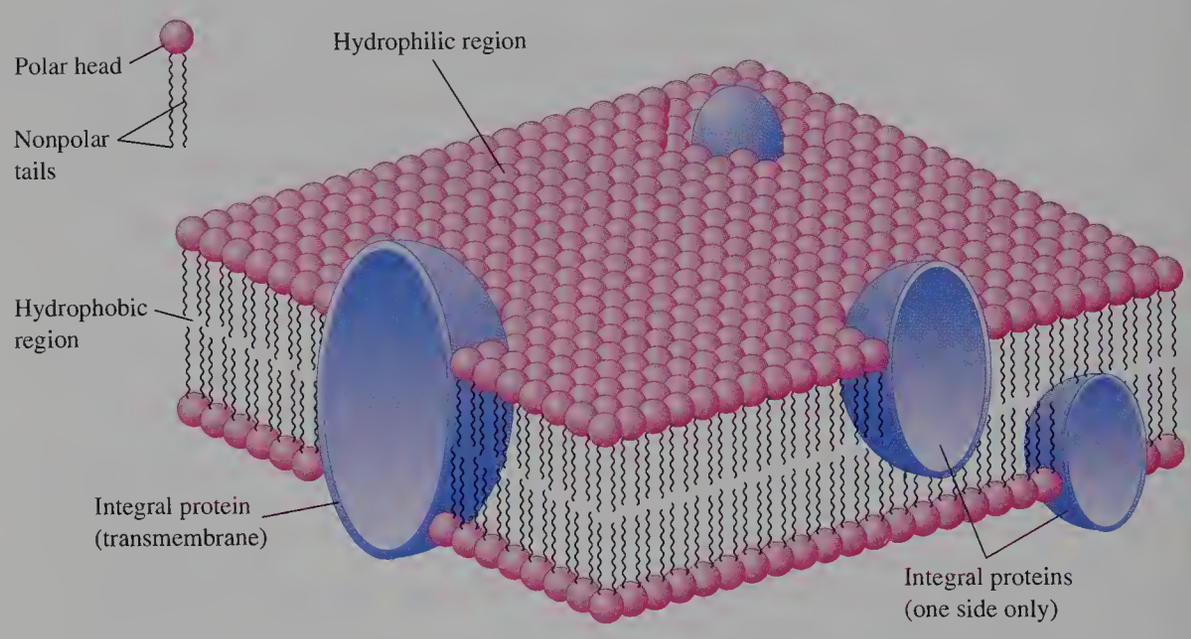


FIGURE 24.8 Model of a Biological Membrane with Lipids and Proteins
The lipids keep their hydrophilic tails in the interior while the hydrophobic heads are in contact with the surrounding aqueous solution.

Proteins in Membranes

Membrane proteins associate with the bilayer in one of two different ways, embedded in the membrane or attached only to the surface. **Integral membrane proteins**

lie embedded in the membrane. Most integral proteins, called **transmembrane proteins**, pass entirely through the membrane, exposing hydrophilic portions both to the environment of the cell and to the cell's interior. Integral membrane proteins interact with the interior of the membrane by hydrophobic forces between certain nonpolar portions of a protein and the tails of the lipid.

Proteins associated with only one surface of the bilayer are called **peripheral proteins**. Peripheral proteins bind to the polar portions of the lipid molecules or to integral membrane proteins by electrostatic forces or hydrogen bonds.

Carbohydrates in Membranes

Membranes contain carbohydrates combined with lipids in glycolipids and combined with proteins in glycoproteins. In mammals, these glycolipids and glycoproteins are always located on the outer surface of the cell membrane. The carbohydrate portion is hydrophilic and remains directed toward the water in the external environment. The protein portion lies anchored in the membrane. The arrangement provides some intercellular recognition. It allows the grouping of cells to form tissue and aids the immune system in the recognition of foreign cells.

Membrane Fluidity

Membranes are stabilized by London forces whose strength depends on both the length and the geometry of the hydrocarbon chain. As chain length increases, London forces become stronger, and the rigidity of the membrane increases. The degree of saturation affects the flexibility of the membrane. We recall that unsaturated fatty acids have bends in the chain, so they do not pack together efficiently in the bilayer. As a result, membranes with a high degree of unsaturation are more flexible.

The lipids and proteins in membranes can move laterally in the bilayer of the lipid membrane. A phospholipid can move about 10^{-4} cm s^{-1}, but the lateral mobility of proteins varies considerably. Some proteins are almost as mobile as lipids, whereas others are essentially immobile because an intracellular structure called the cytoskeleton anchors them.

Lipid movement from one side of a membrane to the other is very slow. Such transverse diffusion or "flip-flop" of the polar head from one side to the other occurs at a rate only 10^{-9} times as fast as lateral movement. Proteins, which are much more polar than lipids, do not undergo transverse diffusion.

Transport Across Membranes

Molecules and ions pass through a biological membrane in the process of acquiring food for the cell and releasing waste products from the cell. Smaller hydrophobic molecules, such as O_2, and polar uncharged molecules, such as H_2O, urea, and ethanol, diffuse across the membrane relatively rapidly. Charged ions, such as Na^+ and K^+, and large polar molecules diffuse very slowly. Glucose and similar polar molecules diffuse so slowly that a cell could not obtain sufficient energy to maintain its metabolic processes if it relied upon the unaided diffusion of glucose across the cell membrane. Molecules move across membranes by two other processes called facilitated diffusion and active transport. The processes differ in energy requirements.

Facilitated diffusion occurs without consuming cellular energy and in a direction from high to low concentration. Materials move across the membrane faster

than in simple diffusion because a "carrier" facilitates the process. These carriers are transmembrane proteins with molecular weights in the range of 9000 to 40,000. There are many different carriers, each specific for only a few molecules. The carrier protein meets a specific molecule or ion at one surface of the membrane and forms a complex. Formation of the complex causes a conformational change in the protein, allowing the carried molecule to slip through a "channel" to the other side of the membrane. Once the molecule is released, the protein returns to its original conformation. Glucose enters cells in this manner.

The transport of anions in human erythrocytes occurs in the same way. In one anion transport system, a protein exchanges the bicarbonate ion inside the cell for the chloride ion outside the cell. Carbon dioxide produced by cellular metabolism dissolves in aqueous media as the bicarbonate ion. Its concentration within the cell is higher than outside the cell, and it diffuses spontaneously to the region of lower concentration. Chloride ion flows into the cell, maintaining charge balance.

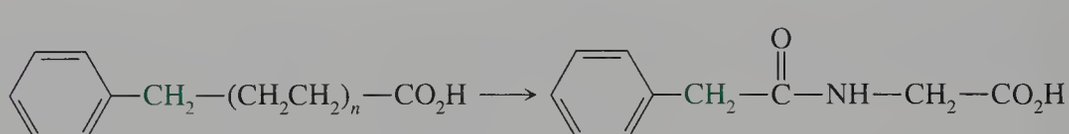
Active transport is similar to facilitated diffusion: A specific interaction takes place between a transmembrane protein and the molecule to be transported. However, active transport occurs against the "natural" flow expected from concentration differences, and material moves from a region of low concentration to one of high concentration. The energy needed for active transport comes from hydrolysis of ATP.

24.8 Catabolic Reactions of Fatty Acids

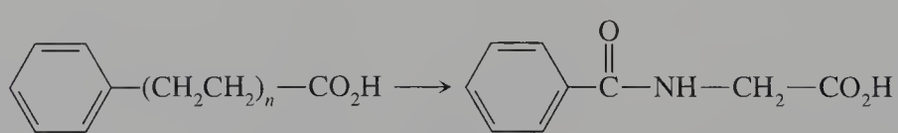
Survival on the cellular level has many chemical requirements, including a need for compounds that can be used to generate energy. Fatty acids are one class of fuel molecules. In this section we consider only a part of the total process of degradative, or **catabolic**, reactions. The products of the catabolism of fatty acids are further processed in the citric acid cycle, producing additional chemical energy. We will not study the interrelationship of the catabolism of fatty acids and other metabolic processes.

The two components of triacylglycerols resulting from the action of lipases are glycerol and fatty acids. However, glycerol contains only a small fraction of the carbon atoms of the triglyceride. Thus, the major source of energy from triacylglycerols is the catabolism of fatty acids.

The catabolism of fatty acids occurs by reactions that shorten the carbon chain two carbon atoms at a time. Franz Knoop established this fact in 1904 in a study of the metabolism of fatty acids by dogs. He fed fatty acids containing a phenyl group at the terminal carbon atom. When Knoop fed the dogs a fatty acid with an even number of carbon atoms in the chain, the metabolic product was phenylaceturic acid, a derivative of phenylacetic acid and glycine. In similar studies with fatty acids with an odd number of carbon atoms, the product was hippuric acid (*N*-benzoylglycine)—a derivative of benzoic acid and glycine.



phenylaceturic acid



hippuric acid

If the chains were degraded one carbon atom at a time, both types of acids would yield hippuric acid. Although the supporting experiments are beyond the scope of this text, the two carbon atoms are released as an acetyl group in the form of acetyl CoA. The oxidation of a fatty acid to form acetyl CoA is called β oxidation. The individual steps of the degradation are "common" organic reactions, although they are enzyme catalyzed.

Fatty Acids Are Linked to Coenzyme A

Initially, fatty acids are first activated by coenzyme A (CoA) conversion to thioesters (Section 22.4). The reaction occurs in two steps. First, a mixed anhydride forms as the carboxyl group displaces pyrophosphate (PP_i) from ATP. The sulfhydryl group of coenzyme A then attacks the acyl adenylate to form acyl CoA and AMP.

$$R{-}\overset{\overset{O}{\|}}{C}{-}O^- + ATP \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}AMP + PP_i$$

(a mixed anhydride)

$$R{-}\overset{\overset{O}{\|}}{C}{-}AMP + HS{-}CoA \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}S{-}CoA + AMP$$

(a thioester)

The equilibrium constant for the sum of the two reactions is close to 1, so the reaction is reversible.

$$RCO_2^- + CoA{-}SH + ATP \rightleftharpoons \text{acyl } S{-}CoA + AMP + PP_i$$

The energy released in the conversion of ATP into AMP and PP_i is approximately equal to the energy required to form the thioester linkage in the acyl CoA. However, the reaction continues in the forward direction because pyrophosphate is rapidly hydrolyzed.

Fatty Acids Are Degraded into Two-Carbon Units

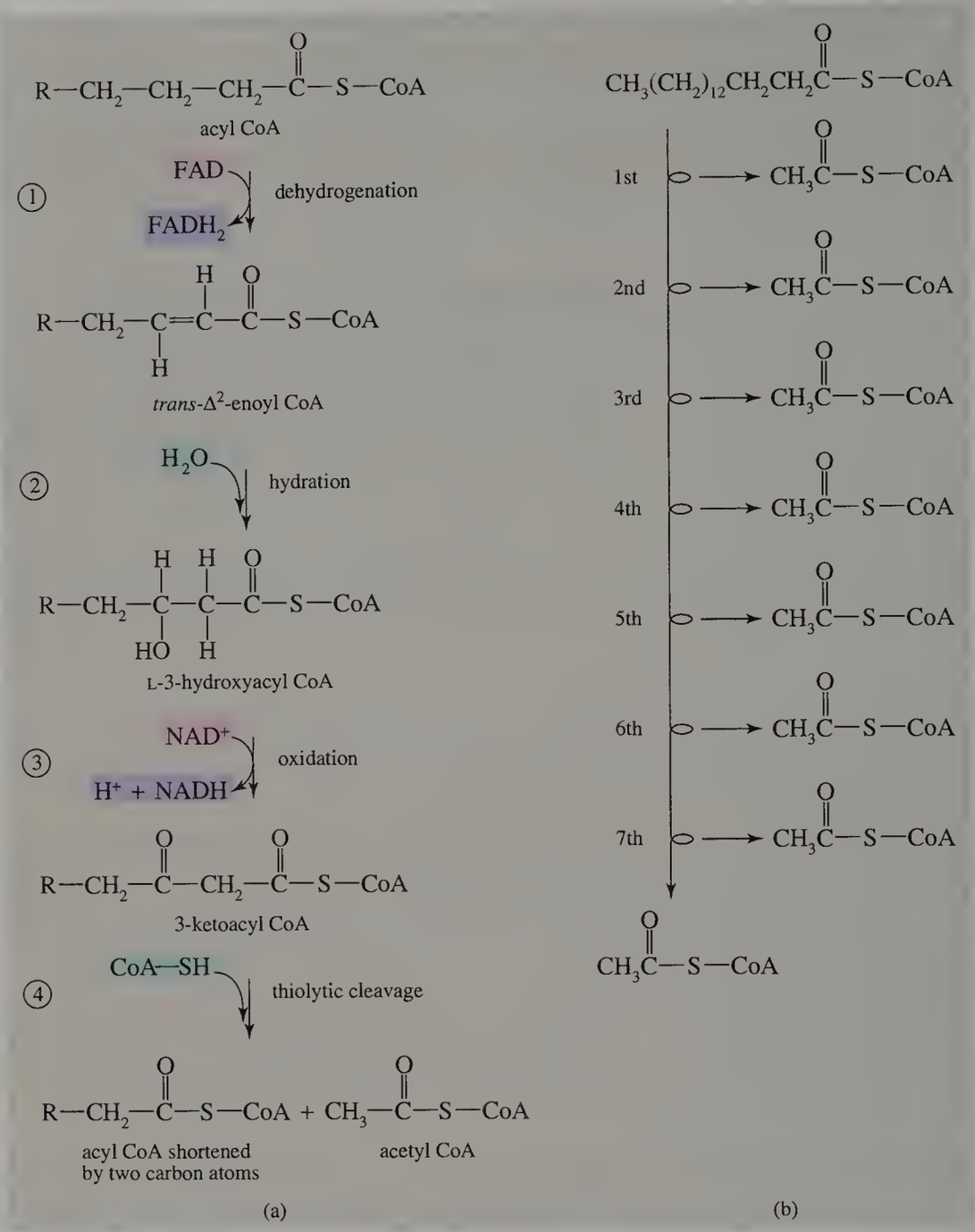
The acyl CoA is degraded in a recurring sequence of four reactions in the mitochondria of eukaryotic cells. In each sequence, the chain length of the fatty acid drops by one two-carbon unit, forming acetyl CoA. The acetyl CoA is then oxidized in the citric acid cycle. The degradation involves four steps: dehydrogenation, hydration, oxidation, and thiolytic cleavage (Figure 24.9).

Step 1 The enzyme acyl CoA dehydrogenase catalyzes the dehydrogenation of the activated acid to form a *trans* double bond between the α and β carbon atoms of the acid.

$$\text{acyl CoA} + FAD \longrightarrow \textit{trans}\text{-}\Delta^2\text{-enoyl CoA} + FADH_2$$

Four enzymes catalyze this reaction. Each requires flavin adenine dinucleotide (FAD) as an oxidizing agent. Each enzyme catalyzes the dehydrogenation of acids most efficiently for a certain range of chain lengths.

FIGURE 24.9 The Fatty Acid Cycle
(a) The four steps in one cycle for a fatty acid.
(b) The sequence of cycles for oxidation of palmitic acid. Each loop represents one cycle.



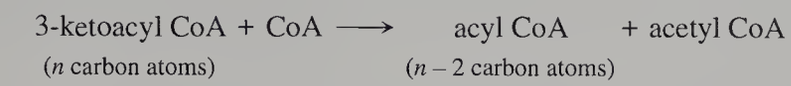
Step 2 This step is a hydration of the double bond of the *trans*-Δ^2-enoyl CoA, catalyzed by enoyl CoA hydrase. The addition of water to the trans double bond occurs stereospecifically; the hydroxyl group is placed on the β carbon atom, and only the L isomer results.

$$\textit{trans}\text{-}\Delta^2\text{-enoyl CoA} + H_2O \longrightarrow \text{L-3-hydroxyacyl CoA}$$

Step 3 The L-3-hydroxyacyl CoA is oxidized by NAD^+ in a reaction catalyzed by L-3-hydroxyacyl CoA dehydrogenase. The enzyme is stereospecific for the L stereoisomer, but works for any chain length.

$$\text{L-3-hydroxyacyl CoA} + NAD^+ \longrightarrow \text{3-ketoacyl CoA} + NADH + H^+$$

Step 4 β-Ketothiolase catalyzes a thiolytic cleavage in which a molecule of CoA reacts with acyl CoA to cleave a two-carbon fragment from the carboxyl end of the acid. The sulfur atom of CoA serves as a nucleophile, attacking the 3-keto carbon atom and displacing acetyl CoA. This reaction is a reverse of the Claisen condensation (Section 23.15) and yields a coenzyme A ester that is shorter by two carbon atoms.



The Process Is Repeated

The catabolism of fatty acids continues in a repeated pattern called the **fatty acid cycle**. Each time the series of four steps occurs, one mole of acetyl CoA for each mole of acid is produced and the carbon chain of the acyl CoA is shortened by two carbon atoms. Finally, butyryl CoA, a four-carbon unit, is formed, and it proceeds around the cycle for the last time to give 2 moles of acetyl CoA per mole of the original acid.

Note that the original activation step does not occur again. It is needed only to convert the original acid to the thioester acyl CoA. After the release of acetyl CoA, the shortened acid chain is present as an acyl CoA that can react through the cycle again.

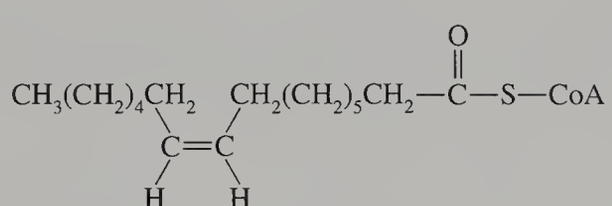
Problem 24.5

How many moles of acetyl CoA are produced from the catabolism of 1 mole of $CH_3(CH_2)_{12}CO_2H$? How many times must the fatty acid cycle occur?

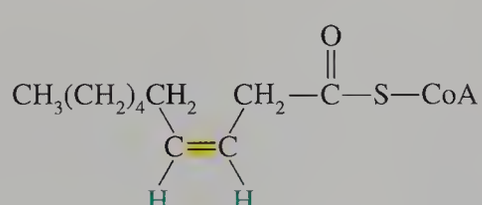
24.9 Catabolism of Unsaturated Fatty Acids

Most of the reactions for the oxidation of unsaturated fatty acids are the same as for the oxidation of saturated fatty acids. However, two additional enzymes, an isomerase and an epimerase, are required.

Palmitoleic acid, a Δ^9-unsaturated acid with a cis double bond, is activated in the mitochondrial membrane in the same way as saturated fatty acids.

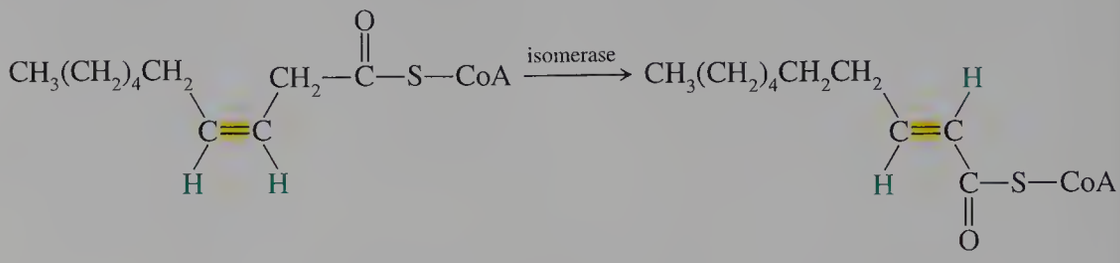


The palmitoleoyl CoA undergoes three turns in the fatty acid cycle, generating 3 moles of acetyl CoA. At this point a *cis*-Δ^3-enoyl CoA forms that cannot directly undergo continued degradation through the fatty acid cycle.



The enzyme acyl CoA dehydrogenase cannot form a double bond between C-2 and

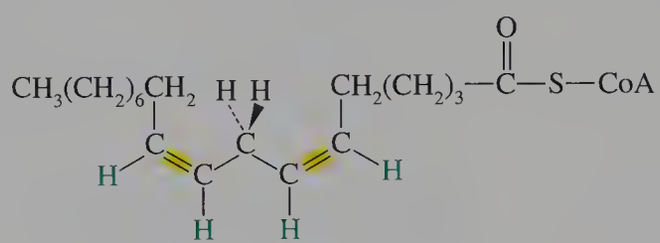
C-3 because there is already a double bond between C-3 and C-4. However, an isomerase converts the cis-Δ^3 double bond into a trans-Δ^2 double bond, which is a substrate in step 2 of the fatty acid cycle.



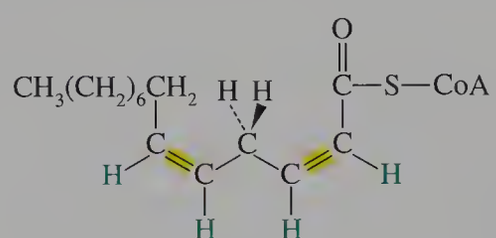
cis-Δ^3-enoyl CoA

trans-Δ^2-enoyl CoA

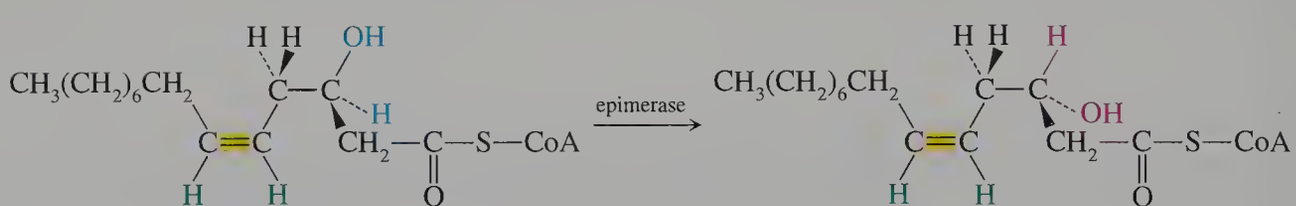
Polyunsaturated fatty acids require an additional enzyme. Consider the following 18-carbon acid with cis-Δ^6 and cis-Δ^9 double bonds.



This compound undergoes two rounds of the fatty acid cycle and produces a *cis*,*cis*-$\Delta^{2,5}$-enoyl CoA that can be hydrated in step 2 of the next cycle.



The enzyme that hydrates the trans double bond to form the L-hydroxy compound now yields the D-hydroxy compound from the cis double bond. An epimerase then inverts the configuration of the hydroxyl group at C-3, and the compound can be degraded further in the fatty acid cycle, continuing from step 3.



D-3-hydroxy-*cis*-Δ^5-enoyl CoA

L-3-hydroxy-*cis*-Δ^5-enoyl CoA

24.10 Biosynthesis of Fatty Acids

The body synthesizes fats when more nutrients are digested than are required to fuel the biosynthetic reactions that maintain the organism. The biosynthesis of fatty acids from acetyl CoA occurs in liver cells and in adipose tissue. It occurs by a mechanism that adds two carbon atoms at a time to the growing fatty acid chain. However, the series of biochemical reactions is not the reverse of β oxidation. This is a common feature of metabolic pathways. Synthetic and degradative pathways are usually

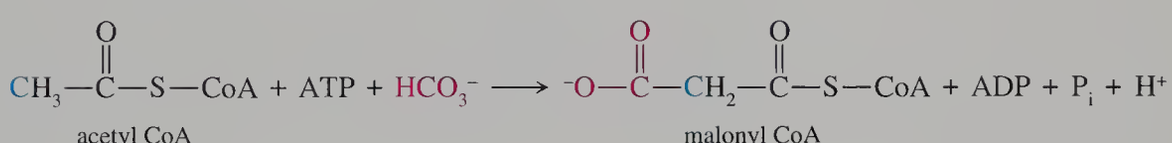
quite distinct. Furthermore, different enzymes are usually involved. In the case of fatty acid degradation and synthesis, the two pathways even occur in different cellular compartments. Degradation occurs in the mitochondria, and biosynthesis takes place in the cytosol. Thus, the two sets of reactions can proceed at the same time, each controlled separately.

The following statements outline the differences between oxidative degradation and biosynthesis of fatty acids.

1. The intermediates of fatty acid synthesis are bonded to an **acyl carrier protein** (ACP), whereas in oxidative degradation, coenzyme A is bonded to the intermediates.
2. The enzymes required in reductive biosynthesis form a single polypeptide chain called a **fatty acid synthetase** system. All the intermediates remain with the system until all reactions are completed. Degradative enzymes used in oxidation in the cytoplasm are not associated, and the steps occur independently.
3. The reduction occurs with the coenzyme nicotinamide adenine dinucleotide phosphate (NADPH), rather than the NAD^+ used in oxidation.
4. The growing fatty acid chain receives its two-carbon units from malonyl ACP. Acetyl CoA is involved in the formation of malonyl ACP, but it is not involved in subsequent steps. Coenzyme A derivatives are involved in all steps in oxidative degradation.

Formation of Malonyl CoA Starts the Process

An irreversible preliminary step is required before the series of fatty acid synthesis reactions begins. This step converts acetyl CoA into malonyl CoA by a reaction with bicarbonate catalyzed by acetyl CoA carboxylase.



The reaction formally is a carboxylation reaction of the anion derived from the loss of an α hydrogen atom of acetyl CoA. The reaction requires ATP.

The Chain Elongation Steps

Fatty acid synthesis, which occurs by a repeating series of steps, follows formation of acetyl ACP and malonyl ACP catalyzed by acetyl transacylase and malonyl transacylase, respectively.

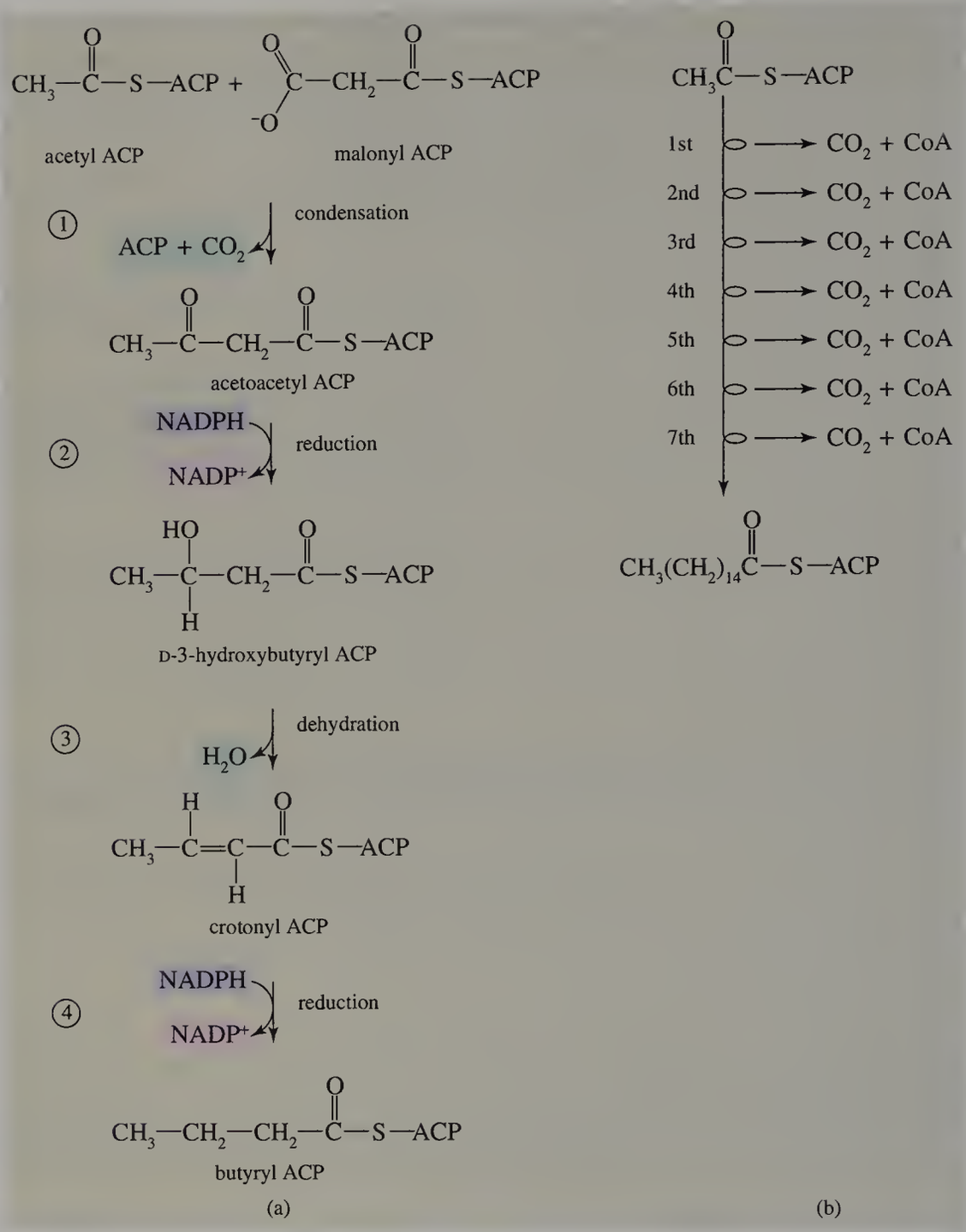
$$\text{acetyl CoA} + \text{ACP} \rightleftharpoons \text{acetylACP} + \text{CoA}$$

$$\text{malonyl CoA} + \text{ACP} \rightleftharpoons \text{malonyl ACP} + \text{CoA}$$

Figure 24.10 shows the series of four steps that occur in the multienzyme fatty acid synthetase system.

Step 1 Carbon–carbon bond formation occurs by way of a condensation of a two-carbon unit and a three-carbon unit to produce a four-carbon unit and CO_2.

FIGURE 24.10 Biosynthesis of Fatty Acids
(a) The four steps in one cycle for the biosynthesis of a fatty acid.
(b) The sequence of cycles for the synthesis of palmitic acid. Each loop represents one cycle.



Condensation of 2 moles of acetyl ACP to produce acetoacetyl ACP would be unfavorable. However, with malonyl ACP as a reactant, the release of CO_2 provides an important decrease in free energy that drives the reaction.

Step 2 Reduction of a ketone to an alcohol may look like the reverse of the oxidation of an alcohol in the degradation of fatty acids. However, the differences are substantial. The D isomer is involved rather than the L isomer. NADPH is the reducing agent, whereas NAD^+ is the oxidizing agent in the related fatty acid degradation step.

Step 3 Dehydration of an alcohol forms the trans isomer. In the first series of reactions, the product is crotonyl ACP. In repeating sequences the general product is a *trans*-Δ^2-enoyl ACP.

Step 4 Reduction of an alkene produces butyryl ACP in the first cycle. NADPH is again the reducing agent, whereas FAD is the oxidizing agent in the first step of the oxidation of fatty acids.

The Process Is Repeated

The product of step 4 in the series of four steps becomes the reactant in the next series of four steps. In the first series of steps, acetyl ACP is converted into butyryl ACP. Butyryl ACP then reacts with malonyl ACP and eventually gives a six-carbon acid. Continued series of reactions produce compounds having 8, 10, etc., carbon atoms. However, this process ceases at the 16-carbon carboxylic acid, palmitic acid. Further elongation occurs by an alternative enzyme system that will not be discussed. To produce palmitic acid from eight acetyl CoA precursors, the series of steps must occur seven times.

EXERCISES

Waxes

24.1 What are the structures and molecular formulas of the products of hydrolysis of carnauba wax?

24.2 Describe how whale oil could be converted into a soap.

24.3 State whether each of the following structures could be a naturally occurring wax.
(**a**) $CH_3(CH_2)_{30}CO_2CH_2CH_2CH_3$ (**b**) $CH_3(CH_2)_{28}CO_2CH_2(CH_2)_{19}CH_3$
(**c**) $CH_3(CH_2)_{27}CO_2CH_2(CH_2)_{18}CH_3$

24.4 The wax of a particular copepod is unsaturated. This species lives in cold water and uses the wax as a source of metabolic energy. Explain the benefit of the unsaturation in the acid portion of this ester.

Fatty Acids

24.5 Cod liver oil is a triglyceride containing palmitoleic acid. Draw a structure for the acid.

24.6 Steareolic acid is named 9-octadecynoic acid by the IUPAC method. The molecular formula is $C_{18}H_{32}O_2$. Write its structure.

24.7 A compound called hypogeic acid is prepared in the laboratory and is now named 7-hexadecenoic acid. Its melting point is 33 °C. What is the geometry at the double bond?

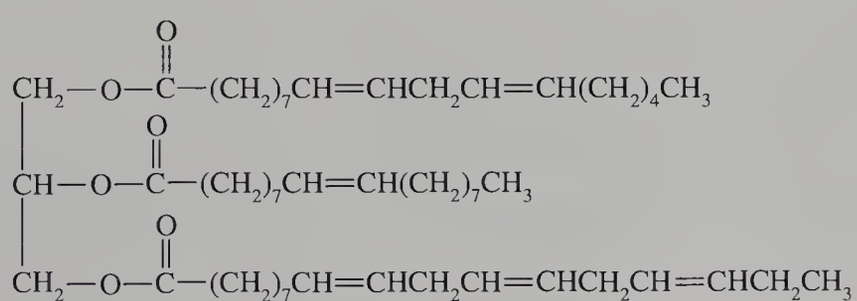
24.8 The melting point of elaidic acid (*trans*-9-octadecenoic acid) is 45 °C. Compare this value to the melting points of stearic acid and oleic acid and explain the differences.

Triglycerides

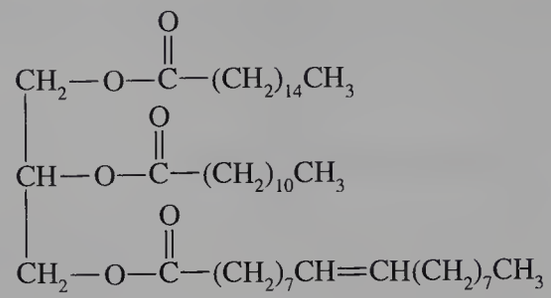
24.9 Write a balanced equation for the hydrolysis of a fat molecule using a base.

24.10 A sample of one oil is hydrolyzed to produce 50% oleic acid and 35% linoleic acid. A second oil produces 25% oleic acid and 50% linoleic acid. Which oil is more unsaturated?

24.11 Identify the following compound as a fat or an oil and identify the component fatty acids.



24.12 Identify the following compound as a fat or an oil and identify the component fatty acids.

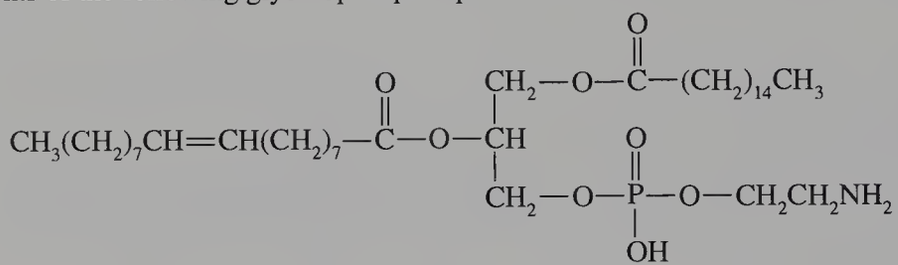


24.13 Draw the structure of a triacylglycerol containing palmitic acid as an ester at the secondary carbon atom and stearic acid as an ester at the two primary carbon atoms of glycerol. Can this compound exist in an optically active form?

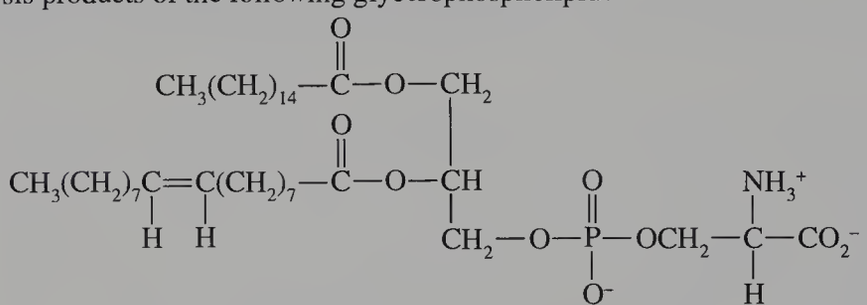
24.14 Hydrolysis of an optically active triacylglycerol gives 1 mole each of glycerol and oleic acid and 2 moles of stearic acid. Write a structure for the triglyceride.

Glycerophospholipids

24.15 Identify the components of the following glycerophospholipid.



24.16 What are the hydrolysis products of the following glycerophospholipid?



Sphingophospholipids

24.17 Why are sphingophospholipids not hydrolyzed as readily as glycerophospholipids?

24.18 Sphingophospholipids are said to have two nonpolar tails. One is a fatty acid residue. What is the structure of the second chain?

Glycosphingolipids

24.19 How are glycosphingolipids similar to sphingophospholipids? In what ways do the two types of compounds differ?

24.20 What is the difference between a cerebroside and a ganglioside?

24.21 What type of bond joins the sugar unit to the sphingosine part of a glycosphingolipid?

24.22 Based on the structure of glycosphingolipids, predict whether these molecules are more stable in acidic or basic solution.

Biological Membranes

24.23 How does the structure of the fatty acid affect the rigidity of a cell membrane?

24.24 What kind of forces hold a cell membrane together?

24.25 Peripheral proteins can be removed from a membrane by washing it with a detergent solution. Explain why.

24.26 Where is the sugar portion of a glycolipid located in a cell membrane?

Catabolic Reactions of Triglycerides

24.27 What is the configuration of the unsaturated fatty acid formed by dehydrogenation in the fatty acid cycle?

24.28 What is the configuration of the 3-hydroxy fatty acid in the fatty acid cycle?

24.29 How many moles of acetyl CoA are produced in the metabolism of stearic acid? How many times does the fatty acid cycle occur for stearic acid?

24.30 How many moles of acetyl CoA are produced in the metabolism of palmitic acid? How many times does the fatty acid cycle occur for palmitic acid?

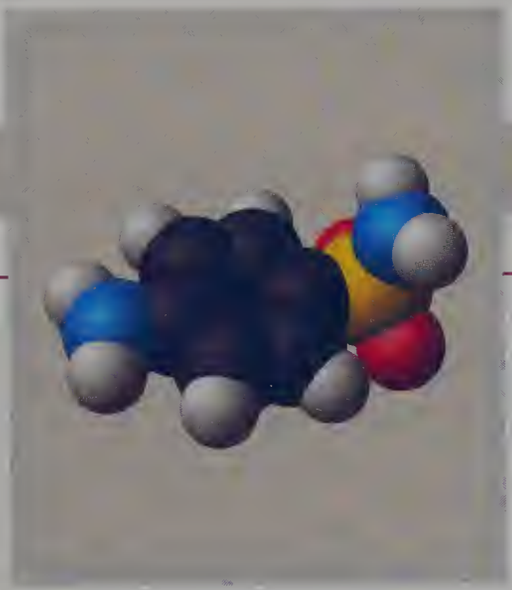
24.31 How many moles of acetyl CoA would be produced in the oxidation of decanoic acid? How many moles of acetyl CoA would be produced in the oxidation of myristic acid?

24.32 What carboxylic acid is produced in the last turn of the fatty acid cycle if 10-phenyldecanoic acid is introduced into a cell? What carboxylic acid is produced in the last turn of the fatty acid cycle if 9-phenylnonanoic acid is introduced into a cell?

Biosynthesis of Fatty Acids

24.33 What types of reactions occur in each of the four steps of fatty acid biosynthesis?

24.34 How many moles of acetyl CoA are required for the biosynthesis of myristic acid?



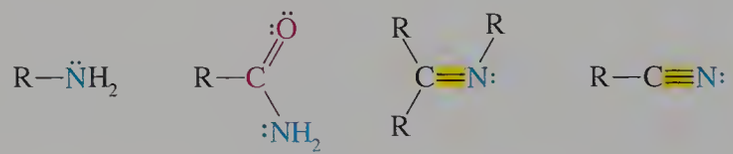
25

Amines and Amides

25.1 Organic Nitrogen Compounds

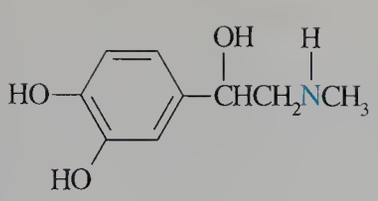
For most of this text we have concentrated on the compounds of carbon, hydrogen, and oxygen. We have paid less attention to compounds containing halogens, sulfur, and nitrogen. Nitrogen is the fourth most common element in living systems, after carbon, hydrogen, and oxygen. Organic compounds containing nitrogen not only are widely distributed in plants and animals, but are necessary for life. Nitrogen is present in many vitamins and hormones. Nitrogen is essential in amino acids and proteins (Chapter 26), as well as in nucleotides and polynucleotides. In addition, some nitrogen-containing compounds are important industrial products, including polymers such as nylon, many dyes, explosives, and pharmaceutical agents.

A nitrogen atom with five valence electrons forms a total of three covalent bonds to carbon or hydrogen atoms. A nitrogen atom in a functional group can form single, double, or triple bonds. In this chapter we will focus on amines, but will also discuss the other functional groups that are either the reactants required to form amines or the products of amine reactions.

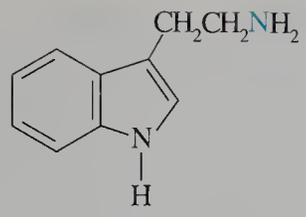


(an amine) (an amide) (an imine) (a nitrile)

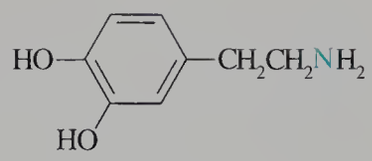
Many amines are physiologically active. They affect the brain, spinal cord, and nervous system. These compounds include the neurotransmitters epinephrine, serotonin, and dopamine. Epinephrine, commonly called adrenaline, stimulates the conversion of glycogen into glucose. Serotonin is a hormone that causes sleep. Serotonin deficiency is responsible for some forms of mental depression. Parkinson's disease is accompanied by a low concentration of dopamine.



epinephrine

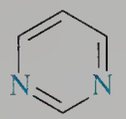


serotonin

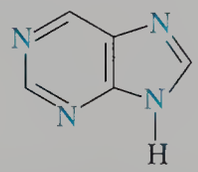


dopamine

Heterocyclic compounds containing two or more nitrogen atoms are required for the transmission of genetic information. DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) contain substituted pyrimidine and purine rings.

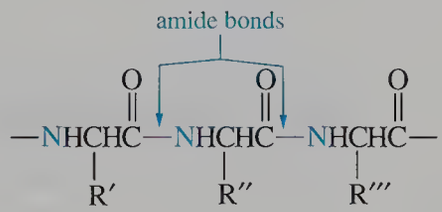


pyrimidine



purine

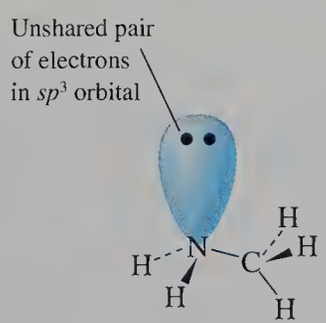
Proteins, some of the most important and versatile biological compounds, consist of nitrogen-containing molecules called α-amino acids. The amine functional group of one α-amino acid reacts with the carboxyl group of another α-amino acid to form an amide bond. The chemistry of these compounds will be presented in Chapter 26.



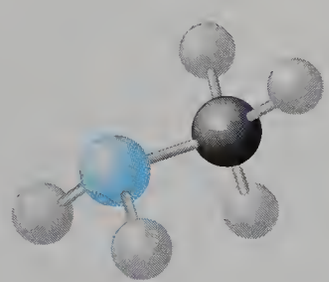
25.2 Bonding and Structure of Amines

In the simplest amine, methylamine (CH_3NH_2), a methyl group has replaced one hydrogen atom of ammonia (Figure 25.1). The C—N—H and H—N—H bond angles are approximately 112° and 106°, respectively, so methylamine has a pyramidal shape around the nitrogen atom. In methylamine and other amines, the nitrogen atom has five valence electrons in four sp^3 hybrid orbitals. As expected from VSEPR theory, these orbitals point to the corners of a tetrahedron. Three are half-filled and form three covalent bonds. The fourth orbital contains a pair of nonbonded electrons that plays an important role in the chemical properties of amines.

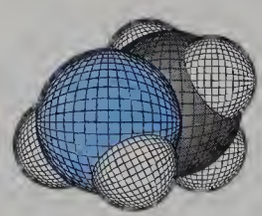
FIGURE 25.1 Structure of Methylamine



Perspective structural formula



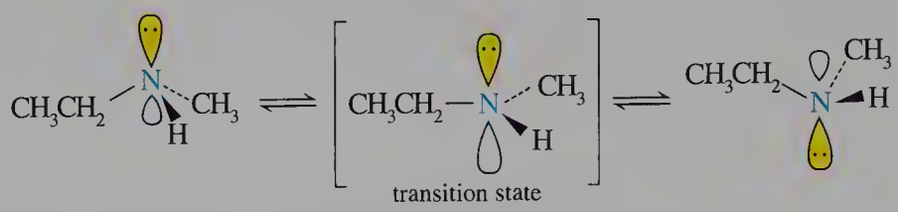
Ball-and-stick model



Space-filling model

Nitrogen Inversion

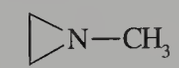
If the pyramidal structure of acyclic amines were static, compounds with three different groups around the nitrogen atom would be chiral. However, the nonbonded electron pair, which we could regard as the fourth group required for a stereogenic center, does not remain in one place. Amines undergo **nitrogen inversion** by a process in which the three bonded groups temporarily occupy a common plane.



The planar form of the amines resembles an S_N2 transition state in which an electron pair of one group attacks from one side of a plane while another group leaves with an electron pair from the other side. In nitrogen inversion, an electron lone pair pushes the three bonded groups from one side to the other and inverts the configuration. Because the process requires only 25 kJ mole^{-1} (6 kcal mole^{-1}), the rate of inversion is so fast that the enantiomers cannot be resolved. In effect, an amine with three different bonded groups is a racemic mixture.

Problem 25.1

Explain why the inversion barrier for *N*-methylaziridine (80 kJ mole^{-1}) is larger than the inversion barrier for trimethylamine (25 kJ mole^{-1}).



N-methylaziridine

Problem 25.2

Explain why the N—H bond of ammonia is 6 pm shorter than the C—H bond in methane. Using appropriate models, predict the N—H bond length in methyleneimine (CH_2=NH).

Problem 25.3

The C—N bond length of aniline is 140 pm. Give two reasons why this bond length is shorter than the 147 pm C—N bond length of alkylamines.

Sample Solution

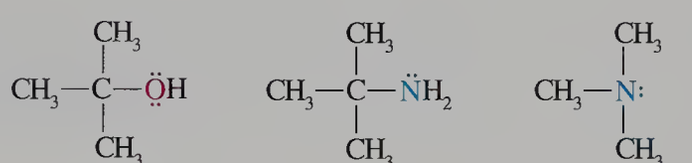
The C—N bond of aniline is formed with an sp^2 hybrid orbital of carbon compared to the sp^3 hybrid orbital of carbon in alkylamines. The greater *s* character decreases the resulting bond length because the bonding electron supplied from carbon is closer to the nucleus. The bond is also shorter because the nonbonding electrons of nitrogen can contribute to resonance forms in which the electrons are supplied to the aromatic ring. These resonance forms have a carbon–nitrogen double bond. To the extent that these resonance forms contribute, the resulting carbon–nitrogen bond will be shorter.

25.3 Classification and Nomenclature of Amines

Just as we can regard alcohols and ethers as organic derivatives of water, we can regard amines as organic derivatives of ammonia. However, amines are not classified like alcohols. The classification of alcohols is based on the number of groups attached to the carbon atom bearing the hydroxyl group. Amines are classified by the number of alkyl (or aryl) groups attached to the nitrogen atom.

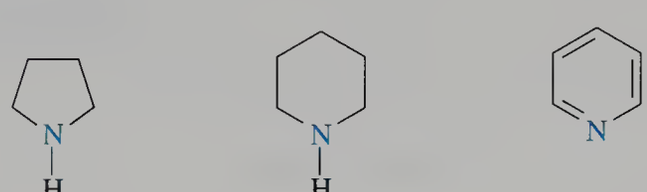
ammonia | primary (1°) amine | secondary (2°) amine | tertiary (3°) amine

For example, *tert*-butylamine has a *tert*-butyl group attached to an $—NH_2$ group. However, the amine is primary because only one alkyl group is bonded to the nitrogen atom. In contrast, *tert*-butyl alcohol is a tertiary alcohol because the carbon atom bonded to the —OH group is bonded to three alkyl groups. Trimethylamine is a tertiary amine because the nitrogen atom is bonded to three alkyl groups.



tert-butyl alcohol (a tertiary alcohol) | *tert*-butylamine (a primary amine) | trimethylamine (a tertiary amine)

Amines in which a nitrogen atom is part of a ring are common in nature. Compounds that have one or more atoms other than carbon in the ring are heterocyclic compounds. For example, pyrrolidine and piperidine are five- and six-membered heterocyclic compounds that are secondary amines. Pyridine is an aromatic amine considered a tertiary amine.

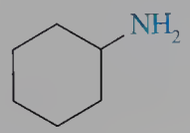


pyrrolidine (a secondary amine) | piperidine (a secondary amine) | pyridine (a tertiary amine)

Common Names of Amines

In common nomenclature, amines are described as *alkylamines*. The common name of a primary amine results from naming the alkyl group bonded to the amino group ($—NH_2$) and adding the suffix *-amine*. The entire name is written as one word. The common name for a secondary or tertiary amine is obtained by listing the alkyl

groups alphabetically. When two or more identical alkyl groups are present, the prefixes *di-* and *tri-* are used.

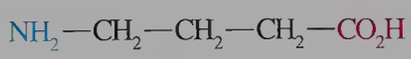


cyclohexylamine

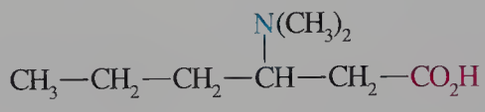
ethylmethylamine

diethylamine

For more complex primary amines, the amino group is treated as a substituent. The nitrogen-containing substituent in complex secondary and tertiary amines is named as an *N*-alkylamino (—NHR) or *N,N*-dialkylamino (—NRR′) group. The capital *N-* indicates that the alkyl group is bonded to the nitrogen atom and not to the parent chain. The largest or most complicated group is used as the parent molecule.

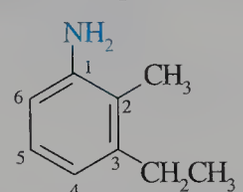


γ-aminobutyric acid

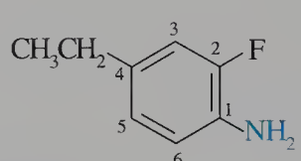


β-(*N,N*-dimethylamino)caproic acid

As we already know, amino-substituted benzene compounds are anilines. They are numbered starting at the carbon atom bearing the amino group if the other groups bonded to the ring have a lower priority for citation than the amino group. The direction of the numbering is based on the location of the second group, using the first point of difference concept established with our early study of alkanes. Substituents are listed in alphabetical order.



3-ethyl-2-methylaniline

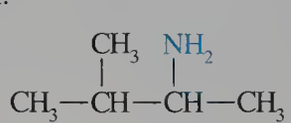


4-ethyl-2-fluoroaniline

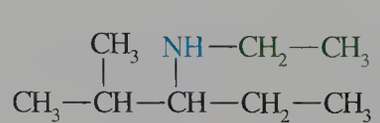
However, the priority for citation of an amino group is low. It ranks below all carbonyl compounds (acids, acid derivatives, aldehydes, ketones) and even the hydroxyl group. Thus, a benzene compound containing both a carboxylic acid group and an amino group is an amino-substituted benzoic acid, not a carboxylic acid–substituted aniline.

IUPAC Names

The systematic nomenclature of amines was devised by the Chemical Abstracts Service (CAS) and has been adopted as one of two systematic methods accepted by IUPAC. Because the CAS system is "logical" and based on the same system used for alcohols, we will use this method. The longest continuous chain to which the amino group is attached is the parent alkane. The *-e* ending of the alkane is changed to *-amine*. Substituents on the carbon chain, including the amino group, are designated by number. The prefix *N-* is used for each substituent on the nitrogen atom.



3-methyl-2-butanamine

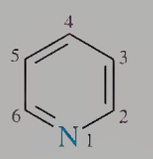


N-ethyl-2-methyl-3-pentanamine

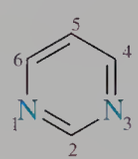
The CAS system uses the term areneamine for aromatic amines. Thus, aniline is benzeneamine. However, this systematic name is rarely used, and we shall continue to use the common name aniline.

The concepts used to name heterocyclic compounds containing oxygen were developed in Chapter 17. Similar concepts are used to name heterocyclic compounds containing nitrogen. Saturated three-, four-, five-, and six-membered rings containing one nitrogen atom are named aziridine, azetidine, pyrrolidine, and piperidine. The rings are numbered from the heteroatom.

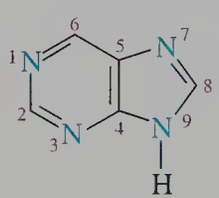
Amines in which the nitrogen atom is part of an aromatic ring are called **heterocyclic aromatic amines**. In these compounds, the positions of substituents are established by using the numbering system indicated below. A nitrogen atom is assigned the number 1, and the direction of numbering provides the lowest possible numbers if the ring has more than one nitrogen atom.



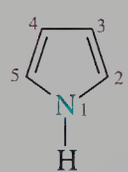
pyridine



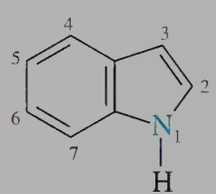
pyrimidine



purine



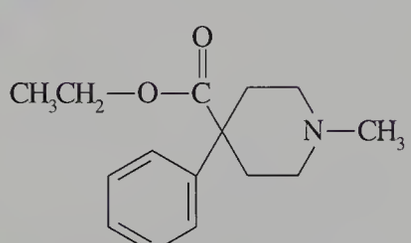
pyrrole



indole

Problem 25.4

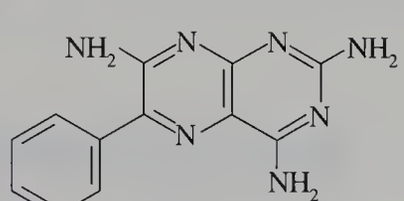
Classify Demerol, a synthetic narcotic analgesic, as an amine.



Demerol

Problem 25.5

The systematic name for Dyrenium, a diuretic, is 2,4,7-triamino-6-phenylpteridine. Number the pteridine ring and explain the basis for this choice of numbers.



Problem 25.6

The thiosemicarbazide of 5-hydroxypyridine-2-carbaldehyde has some antitumor activity. Write the structure of the aldehyde and the thiosemicarbazide.

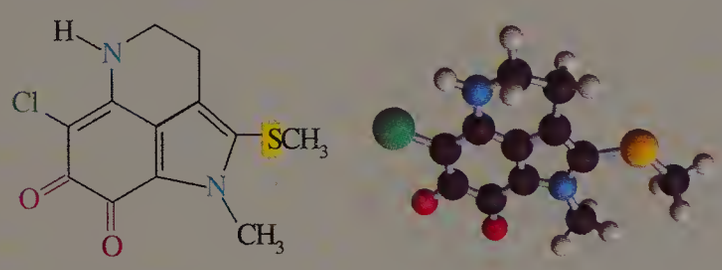
Problem 25.7

2-(3,4,5-Trimethoxyphenyl)ethanamine is the systematic name of mescaline, a hallucinogen. Write its structure.

Heterocyclic Compounds from the Ocean

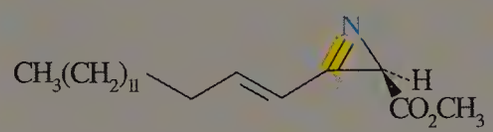
Heterocyclic compounds of nitrogen, oxygen, and sulfur occur widely in plants and terrestrial animals and may constitute more than half of all of the known compounds. As illustrated by the many examples given in this text, a high percentage of drugs are heterocyclic compounds. Many of these drugs were developed from naturally occurring compounds found in terrestrial plants. It has been only recently that the chemistry of the organisms of the ocean have been examined in the search for new compounds that might be useful in the design of drugs. Given the diversity of species in the ocean, there must be a wealth of potentially useful heterocyclic compounds to be discovered.

As in terrestrial plants and animals, most of the heterocyclic compounds in the ocean have five- and six-membered rings. In contrast to compounds obtained from terrestrial sources, a high percentage of heterocyclic compounds from oceanic organisms are often halogenated. For example, a Bahamian sponge produces several chlorinated indoles or indole-derived compounds such as batzelline.

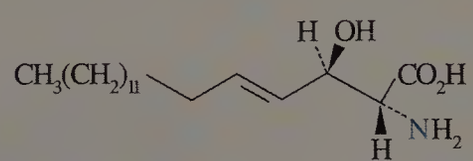


batzelline

Although less common, three-membered heterocyclic compounds have also been found in marine products. In 1988 the structure of dysidazirine contained in *Dysidea fragilis*, a species of sponge found in Fiji, was determined. The substance contains an azacyclopropene ring, which should be quite reactive because of ring strain, and is an α,β-unsaturated imine, whose chemistry should be similar to that α,β-unsaturated carbonyl compounds.



dysidazirine

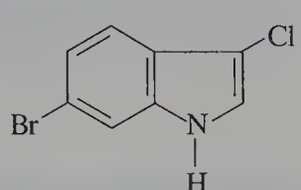


D-sphingosine

The origin of this conjugated imine is not clear. Although it has the same configuration as D-sphingosine, a component of cell membranes (Chapter 24), this relationship may be coincidental. However, the oxidation of the secondary alcohol of sphingosine to a ketone followed by the intramolecular condensation with the amino group would give the azacyclopropene. A subsequent step to form dysidazarine would be esterification of the carboxylic acid.

Problem 25.8

Name the following compound, which is produced by the marine acorn worm.



25.4 Physical Properties of Amines

Boiling Point

Amines with low molecular weights are gases at room temperature, but amines with higher molecular weights are liquids or solids (Table 25.1). Amines have higher boiling points than alkanes of similar molecular weight, but lower boiling points than alcohols.

$CH_3—CH_2—CH_3$ bp –42 °C $CH_3—CH_2—NH_2$ bp 17 °C $CH_3—CH_2—OH$ bp 78 °C

Amines have higher boiling points than hydrocarbons of comparable molecular weight because the C—N bond is more polar than a C—C bond. Also, primary and secondary amines can form intermolecular hydrogen bonds because they can serve as both hydrogen bond donors and acceptors. Tertiary amines have no hydrogen atoms bonded to the nitrogen atom and therefore are not hydrogen bond donors. Thus, these amines cannot form intermolecular hydrogen bonds. As a consequence, they have lower boiling points than primary and secondary amines of comparable molecular weight.

Amines have lower boiling points than alcohols because nitrogen is less electronegative than oxygen. As a result the N—H bond is less polar than the O—H bond, and the N—H···N hydrogen bond in amines is weaker than the O—H···O hydrogen bond in alcohols.

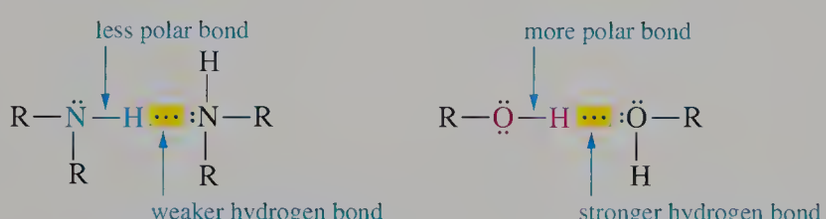
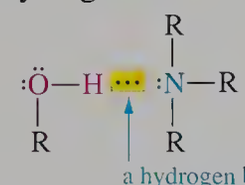


Table 25.1
Boiling Points of Amines

Name	*Boiling point (°C)*
methylamine	–7
ethylamine	17
propylamine	48
isopropylamine	33
butylamine	77
isobutylamine	68
sec-butylamine	63
tert-butylamine	45
cyclohexylamine	134
dimethylamine	7
ethylmethylamine	37
diethylamine	56
dipropylamine	111
trimethylamine	3
triethylamine	90
tripropylamine	156

Solubility in Water

Amines with five or fewer carbon atoms are miscible with water. As we have seen for other types of compounds, the solubility of amines decreases with increasing molecular weight because the functional group is a less significant part of the structure. Primary and secondary amines function as both hydrogen bond donors and acceptors, and they readily form hydrogen bonds with water. Even tertiary amines are soluble in water because the nonbonded electron pair of the nitrogen atom is a hydrogen bond acceptor of a hydrogen atom of water.



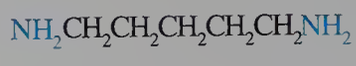
The solubilities of toluene (0.05 g/100 mL) and aniline (3.5 g/100 mL) illustrate the effect of hydrogen bonding on the solubilities of arylamines. Aniline forms hydrogen bonds with water, toluene does not.

Odor and Toxicity of Amines

Amines with low molecular weights have sharp penetrating odors similar to ammonia. Amines with higher molecular weights smell like decaying fish. Two compounds

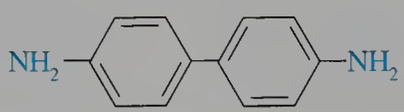
responsible for the odor of decaying animal tissue are appropriately named putrescine and cadaverine.

putrescine

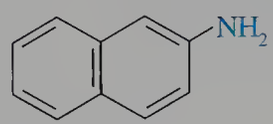


cadaverine

Because amines have high physiological activity, the ingestion of an amine not normally used by a living organism can cause poisoning and death. In addition, the skin absorbs arylamines, and care should be used in handling them. Some arylamines such as benzidine and β-naphthylamine are carcinogenic.



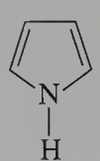
benzidine



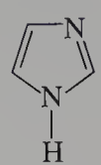
β-naphthylamine

Problem 25.9

The boiling points of pyrrole and imidazole are 130 °C and 263 °C, respectively. Explain the large difference.



pyrrole



imidazole

Sample Solution

Both pyrrole and imidazole are hydrogen bond donors. Only imidazole is a hydrogen bond acceptor because it has a nonbonded electron pair in an sp^2 hybrid orbital on a pyridine-like nitrogen atom. The valence electrons of the nitrogen atom of the N—H bonds in both pyrrole and imidazole are incorporated in the π system of an aromatic ring and are not available to form hydrogen bonds. Because imidazole forms intermolecular hydrogen bonds, its boiling point is higher than that of pyrrole.

Problem 25.10

The dipole moments of pyridine (2.26 D) and piperidine (1.17 D) are both directed toward nitrogen. Explain why the dipole moment of pyridine is larger than that of piperidine.

25.5 Basicity of Amines

The basicity of an amine is usually listed as a pK_b, the negative logarithm of K_b (Section 3.3). For an amine with $K_b = 10^{-4}$, the pK_b is 4. The pK_b values of strong bases are small. Thus, as pK_b increases, base strength decreases. It is also common practice to indicate the relative base strength of amines in terms of the pK_a of their conjugate acids. (Recall that $pK_a = -\log K_a$.) If an amine base has a small pK_b, its conjugate ammonium ion has a large pK_a. The values of pK_a and pK_b for a conjugate acid–base pair are related as follows.

$$pK_a + pK_b = 14$$

To understand the basicity of amines, we must consider the effect of a structural feature on both the amine and its conjugate acid. Any feature that stabilizes

the amine relative to the ammonium ion makes the amine a weaker base. Any feature that stabilizes the ammonium ion relative to the amine makes the amine a stronger base.

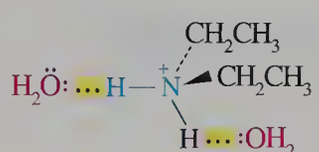
Table 25.2 lists the base ionization constants for several amines. We recall that alkyl groups donate electrons to carbocations, and that they donate electrons in electrophilic aromatic substitution reactions. We might expect alkyl-substituted amines to be slightly stronger bases than ammonia because the inductive donation of electrons to the nitrogen atom by alkyl groups makes the unshared pair of electrons more available to a proton. However, the order of basicities does not increase in a simple order.

	NH_3	$CH_3CH_2NH_2$	$(CH_3CH_2)_2NH$	$(CH_3CH_2)_3N$
pK_b	4.7	3.36	3.01	3.24

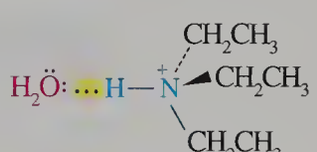
Table 25.2
K_b and pK_b of Alkylamines

Name	K_b	pK_b
methylamine	4.3×10^{-4}	3.37
ethylamine	4.4×10^{-4}	3.36
propylamine	4.7×10^{-4}	3.33
isopropylamine	4.0×10^{-4}	3.40
butylamine	4.8×10^{-4}	3.22
cyclohexylamine	4.7×10^{-4}	3.33
dimethylamine	5.3×10^{-4}	3.28
diethylamine	9.8×10^{-4}	3.01
dipropylamine	1.0×10^{-3}	3.00
trimethylamine	5.5×10^{-5}	4.26
triethylamine	5.7×10^{-4}	3.24
tripropylamine	4.5×10^{-4}	3.35

The reversal of the expected order for a secondary and a tertiary amine indicates that a second factor affects the basicity of amines. That factor operates in a direction opposite to the inductive effect of the alkyl groups. It is the difference in the degree of solvation of the ammonium ions and the resultant stabilization of that product. The dialkylammonium ion has two N—H bonds that can form hydrogen bonds with water. The trialkylammonium ion has only one N—H bond.



diethylammonium ion



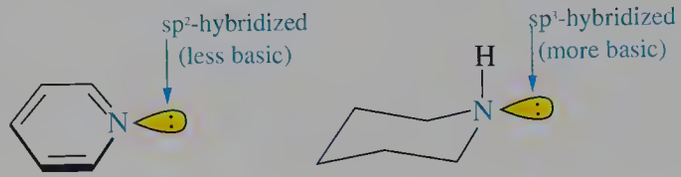
triethylammonium ion

Thus triethylamine is a weaker base than diethylamine because its conjugate acid is not as effectively solvated. Diethylamine is the strongest base of the series because it has the best balance of inductive electron donation by alkyl groups and stabilization by solvation of the conjugate acid.

Heterocyclic Amines

The basicity of heterocyclic amines varies over a wide range and reflects both the hybridization of the orbital of nitrogen containing the lone pair electrons and

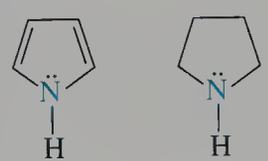
the effects of delocalization. Pyridine is a substantially weaker base than alkylamines such as piperidine. The electron pair of pyridine occupies an sp^2-hybridized orbital and lies closer to the nucleus than the electron pair in the sp^3-hybridized orbital of alkylamines. As a result, pyridine is a weaker base (larger pK_b) than an alkylamine.



pyridine
$pK_b = 8.75$

piperidine
$pK_b = 2.88$

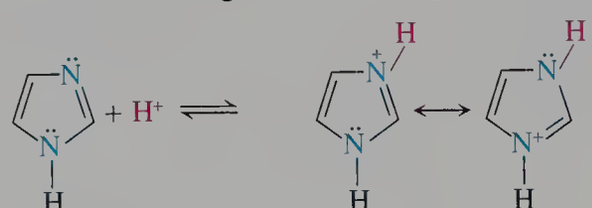
Pyrrole is an exceedingly weak base. The pair of electrons that might be protonated is not readily available because it is required to maintain the sextet of electrons in the ring required for aromaticity.



pyrrole
$pK_b = 15$

pyrrolidine
$pK_b = 2.73$

Imidazole is an important aromatic ring found in many biological molecules. It has two nitrogen atoms. One resembles that of pyrrole and is not basic. The second nitrogen is structurally similar to the nitrogen atom of pyridine. However, imidazole is about 100 times as basic as pyridine. The increased basicity results from resonance stabilization of the charge to both nitrogen atoms.

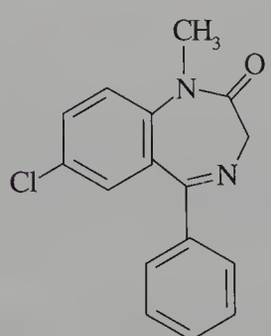


imidazole

resonance-stabilized conjugate acid

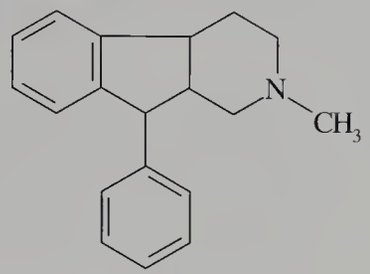
Problem 25.11

The pK_a of the conjugate acid of diazepam (Valium) is 3.3. What is the K_a? Calculate the K_b and pK_b of diazepam.



Problem 25.12

Estimate the pK_a of phenindamine, an antihistamine.



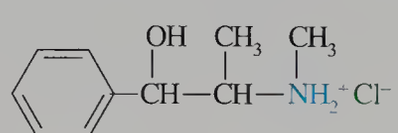
25.6 Solubility of Ammonium Salts

When an amine is added to a solution of a strong acid, such as hydrochloric acid, the amine nitrogen atom is protonated to produce an ammonium salt.

$$RNH_2 + HCl \rightleftharpoons RNH_3^+Cl^-$$

Ammonium salts of low molecular weight are soluble in water if the hydrocarbon portion of the amine is small. Because the nitrogen atom of an ammonium salt has a positive charge, ammonium salts are more soluble than amines. Drugs containing an amino group are often prepared as ammonium salts to improve their solubility in body fluids.

The ammonium salts of many drugs are more stable and less prone to oxidation than the amine itself. In addition, the ammonium salts have higher melting points and virtually no odor. For example, ephedrine melts at 79 °C and has a fishy odor. Its hydrochloride salt, used in cold and allergy medications, melts at 217 °C and has no odor.



ephedrine hydrochloride

Amines can be separated from other substances by converting them to ammonium salts. Consider, for example, the separation of 1-chlorooctane from 1-aminooctane. Both compounds are insoluble in water. Adding HCl to a solution containing both compounds converts the 1-aminooctane into its ammonium salt, whereas 1-chlorooctane is not affected.

$$CH_3(CH_2)_6CH_2NH_2 + HCl \longrightarrow CH_3(CH_2)_6CH_2NH_3^+Cl^-$$

(insoluble in water) (soluble in water)

$$CH_3(CH_2)_6CH_2Cl + HCl \not\longrightarrow \text{no reaction}$$

(insoluble in water)

The 1-chlorooctane is physically separated from the aqueous acid solution. Then the acid solution is neutralized with sodium hydroxide to form the free amine. The amine can then be physically separated from the aqueous solution.

$$CH_3(CH_2)_6CH_2NH_3^+ + OH^- \longrightarrow CH_3(CH_2)_6CH_2NH_2 + H_2O$$

(soluble in water) (insoluble in water)

25.7 Synthesis of Amines by Displacement Reactions

Many general methods to synthesize amines have already been discussed in prior chapters. In this section we consider the displacement reactions of alkyl halides with ammonia or an amine, and a variation on this method that improves yields.

Alkylation of Amines by Alkyl Halides

The nucleophilic substitution reaction of ammonia with an alkyl halide yields a mixture of products resulting from competitive alkylation of the product. A complex mixture of ammonium ions results.

$$CH_3I + NH_3 \longrightarrow CH_3NH_3^+I^- + (CH_3)_2NH_2^+I^- + (CH_3)_3NH^+I^- + (CH_3)_4N^+I^-$$

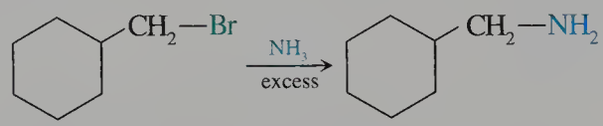
This mixture results because the methylammonium ion initially formed is deprotonated in equilibrium with ammonia to give methylamine, a nucleophile. Methylamine then reacts with methyl iodide.

$$NH_3 + CH_3I \longrightarrow CH_3NH_3^+I^-$$

$$CH_3NH_3^+I^- + NH_3 \rightleftharpoons CH_3NH_2 + NH_4^+I^-$$

$$CH_3NH_2 + CH_3I \longrightarrow (CH_3)_2NH_2^+I^-$$

Continued deprotonation of the ammonium ion product in equilibrium reactions, followed by alkylation, eventually leads to products with all possible degrees of alkylation. The exact amounts of the products depend on the relative amounts of the starting materials and on the reaction conditions. Selecting the proper reaction conditions can diminish chances for multiple alkylation. For example, if an alkyl halide reacts with ammonia in the presence of excess ammonia, the reaction can convert an alkyl halide to a primary amine. When the concentration of ammonia is greater than the concentration of the primary amine product, the probability decreases that the primary amine will react with the alkyl halide.



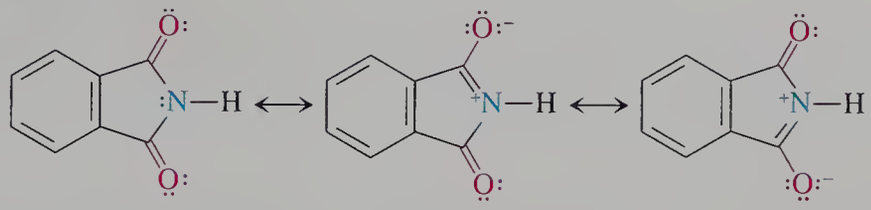
By analogy, we expect that secondary amines could be prepared by reaction of an alkyl halide with an excess of a primary amine. In general, this reaction is not used because the excess amine, which is more expensive than the ammonia used to prepare primary amines, is wasted.

In general, the preparation of amines by nucleophilic displacement is restricted to inexpensive alkyl halides and to easily separated amines. Separation by distillation using efficient fractionating columns makes possible the industrial preparation of some simple amines by displacement reactions.

Gabriel Synthesis

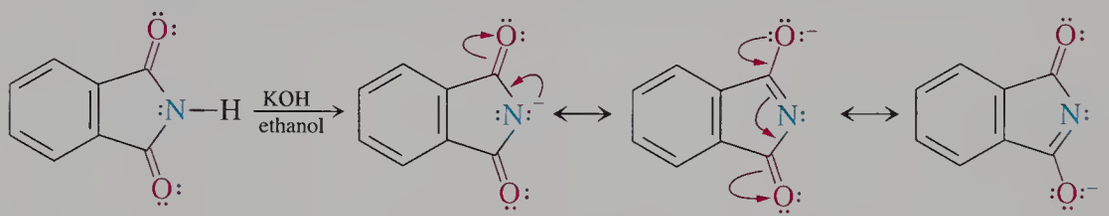
We can circumvent the problem of multiple alkylation of nitrogen in the preparation of primary amines by "protecting" the nitrogen atom of ammonia so that it reacts only once with an alkylating agent. An example of a compound that contains

a protected nitrogen atom with a single N—H bond is phthalimide. Not only is there no possibility for multiple alkylation, but the carbonyl groups modify the reactivity of the nitrogen. Donation of electron density by nitrogen to either carbonyl group decreases the nucleophilicity of nitrogen.



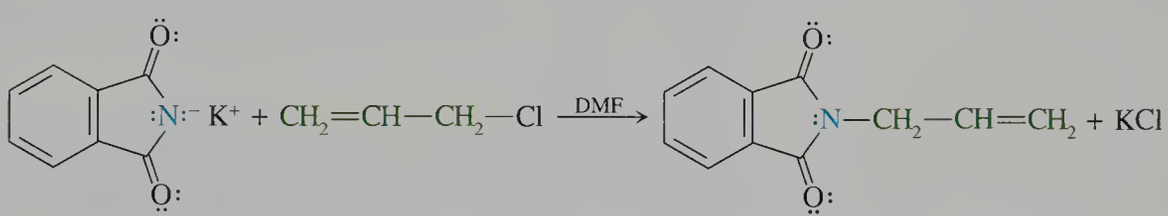
phthalimide dipolar resonance forms

The pK_a of the N—H bond of phthalimide is 8.3. The enhanced acidity of the N—H bond results from both an inductive and a resonance effect. The inductive effect of two carbonyl groups increases the acidity of the N—H bond. The more important effect is the resonance stabilization of the conjugate base by delocalization of the electrons of nitrogen with the carbonyl groups.

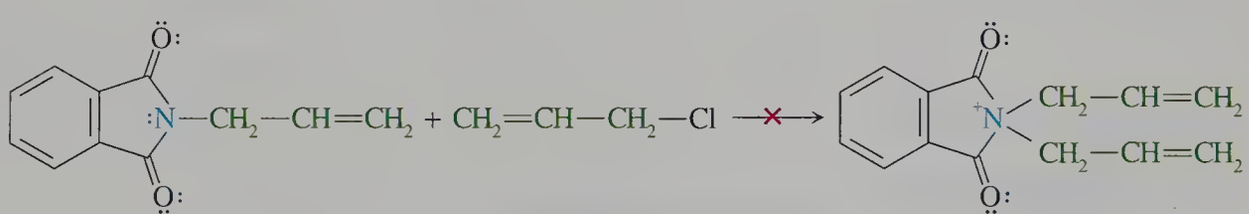


resonance-stabilized conjugate base

The negatively charged nitrogen atom of the salt of phthalimide is a good nucleophile. It displaces halides from primary alkyl halides and tosylate groups from primary tosylates to yield an *N*-alkylated phthalimide. This reaction, with its related workup procedures, is called the **Gabriel synthesis**.

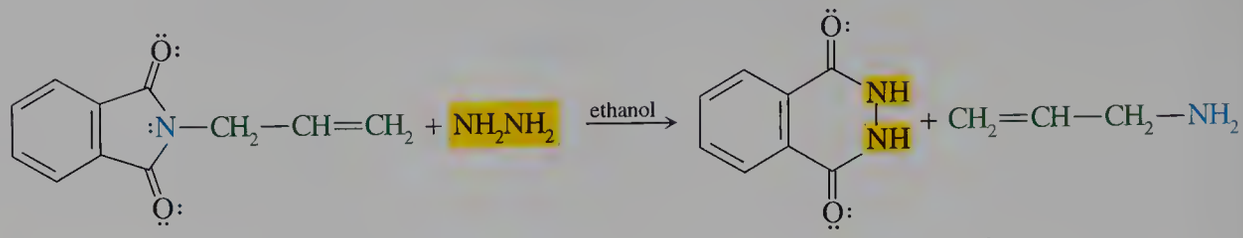


The product is a diacyl derivative of an amine. Thus, the lone pair electrons of nitrogen are so effectively delocalized that they cannot displace a halide even from a compound as reactive as allyl chloride.



The *N*-alkyl phthalimide product can be hydrolyzed with either aqueous acid or base to form phthalic acid and liberate the amine. However, amides are difficult

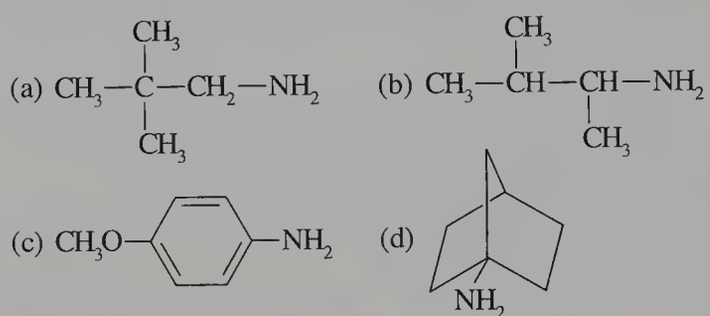
to hydrolyze (Section 22.5). A more effective method uses hydrazine to form a phthalyl hydrazide by acyl transfer.



The Gabriel synthesis is limited to the formation of primary amines because secondary and tertiary alkyl halides undergo competitive elimination reactions. Aryl halides cannot be used because they do not undergo nucleophilic substitution.

Problem 25.13

Consider the possible synthesis of each of the following amines using the Gabriel synthesis. What limitations are there in each case?



Problem 25.14

4-Aminobutanoic acid, commonly known as γ-aminobutyric acid or GABA, is involved in the transmission of nerve impulses. Explain why it cannot be synthesized by a Gabriel synthesis using 4-chlorobutanoic acid. What alternate chlorinated acid derivative might be used.

Sample Solution

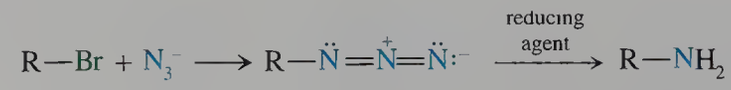
The carboxylic acid is sufficiently acidic to rapidly protonate the salt of the phthalimide prior to the S_N2 displacement of the chloride ion. The related ester and nitrile are possible alternative reactants. However, the imide salt would displace an alkoxide of the ester and form an amide. The nitrile, 4-chlorobutanenitrile, is a better choice. The resultant 4-aminobutanenitrile can be hydrolyzed to the corresponding carboxylic acid.

25.8 Synthesis of Amines by Reduction

Amines are the most reduced form of nitrogen in organic compounds. Thus, almost any functional group containing nitrogen in a higher oxidation state or with multiple bonds to nitrogen can be reduced to an amine.

Reduction of Azides

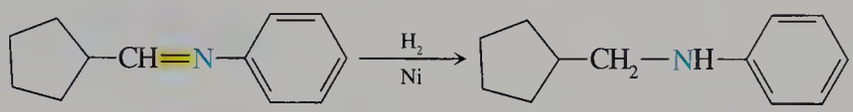
Alkyl azides are unstable compounds, but they can be easily prepared by nucleophilic substitution of a halide by the very nucleophilic azide ion (N_3^-). Reduction of azides yields amines.

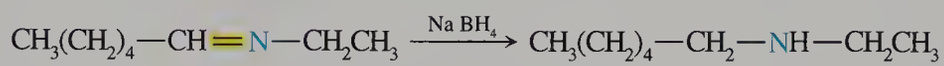


Catalytic hydrogenation using hydrogen and platinum may be used, but lithium aluminum hydride in an ether solvent is the more common reducing agent.

Reduction of Imines

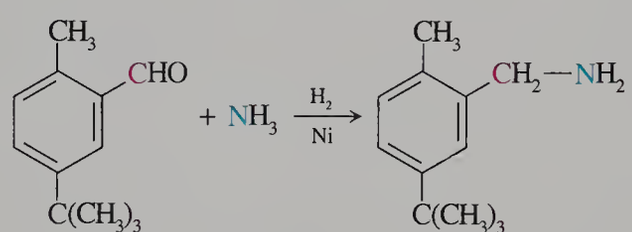
We recall that the carbonyl group of aldehydes or ketones is reduced to an alcohol by either catalytic hydrogenation or metal hydrides. Imines are the nitrogen analogs of carbonyl compounds and are also reduced by the same reagents.



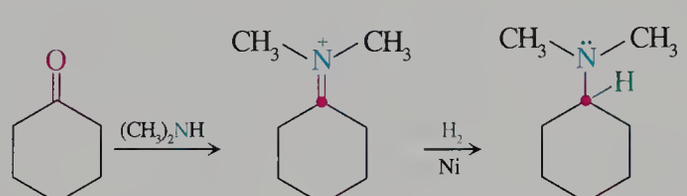


Imines are less stable than carbonyl compounds and the reaction conditions must be selected to drive the equilibrium reaction of a carbonyl compound with an amine toward an imine (Section 19.10). Only imines of aromatic amines are easily prepared and isolated.

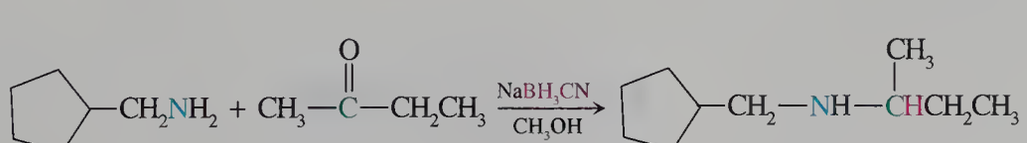
Imines do not have to be separately prepared and isolated for subsequent reduction. A mixture of a carbonyl compound and ammonia or the appropriate amine reacts in the presence of hydrogen gas and a metal catalyst. The imine initially formed is reduced to an amine. The overall process is called **reductive amination**. Primary amines are prepared using ammonia as the nitrogen source.



Secondary amines are prepared using a primary amine as the nitrogen source. Condensation of an aldehyde or ketone with a secondary amine gives an iminium salt, which is subsequently reduced to a tertiary amine.



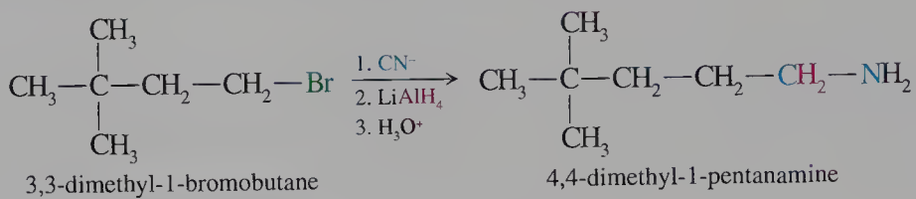
Reductive amination can also be accomplished by using a modified borohydride called sodium cyanoborohydride. This reagent reduces the intermediate imine functional group but not the carbonyl group of the reactant.



Reduction of Nitriles

Nitriles can be prepared from primary alkyl halides by a direct S_N2 displacement reaction using sodium cyanide as the nucleophile. The nitrile is then reduced to a primary amine with lithium aluminum hydride.

$$R{-}X \xrightarrow{CN^-} R{-}C{\equiv}N \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} R{-}CH_2{-}NH_2$$

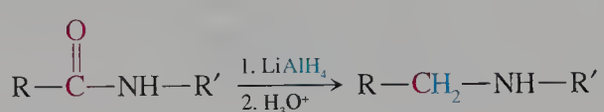


3,3-dimethyl-1-bromobutane

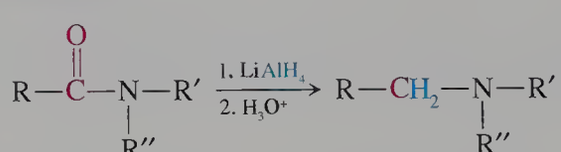
4,4-dimethyl-1-pentanamine

Reduction of Amides

Reduction of amides is one of the most frequently used methods of preparing amines. The method is very versatile because primary, secondary, and tertiary amines are easily prepared from the corresponding classes of amide. Amides are prepared by acylation of amines using activated acyl derivatives such as acid chlorides or acid anhydrides (Section 22.7).



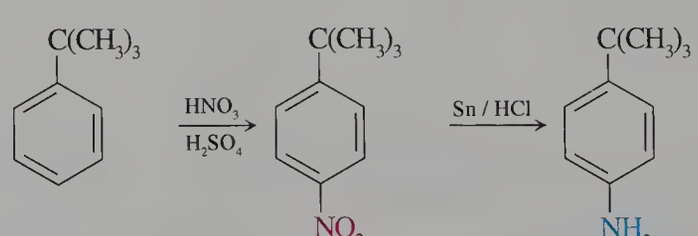
(a secondary amide) (a secondary amine)



(a tertiary amide) (a tertiary amine)

Reduction of Nitro Compounds

There is no synthetic procedure to introduce an amino group onto an aromatic ring in one step. However, it is possible to substitute an amino group onto an aromatic ring in two steps. First the ring is nitrated. Then the nitro group is reduced to an amino group.

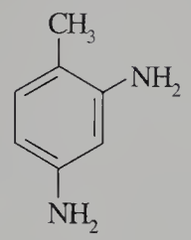


Problem 25.15

Select appropriate reactants and outline three synthetic methods to prepare 2-phenylethylamine using a reductive step.

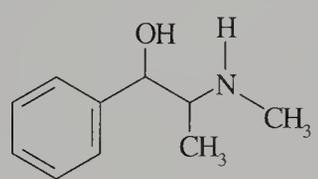
Problem 25.16

Outline a synthesis of the following diamine starting from toluene.



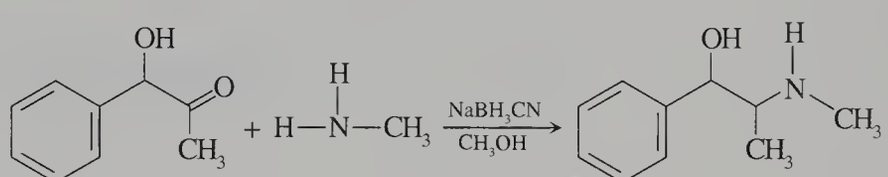
Problem 25.17

Ephedrine is used in the treatment of bronchial asthma. What reactants are required to synthesize this compound using a reductive amination step.



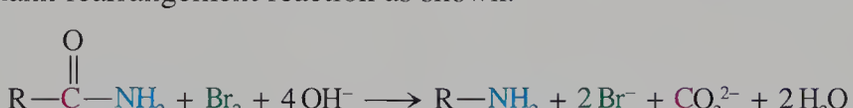
Sample Solution

There are two possible combinations of reactants because either of the two carbon atoms bonded to nitrogen could be the carbonyl carbon atom. Either of the remaining carbon atoms in each case could be bonded to a nitrogen atom of an amine. The required carbonyl compound using methylamine as the reactant is 1-hydroxy-1-phenyl-2-propanone.



25.9 Hofmann Rearrangement

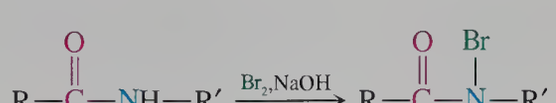
Primary amides can be converted into amines containing one less carbon atom by the Hofmann rearrangement reaction as shown.



The structural change corresponds to removing the carbonyl group and attaching the amino group to the α carbon atom. However, as the name implies, a rearrangement reaction occurs. It involves a migration of the R group from the carbonyl carbon atom to the nitrogen atom.

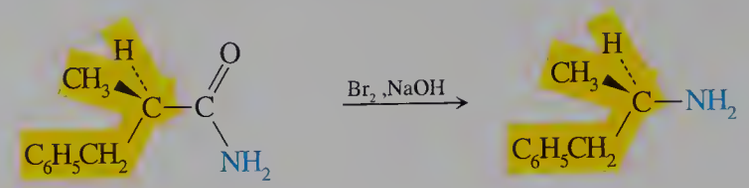
The following experimental observations form the basis of the mechanism.

1. The nitrogen atom must have two protons attached to it. Thus, only primary amides react to give the amine.
2. Under the reaction conditions, secondary amides yield *N*-bromoamides.



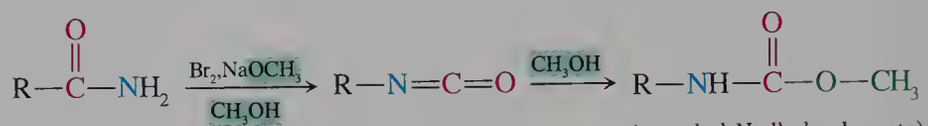
(a secondary amide) (an *N*-bromoamide)

3. The reaction occurs with retention of configuration at the α carbon atom.



(*R*)-2-methyl-3-phenylpropanamide (*R*)-1-phenyl-2-propanamine

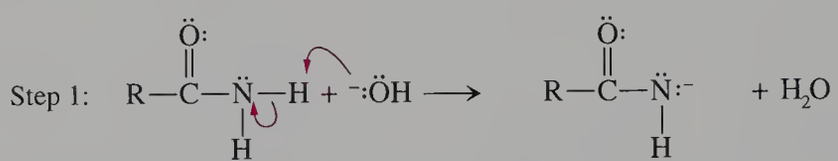
4. An intermediate isocyanate (R—N=C=O) is formed under the reaction conditions. The existence of the isocyanate is shown by "trapping" it using methanol as solvent. Under these conditions a carbamate forms.



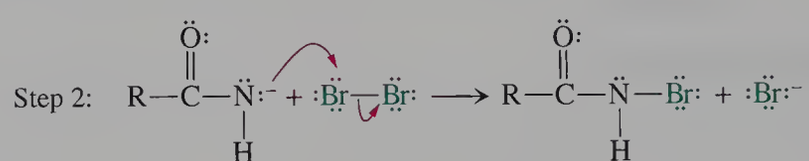
(a methyl *N*-alkylcarbamate)

Mechanism of the Hofmann Rearrangement

The Hofmann rearrangement includes six steps. The *N*-bromoamide forms in two steps. First, the conjugate base of the amide forms by deprotonation of the amide by hydroxide ion. The pK_a of a primary amide is approximately the same as for water. Thus, the equilibrium constant for the reaction is close to 1. The conjugate base then displaces bromide ion from bromine and yields the *N*-bromoamide.

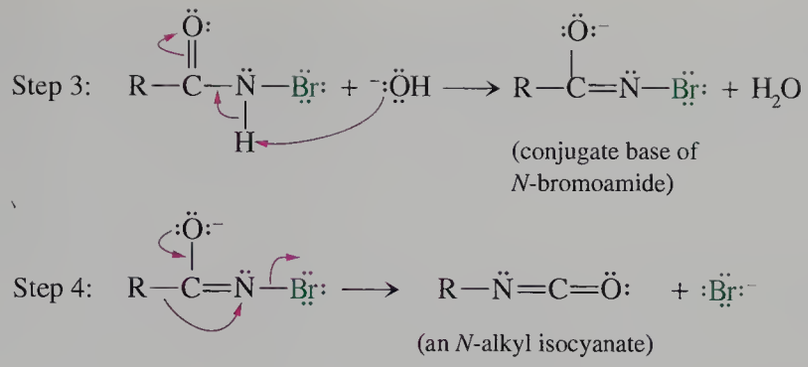


resonance-stabilized ion

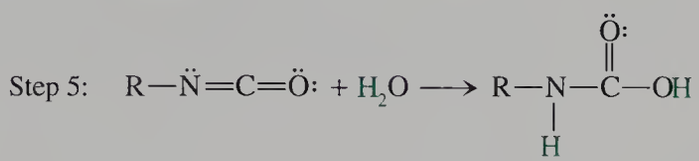


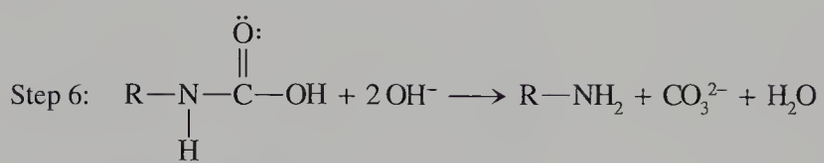
(an *N*-bromoamide)

In the second stage, the *N*-bromoamide is converted into an isocyanate in two steps. The first reaction of this conversion is deprotonation of the *N*-bromoamide, which is even more acidic than the original amide because bromine withdraws electron density. A rearrangement reaction then occurs in which the R group migrates from the carbonyl carbon atom to the nitrogen atom. A bromide ion simultaneously leaves. As the bromide ion departs, the nitrogen atom develops some cationic character, which provides the driving force for the reaction. Thus, the migration of the alkyl group resembles that of alkyl groups in carbocation rearrangement (Sections 11.4 and 14.7).



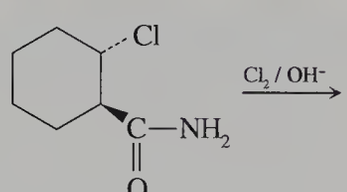
In the third stage, the isocyanate is hydrolyzed in a base-catalyzed reaction to give an *N*-alkylcarbamic acid. The final step is the decomposition of the unstable carbamic acid.





Problem 25.18

Draw the product of the following reaction.



25.10 Overview of Reactions

In Chapter 16, we analyzed the reactions of alcohols based on the number and type of bonds broken. Let's do the same thing for amines and compare the chemistry of amines with alcohols. As we will shortly see, the substitution of the nitrogen atom of Group 5 for the oxygen atom of Group 6 causes amine chemistry to differ dramatically from that of alcohols.

Acid and Base Properties

Alcohols are weak acids, $pK_a \approx 16$, but their conjugate bases form easily. We have seen that the reaction of alkoxides as nucleophiles is an important feature of the chemistry of alcohols. In contrast, amines are very weak acids, $pK_a \approx 35$. The dif-

ference in acidities of alcohols and amines agrees with the periodic trends discussed in Section 3.4 for CH_4, NH_3, and H_2O. Because amines are very weak acids, the chemistry of their conjugate bases is quite limited. In fact, the conjugate bases of amines such as lithium diisopropylamide are used only to form conjugate bases of compounds such as carbonyl compounds.

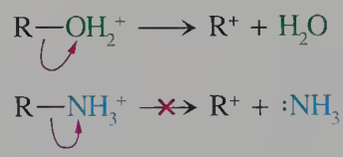
Also based on periodic trends, we know that amines are stronger bases than alcohols. Alcohols are very weak bases and are protonated only in strong acid solutions. Amines are used to neutralize acids generated in reactions, such as the HCl generated in the reaction of an acid chloride with an alcohol. They are also used to catalyze reactions such as the Knoevenagel reaction.

Nucleophilicity

We recall that within the same period, nucleophilicity and basicity parallel each other (Section 10.1). Thus, ammonia is a better nucleophile than water and amines are better nucleophiles than alcohols. Most of the reactions of amines result from the nonbonding electron pair on nitrogen. We recall that a nonbonding electron pair of an alcohol is only weakly nucleophilic. For example, it is usually only available to displace leaving groups, such as a halide ion in S_N2 reactions, when the alcohol is converted to the more nucleophilic alkoxide ion. As we saw in Section 25.8, the nonbonding electron pair of the neutral amine can displace a halide ion from alkyl halides. Both alkylation and acylation of an amine result directly from the nucleophilicity of the nonbonding electron pair. The alkyl or acyl group replaces a hydrogen atom of an N—H bond. However, the hydrogen atom leaves in a subsequent step of the reaction after the nonbonding electron pair attacks an electrophilic center.

Substitution Reactions

Many reactions of alcohols break the C—O bond, as in the replacement by a halogen atom in nucleophilic substitution reactions by either an S_N2 or an S_N1 mechanism. However, we recall that the leaving group tendencies within a group are inversely related to their basicity (Section 10.3). Thus, hydroxide ion is a poor leaving group, and it is necessary to protonate the hydroxyl group to generate water as a leaving group. Because NH_2^- is a much stronger base than OH^-, the C—N bond of amines does not break heterolytically in S_N2 or S_N1 reactions. Even if an amine is protonated to provide ammonia as a leaving group, neither S_N1 nor S_N2 reactions occur.



Elimination Reactions

We recall that in some reactions of alcohols in which either the C—O or the O—H bond breaks, a C—H bond also breaks. If this bond is on the carbon atom adjacent to the carbon atom bearing the hydroxyl group, the reaction is a β elimination. The corresponding reaction of the N—H and C—H bonds of amines is relatively unimportant. As in the case of substitution reactions, the basicity of the leaving group is important in

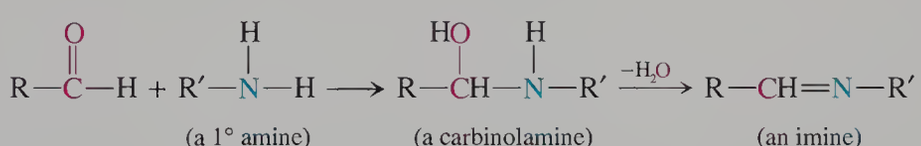
β-elimination reactions. Consequently, amines do not undergo β elimination reactions because both NH_2^- and NH_3 are poor leaving groups. However, one specialized reaction in which an amine is converted into a quaternary ammonium ion is an E2 elimination. This process, known as the Hofmann elimination, is discussed in Section 25.15.

Oxidation Reactions

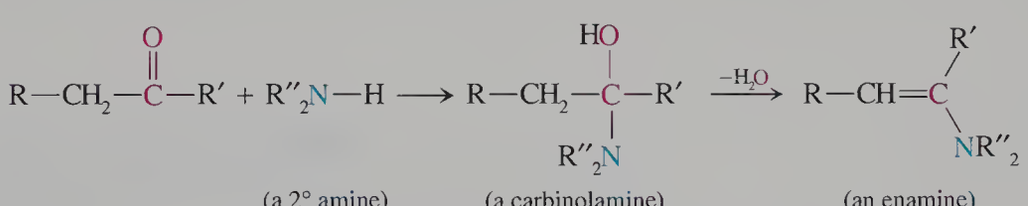
We recall that breaking both the O—H bond of an alcohol and the C—H bond at the carbon atom bearing the hydroxyl group is an oxidation reaction, or an α-elimination reaction. Amines can be similarly oxidized, but the products are sensitive to reaction conditions, and synthetic applications of this chemistry are limited. We recall, for example, that imines are very reactive. In this chapter, we consider only one type of reaction that can be termed an oxidation. Nitrous acid (HNO_2) is a mild oxidizing agent that generates intermediates that are oxidized relative to an amine. We have already seen some of this chemistry in the conversion of aromatic amines into aromatic diazonium ions (Section 14.8). We will expand on this reaction and related chemistry in this chapter for alkylamines.

25.11 Enamines

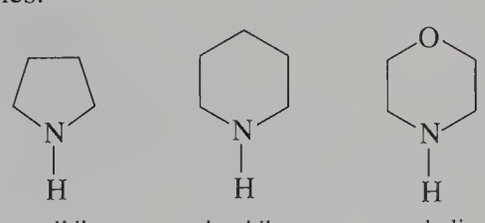
In Section 19.10 we described the addition–elimination reaction of primary amines with carbonyl compounds. An amine adds to the electrophilic carbonyl carbon atom to give a tetrahedral intermediate. This carbinolamine is unstable and loses water to form an imine.



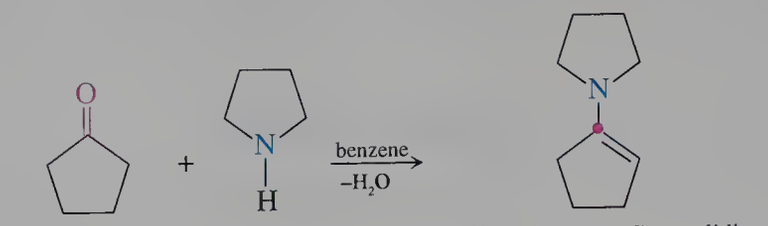
Secondary amines also react with aldehydes or ketones to form carbinolamines, but this intermediate cannot dehydrate to give an imine. However, it can dehydrate to give a carbon–carbon double bond in a compound called an **enamine** (pronounced "ene amine"). The water is removed by azeotropic distillation with benzene.



Pyrrolidine, piperidine, and morpholine are the most common secondary amines used to prepare enamines.



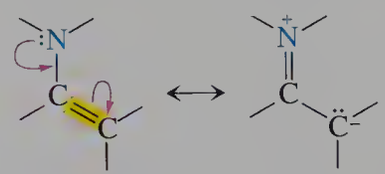
The reaction of cyclopentanone with pyrrolidine is an example of the formation of an enamime.



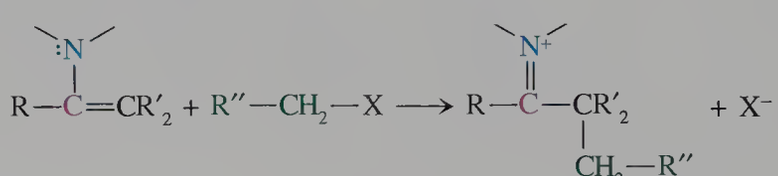
cyclopentanone pyrrolidine *N*-(1-cyclopentenyl)pyrrolidine

Alkylation of Enamines

Enamines are used as intermediates to form carbon–carbon bonds in reactions that parallel those of carbonyl compounds. The carbon–carbon double bond is nucleophilic because the lone pair electrons of nitrogen can be released to the carbon atom that was the α carbon atom of the original carbonyl compound.



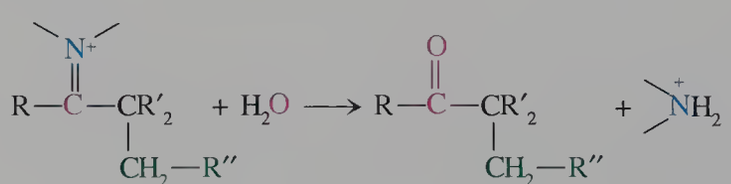
Enamines therefore resemble enols because both have an increased electron density at a structurally related α carbon atom. The electron density at the α carbon atom in enamines is greater than that in enols because nitrogen is less electronegative than oxygen and releases an electron pair more readily. As a result, enamines are more nucleophilic than enols and are useful intermediates in alkylation reactions. We recall that enolate anions react with alkyl halides to give α-alkylated carbonyl compounds (Section 23.6), but uncharged enols are not sufficiently nucleophilic to be alkylated. The more nucleophilic enamine is more easily alkylated, producing an iminium ion.



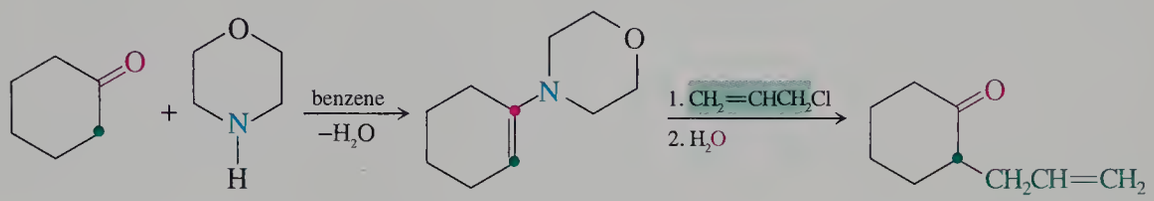
(an enamine) (a 1° alkyl halide) (an alkylated enamine)

The S_N2 displacement reaction by the electron pair of an enamine occurs for primary alkyl halides, α-halo carbonyl compounds, and α-halo ethers.

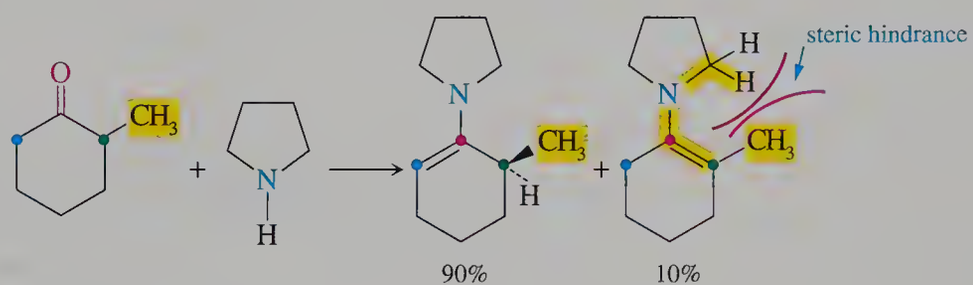
Like imines, the iminium ion is readily hydrolyzed to give an alkylated carbonyl compound.



The use of enamines to alkylate carbonyl compounds at the α-position rather than the direct alkylation of the carbonyl compound has several advantages. First, no strong base is present, so side reactions with the alkyl halide such as substitution and elimination are avoided. Second, because alkylation of the enamine gives an iminium ion, the derivative is no longer nucleophilic. As a result, monoalkylation occurs in good yield. This result contrasts with the alkylation of enolates, where proton transfer between alkylated product and reactant leads to multiple alkylation (Section 23.6).



Two isomeric enamines can form with unsymmetrical ketones. The major isomer is the one with the less substituted double bond, as shown for 2-methylcyclohexanone.



This distribution results from resonance stabilization and steric effects. The enamine is stabilized by overlap of the orbital of nitrogen containing the nonbonded electrons with the π electrons of the double bond. For maximum overlap, the groups bonded to nitrogen and two carbon atoms of the double bond must be coplanar. In the minor isomer there is an unfavorable steric interaction with the methyl group and a methylene unit of the pyrrolidine ring that resembles that of cis alkenes. Although the same interaction may appear to exist in the major isomer, it is less severe. The methyl group of this isomer is bonded to an sp^3-hybridized carbon atom and is not in the same plane as the pyrrolidine ring.

Problem 25.19

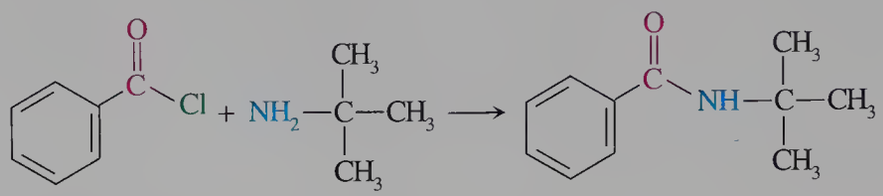
Draw the structure of the enamine formed from cyclopentanone and piperidine. Draw the structure of the product of reaction between this enamine and benzyl chloride.

Problem 25.20

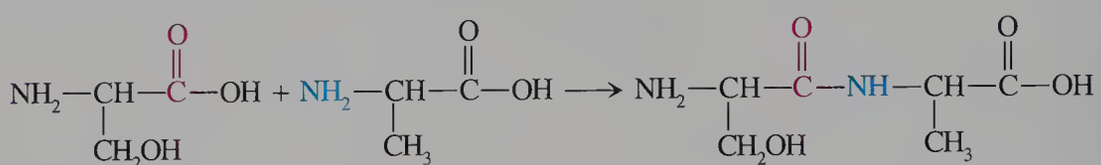
Enamines serve as Michael donors in conjugate addition reactions (Section 23.12). Draw the structure of the product formed by reaction of the enamine of cyclohexanone and pyrrolidine with methyl vinyl ketone.

25.12 Formation of Amides

Amides can be synthesized under mild conditions by the reaction of an acyl chloride or an anhydride with ammonia, a primary amine, or a secondary amine. We described this reaction in Section 22.7 with a different focus, the reaction of acyl derivatives.

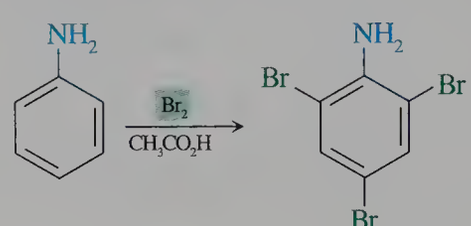


Proteins are polyamides of α-amino acids. The amino group of one amino acid reacts with the acid group of another amino acid in a process that requires many enzyme-catalyzed reactions. The resultant amide still has both an amine and a carboxyl functional group. Continued reaction with the same or different amino acids forms proteins (Chapter 26).



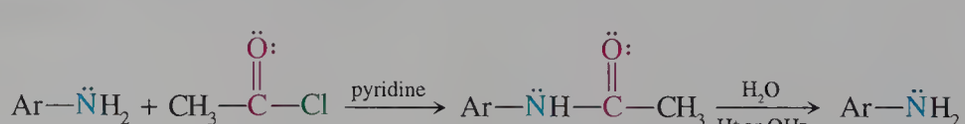
Protection of Amino Groups

We recall that anilines are very reactive toward electrophilic aromatic substitution (Section 14.5). However, some experimental limitations must be considered in relation to substitution reactions on anilines. Because the electron pair of the amino nitrogen is so readily donated to the benzene ring by resonance, multiple substitution commonly occurs. For example, the bromination of aniline yields a tribromo derivative.

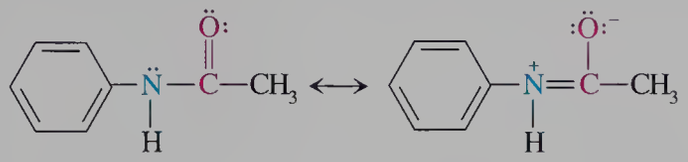


Two other experimental difficulties arise from the amino group itself. First, because an amino group is basic, reactions in strongly acidic media produce an ammonium ion, a meta director that deactivates the aromatic ring. Second, the electron-rich nitrogen atom of anilines can be oxidized by reagents such as nitric acid, which decreases the yield of desired products.

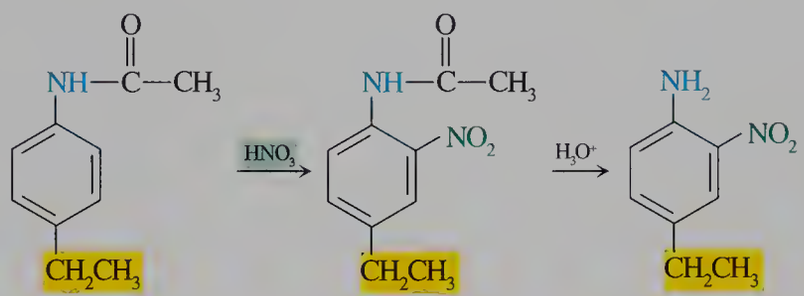
All of these experimental problems are eliminated by acetylating aniline. Either acetyl chloride or acetic anhydride may be used as the acetylating agent. The acetyl group both "protects" the amino group and decreases the reactivity of the aromatic ring toward electrophiles. The protecting group is removed by hydrolysis under acidic or basic conditions after the completion of the electrophilic aromatic substitution reaction.



Acetylating the amino group of an aniline decreases the electron density on nitrogen as a result of the dipolar resonance contributor.

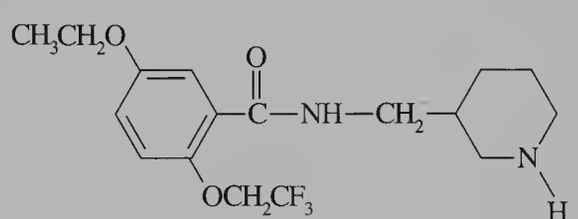


The acetamido group cannot be as easily oxidized and is not basic. It is still an ortho, para director, but is less activating. As a result, monosubstitution reactions occur at the ortho or para position.



Problem 25.21

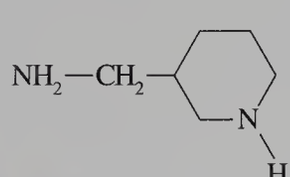
Flecainide, an antiarrhythmic drug, is an amide. Draw the structures of the compounds that could be used to produce the drug. What possible complications might occur with this combination of reactants?



flecainide

Sample Solution

The following primary amine is required to form the amide using an acid derivative. The molecule has a secondary amine site as well. Thus the acid derivative could competively react with either nitrogen atom. Because the nucleophilicity of an amine is affected by steric hindrance, the primary amine should react at the faster rate to give the desired product.

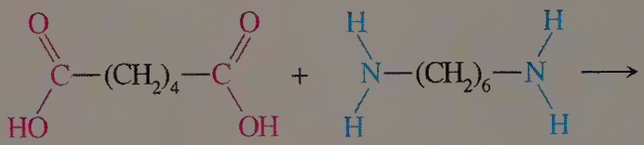


Problem 25.22

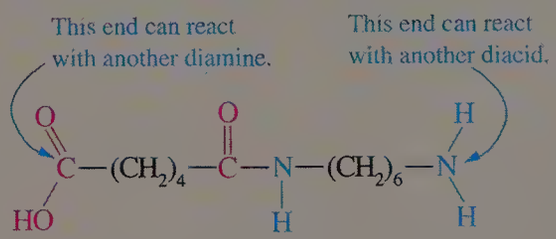
Amides are very weak bases. However, when an amide treated with a strong acid, protonation occurs on the oxygen atom rather than on the nitrogen atom. Compare the structure of this conjugate acid with one that is protonated on nitrogen and explain why protonation occurs preferentially on oxygen.

Polyamides

Many condensation polymers are polyamides. Perhaps the most famous of these is nylon. Synthetic polyamides, such as nylon, are produced from diamines and dicarboxylic acids by condensation polymerization. One type of nylon is made from adipic acid and hexamethylenediamine (1,6-diaminohexane), which condense to form an amide.

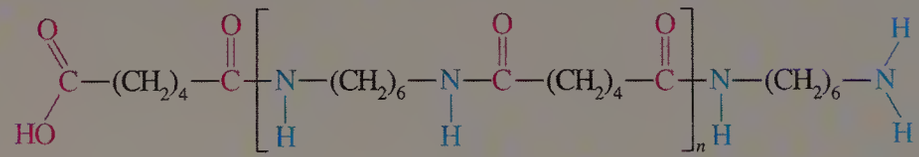


adipic acid hexamethylenediamine



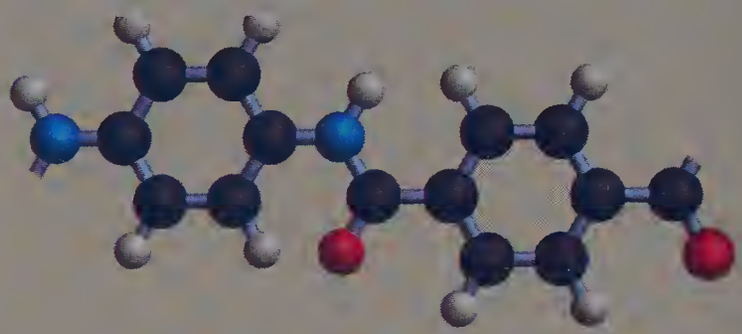
(an amide)

The product of the first condensation reaction is an amide that also contains a free amino group and a free carboxylic acid group. The amine end of this molecule reacts with another molecule of adipic acid to produce another amide linkage. The carboxylic acid end of the new molecule then reacts with another molecule of hexamethylenediamine. This sequence of reactions occurs again and again to produce a polyamide. The nylon formed from adipic acid and hexamethylenediamine is called nylon 66. The "66" refers to the six-carbon diacid and six-carbon diamine reactants.

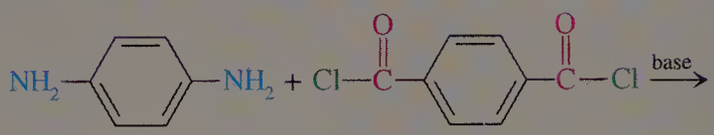


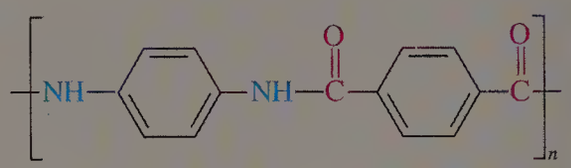
nylon 66

Polyamides containing aromatic rings (aramides) have many special properties. The presence of aromatic rings in the polymer produces a stiff and tough fiber. One commercially important aramide is Kevlar, a polyamide made from *p*-phenylenediamine and terephthaloyl chloride. It is used instead of steel in bullet-resistant vests. These vests are so light and flexible that they can be worn inconspicuously under normal clothing.



repeating unit of Kevlar



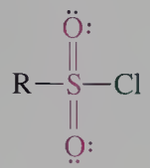


Kevlar

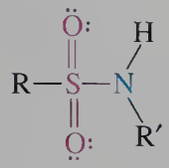
An aramide called Nomex has a structure resembling that of Kevlar. The monomers in Nomex are meta rather than para isomers. Nomex is used in flame-resistant clothing for fire fighters and racing-car drivers. It is so strong that it can be also used in flame-resistant building materials.

25.13 Sulfonamides

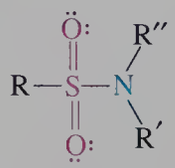
Sulfonyl chlorides are the acid chlorides of sulfonic acids. Like acid chlorides, sulfonyl chlorides react with amines to form amides called **sulfonamides**. These compounds are crystalline solids with high melting points.



a sulfonyl chloride

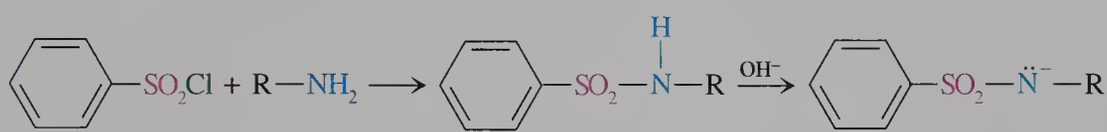


sulfonamide of a 1° amine



sulfonamide of a 2° amine

Sulfonamides properties differ from those of amides. Because the sulfonyl group withdraws electrons more strongly than an acyl group, the N—H bond of the sulfonamide of a primary amine is acidic. Thus, reaction of a primary amine with benzenesulfonyl chloride yields a sulfonamide that is soluble in sodium hydroxide.

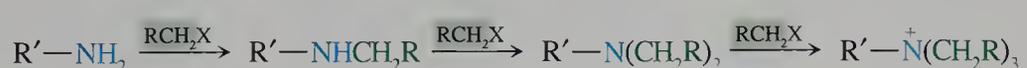


Secondary amines also react with benzenesulfonyl chloride to give sulfonamides. They are insoluble in base because there is no acidic N—H bond. Tertiary amines do not form stable compounds with benzenesulfonyl chloride because they have no hydrogen atom on the nitrogen atom of the amine.

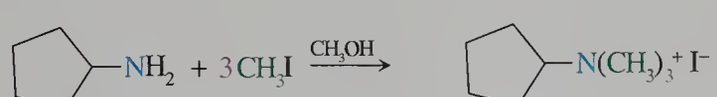
A method of distinguishing between the types of amines is based on the difference in the reactivity of amines with benzenesulfonyl chloride followed by reaction with sodium hydroxide. The procedure is called the **Hinsberg test**. First, benzenesulfonyl chloride is shaken with a mixture of an amine and aqueous base. Then the reaction mixture is examined to determine which of three possible events occurred. If the amine was tertiary, no precipitate appears, and there is no evidence of any reaction. If the amine was secondary, a water-insoluble sulfonamide forms and appears as a precipitate. Primary amines also give no evidence of a reaction because the sulfonamide is soluble in the base, but if the solution is neutralized with an acid, the neutral water-insoluble sulfonamide precipitates. Thus, the experimental results are unique for each class of amine.

25.14 Quaternary Ammonium Salts

Earlier in this chapter we described nucleophilic substitution reactions of primary amines with alkyl halides, which give secondary amines, tertiary amines, and eventually quaternary ammonium salts.



Methyl iodide reacts so readily with nucleophiles that primary amines are completely converted to quaternary ammonium salts by a process called **exhaustive methylation**.

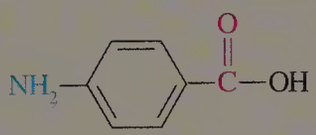


cyclopentylamine

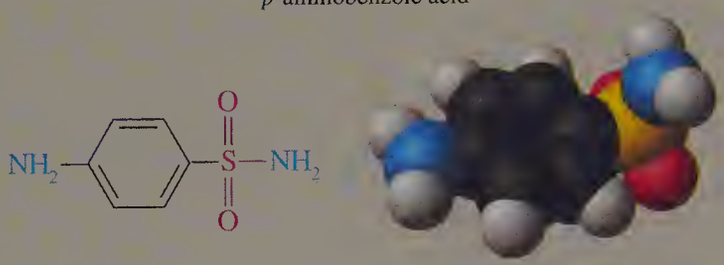
cyclopentyltrimethylammonium ion

Sulfa Drugs

Various derivatives of *p*-aminobenzenesulfonamides are **sulfa drugs**. They were widely used in the 1940s to combat bacterial infections. However, they have been largely replaced because their indiscriminate use resulted in sulfanilamide-resistant strains of bacteria. In addition, they are toxic to some patients. For these reasons, penicillins and then cephalosporins have replaced sulfa drugs as the antibiotics of choice.

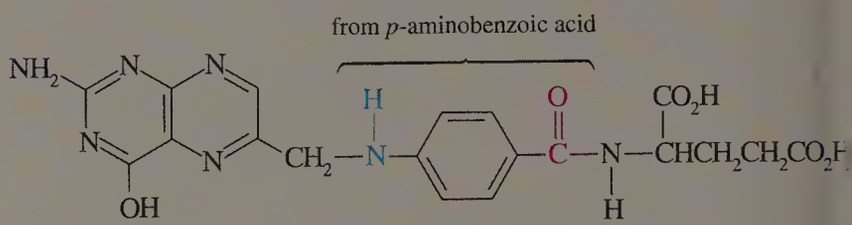


p-aminobenzoic acid



sulfonamide

Sulfa drugs are inhibitors of specific bacterial enzymes. For example, bacteria require *p*-aminobenzoic acid (PABA) to synthesize the vitamin folic acid, which functions as a coenzyme. The sulfa drug sulfanilamide has a structure similar to PABA. Incorporation of a sulfonamide at the active site of an enzyme in competition with PABA so disrupts the metabolic processes in the bacteria that they cannot produce folic acid. In addition, if the sulfonamide is incorporated in a "folic acid" rather than PABA, the "folic acid" cannot function as a coenzyme.



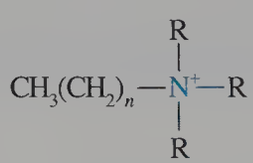
folic acid

The sulfa drugs do not interfere with the metabolism of humans because we do not synthesize our own folic acid. Instead, we obtain folic acid from foodstuffs such as spinach and other leafy green vegetables. This dietary source of folic acid cannot be used by host bacteria because it apparently cannot be transported across the bacterial cell membrane.

One of the side effects of the early use of sulfanilamide as a drug was kidney damage resulting from crystallization of the drug in the kidneys. Both sulfanilamide and the *N*-acetyl derivative of the 4-amino group, which is a metabolite, have $pK_a \approx 10$. Thus, in urine at pH 5–7 the sulfanilamides are present in a nonionized form and are not very soluble. This problem would be alleviated if substituted sulfanilamides became available that are sufficiently acidic to

Invert Soaps

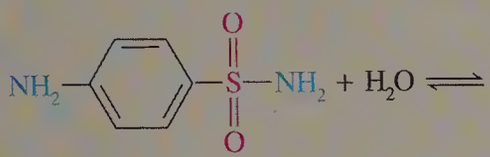
Some quaternary ammonium salts containing a long carbon chain are **invert soaps**. Invert soaps differ from soaps and detergents in that the polar end of the ion is positive rather than negative. As with soaps, the long hydrocarbon tail associates with nonpolar substances and the polar head dissolves in water. Thus invert soaps act by the same cleansing mechanism described in Section 21.5 for soaps and detergents.

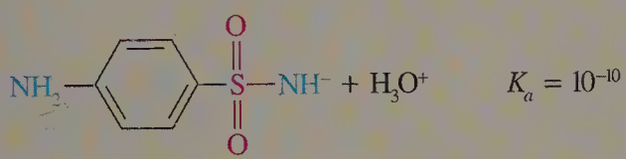


(an invert soap)

Invert soaps are widely used in hospitals, but for their bactericidal properties rather than their cleansing properties. They are active against bacteria, fungi, and protozoans,

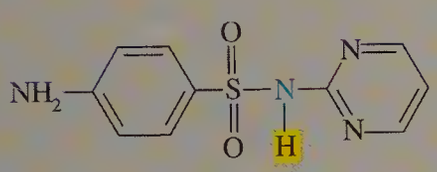
exist to some extent as their conjugate base near pH 6. A compound whose pK_a is equal to the pH of the solution exists as a 50:50 mixture of the acid and conjugate base. For pK_a < pH the conjugate base predominates.



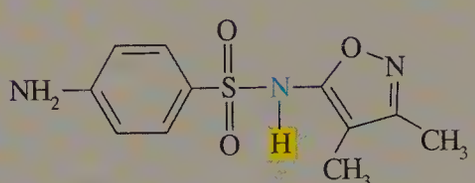


$K_a = 10^{-10}$

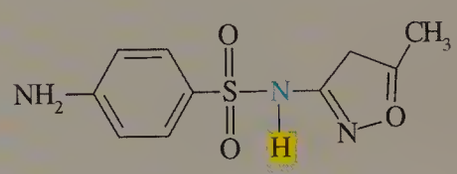
The design of sulfanilamide structures with lower pK_a values is based on relatively simple concepts. Inductively electron-withdrawing groups bonded to a potentially acidic site increase the acid strength. A group that can stabilize the conjugate base by resonance also increases the acid strength. Replacing the 4-amino group by electron-withdrawing groups increases the acidity, but the resulting compounds are not effective drugs because it is the amino group that causes the bactericidal action. Various electron-withdrawing heterocyclic rings bonded to the nitrogen atom of the sulfonamide change the acidity, forming effective bactericides.



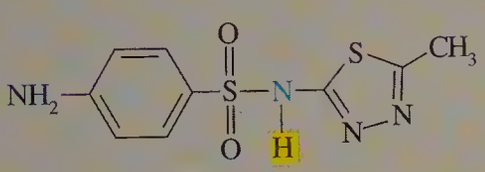
sulfadiazine
$pK_a = 6.5$



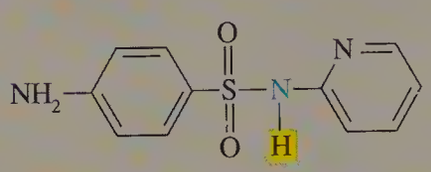
sulfisoxazole
$pK_a = 5.0$



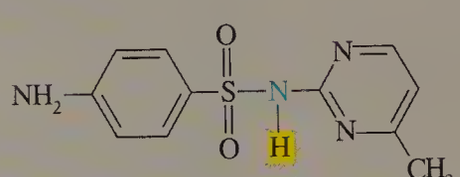
sulfamethoxazole
$pK_a = 6.1$



sulfamethizole
$pK_a = 5.4$

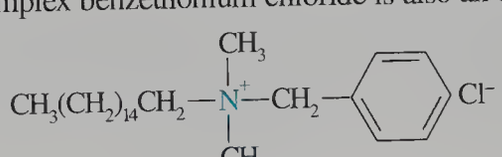


sulfapyridine
$pK_a = 8.4$

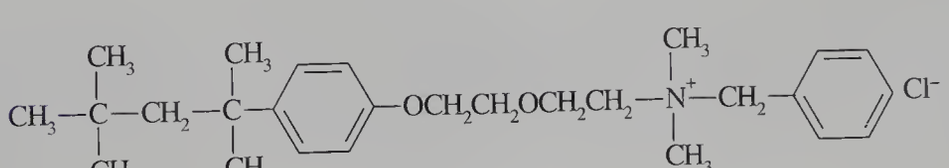


sulfamethazine
$pK_a = 7.4$

but they are not effective against spore-forming microorganisms. One type of invert soap is the family of benzalkonium chlorides. The alkyl groups of these compounds contain from 8 to 16 carbon atoms. These compounds are effective at concentrations of 1:750 to 1:20,000. The more complex benzethonium chloride is also an effective antiseptic.



benzalkonium chloride



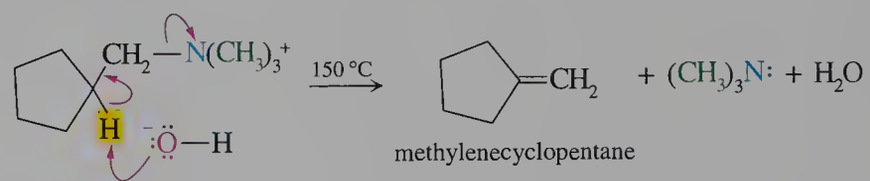
benzethonium chloride

Hofmann Elimination

Quaternary ammonium iodides prepared by the exhaustive methylation of primary amines are converted to quaternary ammonium hydroxides by treatment with silver oxide.

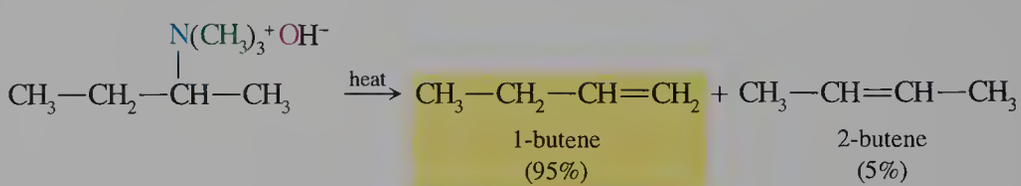
(cyclopentylmethyl)trimethylammonium hydroxide

Quaternary ammonium salts undergo β elimination to form an alkene and trimethylamine when heated.

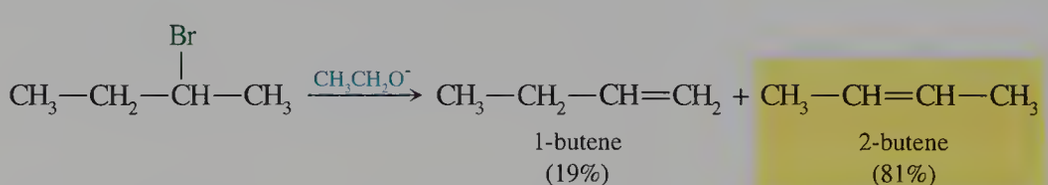


methylenecyclopentane

In the above example, only one elimination product can form. The elimination reaction of quaternary ammonium salts, known as the **Hofmann elimination**, is regioselective. This E2 elimination occurs to give the less substituted alkene by removal of the less sterically hindered β hydrogen atom by base. Hence, methyl groups lose a proton in the elimination reaction in preference to loss of a proton from a methylene group. The less substituted alkene, which forms preferentially, is termed the **Hofmann product**.



We recall that the β elimination of bromoalkanes with ethoxide base gives the more substituted alkene, called the Zaitsev product. The Zaitsev product results from the greater stability of the developing double bond in the alkene generated in the transition state.



The Hofmann reaction is controlled by different factors. First, the regioselectivity results in part from the acidity of the C—H bond β to the positively charged $(CH_3)_3N^+$ group. The acidity of the C—H bond decreases in the order

1° > 2° > 3°, reflecting carbanion stability. Second, the regioselectivity also results from steric effects in the transition state for the E2 elimination. A $(CH_3)_3N^+$ group has approximately the same van der Waals radius as a *tert*-butyl group. A trans periplanar arrangement of the proton to be eliminated and the $(CH_3)_3N^+$ group is required for an E2 elimination reaction of the quaternary ammonium salt to take place. In the transition state required to form 1-butene no steric repulsions occur because the $(CH_3)_3N^+$ group is gauche to two hydrogen atoms (Figure 25.2). In the transition states leading to the two isomeric 2-butenes, the $(CH_3)_3N^+$ group is gauche to a methyl group. As a consequence, the transition state energy required for an E2 elimination to give 2-butene is higher, and these products form more slowly. The cis isomer forms in a smaller amount than the trans isomer because the two methyl groups are gauche in the conformation required for the E2 elimination.

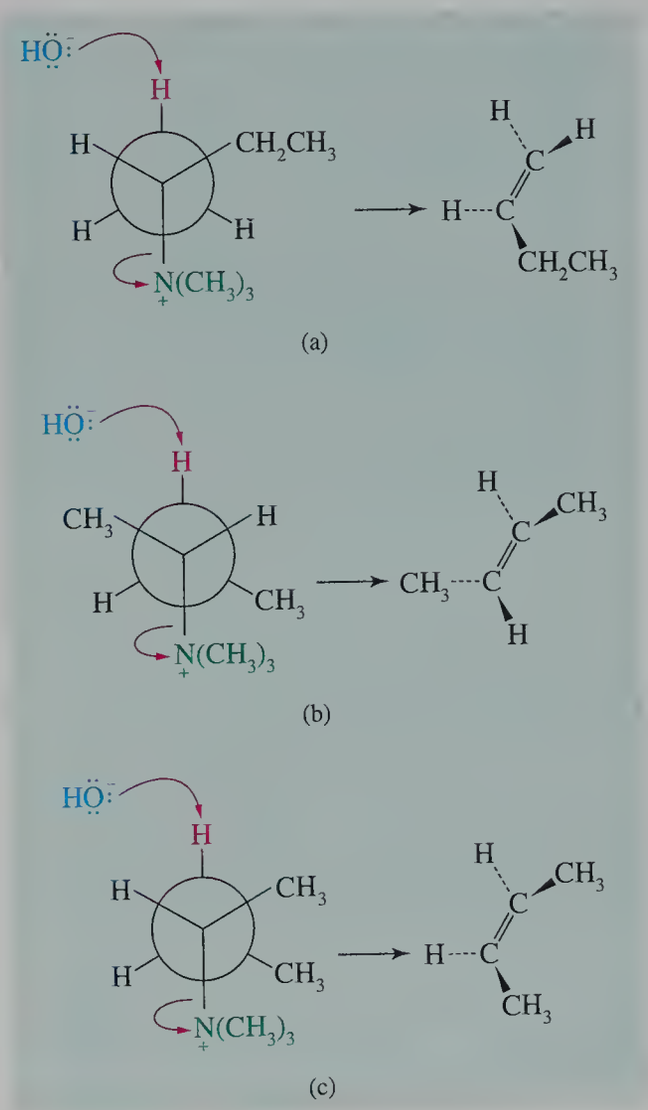


FIGURE 25.2 Hofmann Elimination Reaction
(a) The abstraction of a hydrogen atom at the C-1 atom occurs via a conformation that has no steric crowding of the trimethylammonium group. (b) The abstraction of a hydrogen atom at the C-2 atom occurs via a conformation that has the C-4 methyl group and the trimethylammonium ion gauche and gives *trans*-2-butene. (c) This conformation also has the C-4 methyl group and the trimethylammonium ion gauche. However, the C-4 and C-1 methyl groups are also gauche. The *cis*-2-butene product is formed in smaller amount than the isomeric trans compound derived from (b).

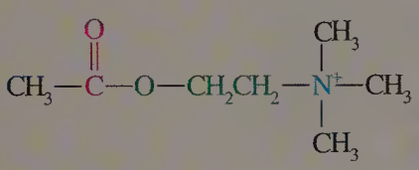
Prior to the development of spectroscopic methods for structure determination, the Hofmann elimination reaction was used to determine the structure of nitrogen-containing compounds. The method depended on the proper assignment of the structure of the alkene and an understanding of the regiochemistry of the elimina-

Muscle Relaxants

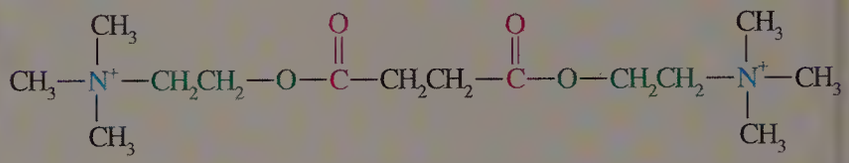
Choline is a quaternary ammonium ion and a component of lipids found in cell membranes (Section 24.5). Acetylcholine, an acetyl ester of its primary hydroxyl group, is a neurotransmitter. When a nerve impulse is transmitted, the nerve cell secretes acetylcholine, which diffuses across the synapse between nerve and muscle cells and bonds to a receptor protein in the muscle cell membrane, triggering contraction. The acetylcholine must be removed to return the muscle to the relaxed state. The enzyme acetylcholinesterase catalyzes the hydrolysis of the ester in acetylcholine, and the muscle returns to its original state. Acetylcholinesterase is not a highly specific enzyme, and it slowly catalyzes the hydrolysis of other esters similar to acetylcholine.

Any substance that interferes with the synthesis of acetylcholine, blocks receptor sites for this quaternary ammonium compound, or interferes with hydrolysis could cause paralysis and death. However, selective use of specifically designed substances that intercede in these processes has beneficial medical applications.

Muscle relaxants are compounds similar to acetylcholine that can bind at the receptor sites in muscles. One such compound, succinylcholine, binds to the receptor site and causes muscle relaxation. However, since acetylcholinesterase does not efficiently catalyze the hydrolysis of succinylcholine, the muscle remains in a relaxed state for a longer period of time than normal. During that time period, medical procedures such as resetting a dislocated shoulder may be performed.

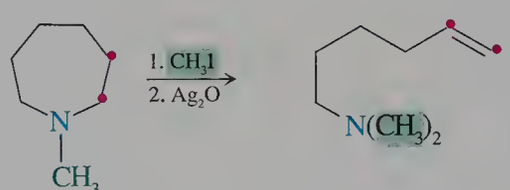


acetylcholine

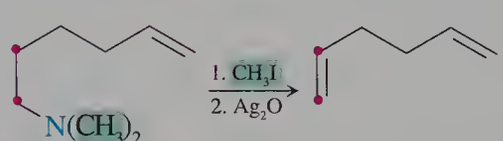


succinylcholine

tion reaction. The method was particularly useful for the structure determination of heterocyclic compounds. Consider the following example.



N,*N*-dimethyl-5-hexenamine



1,5-hexadiene

The location of the nitrogen atom can be deduced from the location of the double bonds in the final product. The nitrogen atom could have bridged the 1 and 6 atoms, the 1 and 5 atoms or the 2 and 5 atoms. As in the case of most determinations of structure by chemical methods, information from additional reactions is needed to further distinguish between these possibilities.

Problem 25.23

Two isomeric alkenes form in a 10:1 ratio when the quaternary ammonium hydroxide

derived from 1-methylcyclohexylamine and methyl iodide is heated. Draw the structures of the isomers and indicate which one forms in the larger amount.

Problem 25.24

Explain why benzylic and allylic C—H bonds are more easily eliminated in the Hofmann reaction than other alkyl C—H bonds.

Problem 25.25

Explain why iodoethane cannot be used in place of iodomethane in the exhaustive alkylation of amines for the Hofmann elimination reaction.

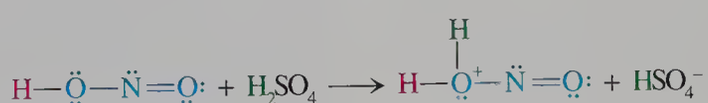
25.15 Reaction of Amines with Nitrous Acid

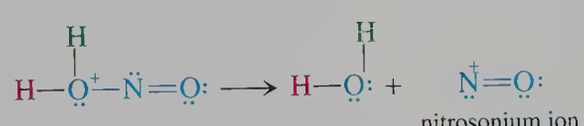
As we indicated in the comparison of the chemistry of alcohols and amines (Section 25.11), one of the major differences between these two classes of compounds is in their oxidation reactions. Alcohols are oxidized by an α elimination in which the C—H bond breaks. Oxidation of amines occurs by "loss" of electrons of the nitrogen atom. One such oxidation occurs in the reaction of amines with nitrous acid.

Nitrous acid (HNO_2) is an unstable compound produced by the reaction of a nitrite salt and a strong acid such as sulfuric acid.

$$H_3O^+ + NO_2^- \longrightarrow H_2O + HNO_2$$

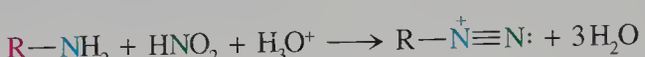
Under the reaction conditions, nitrous acid is a source of the nitrosonium ion.

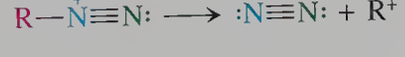




This species is an electrophile that reacts with the nonbonded electron pair of amines. The products of reaction with primary, secondary, and tertiary amines differ, enabling us to classify an unknown amine.

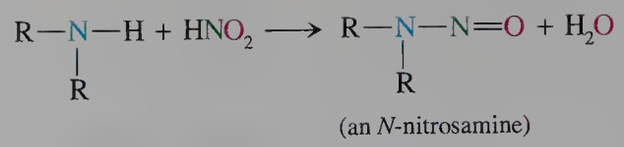
Primary amines react with HNO_2 to produce unstable diazonium salts that decompose to produce nitrogen gas and a mixture of organic products. The evolution of nitrogen gas is a visual confirmation that the amine is primary.





The mechanism of the reaction of the nitrosonium ion with a primary amine is given in Figure 25.3. The organic products of the diazotization reaction derive from the carbocation intermediate. They include substitution and elimination products.

Secondary amines react with the nitrosonium ion from HNO_2 according to the first two steps listed in Figure 25.3. Tautomerization cannot occur because the intermediate contains no N—H bond. The *N*-nitrosoamine formed separates from the reaction mixture as a yellow oil that floats on the acid solution.

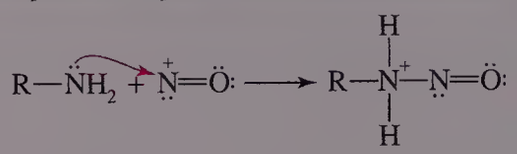


(an *N*-nitrosamine)

The first step shown in Figure 25.3 occurs with tertiary amines. The second step cannot occur because the tertiary amine contains no acidic N—H bond. Thus, the nitrosoammonium ion exists in equilibrium with the amine. Because both species are soluble, there is no visible reaction, and the amine appears to simply dissolve in the acid solution.

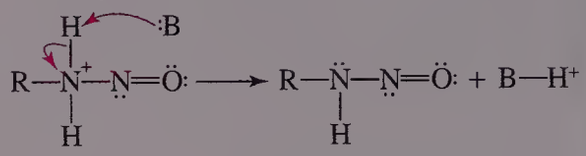
FIGURE 25.3
Mechanism of Diazotization Reaction

Step 1: Nucleophilic reaction with nitrosonium ion



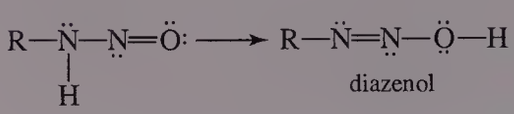
N-nitrosoammonium ion

Step 2: Proton transfer to a base



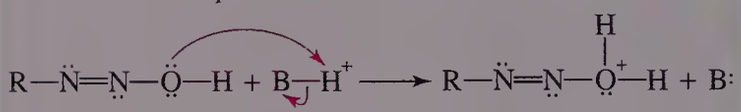
N-nitrosoamine intermediate

Step 3: Tautomerization reaction

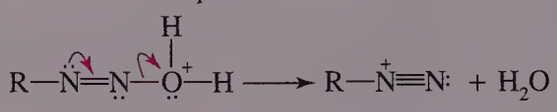


diazenol

Step 4: Proton transfer from an acid

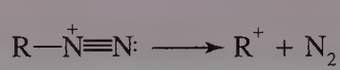


Step 5: Loss of water



diazonium ion

Step 6: Loss of nitrogen gas



In summary, primary amines react with HNO_2 to liberate nitrogen gas; secondary amines form insoluble *N*-nitroso compounds; tertiary amines give no visible reaction. As a result, the three classes of amines are easily distinguished from one other.

25.16 Spectroscopy of Amines

Infrared Spectroscopy

The C—N stretching absorption occurs in the 1050–1250 cm^{-1} region, an area of the infrared spectrum that contains numerous other absorptions. As in the case of the C—O stretching absorptions of alcohols, the identification of an amine is not

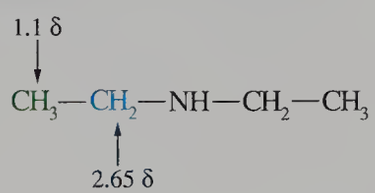
usually based on identification of the C—N stretching absorption. The N—H absorptions that occur in the 3200–3375 cm^{-1} region are diagnostic for amines. Primary amines give two peaks in this region; secondary amines have a single absorption. Tertiary amines have no absorption in the 3200–3375 cm^{-1} because they lack an N—H bond. Because amines form hydrogen bonds, the absorption for N—H stretching is broadened by the presence of a variety of species. However, because amines are not as strongly hydrogen bonded as alcohols, this broadening is less than that of alcohols.

NMR Spectroscopy

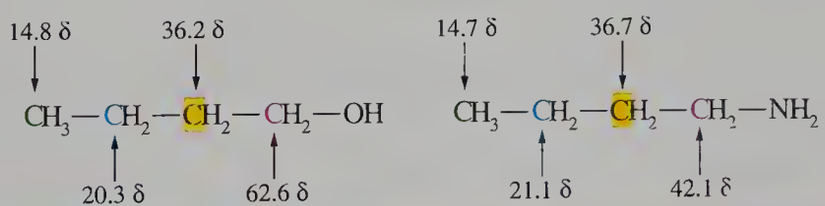
Like the O—H hydrogen atom of an alcohol, the chemical shift of the N—H hydrogen atom of amines is concentration dependent. Because hydrogen bonding is less extensive in amines than in alcohols and because the nitrogen atom is less electronegative than the oxygen atom, the hydrogen resonance of the N—H hydrogen is at higher field than that of the O—H hydrogen atom. Simple alkylamines have the N—H resonance about 1 δ. This chemical shift is at lower field for arylamines as a result of deshielding by the aromatic π electrons (Section 15.13).

The N—H hydrogen atoms of amines undergo sufficiently rapid exchange that their resonance is unsplit by neighboring C—H hydrogen atoms. When D_2O is added, exchange occurs and the resonance attributed to the N—H hydrogen is eliminated.

The C—H resonance of the groups directly attached to the nitrogen atom are shifted to lower field as a result of the inductive effect of the nitrogen atom. The resonances of hydrogen atoms on carbon atoms further removed from the nitrogen atom are essentially that of structurally similar alkanes, as shown for diethylamine.



The carbon NMR of amines is characterized by the deshielding of the carbon atom bonded directly to the nitrogen atom; other carbon atoms are less affected. The carbon absorptions of the N—C unit are in the 30–50 δ range. Thus the deshielding of carbon by nitrogen is less than the deshielding of carbon by the more electronegative oxygen atom, as illustrated by the following examples.



Problem 25.26

Write the structures of all compounds with molecular formula $C_5H_{13}N$ that have no absorption in the 3200–3400 cm^{-1} region.

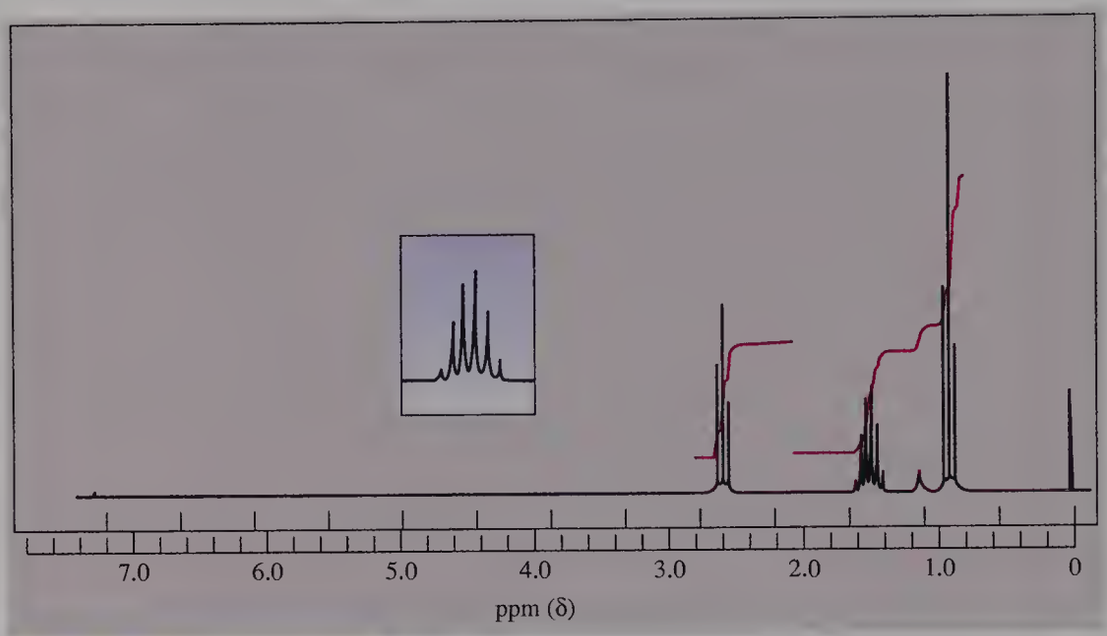
Problem 25.27

Deduce the structure of a compound with molecular formula $C_8H_{19}N$ that has the following absorptions in its hydrogen NMR spectrum, all of which are singlets. The resonance at 1.28 δ is eliminated by exchange with D_2O. The number of hydrogen atoms in indicated within parentheses.

1.00 δ (9), 1.17 δ (6), 1.28 δ (2), 2.42 δ (2)

Problem 25.28

Deduce the structure of a compound with molecular formula $C_6H_{15}N$ that has the following hydrogen NMR spectrum.



Problem 25.29

Deduce the structure of a compound with molecular formula $C_5H_{11}N$ that has ^{13}C absorptions at 25.5, 26.6, and 47.5 δ, all of which are triplets.

EXERCISES

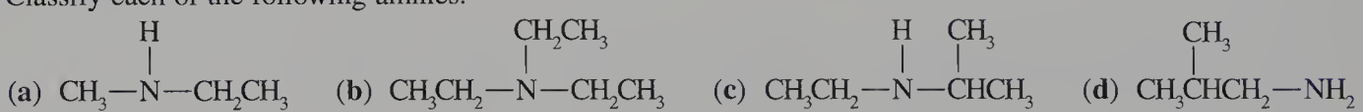
Bonding and Structure

25.1 Which compound has the greater N—H bond length, pyrrole or pyrrolidine?

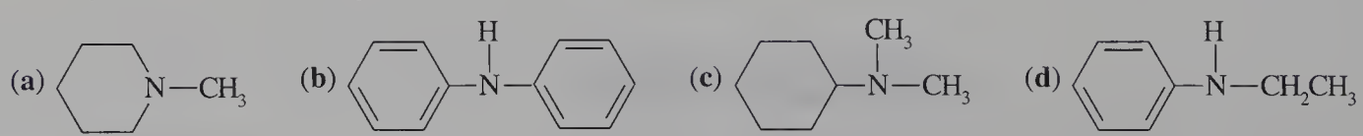
25.2 Which compound has the larger activation energy for the nitrogen inversion, *tert*-butyldimethylamine or trimethylamine?

Classification of Amines

25.3 Classify each of the following amines.

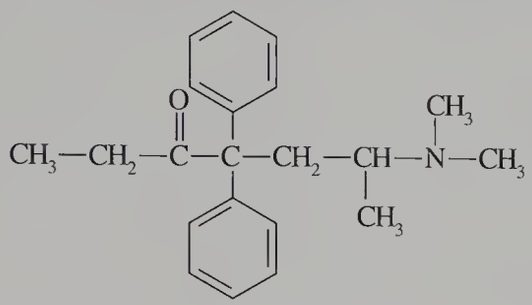


25.4 Classify each of the following amines.

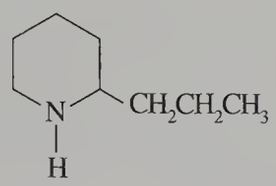


25.5 Classify the nitrogen-containing functional group in each of the following structures.

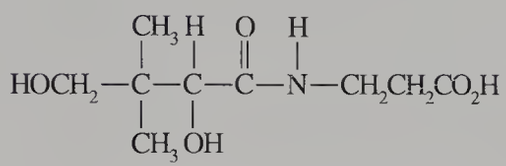
(**a**) methadone, a heroin substitute used in treating addicts



(**b**) coniine, the hemlock poison used to execute Socrates

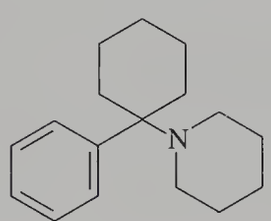


(**c**) pantothenic acid, vitamin B_5

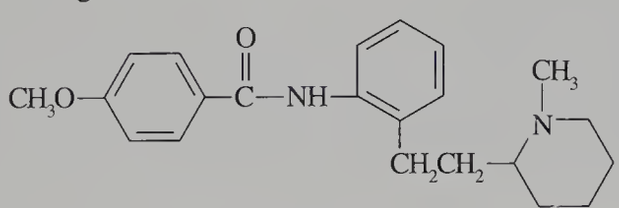


25.6 Classify the nitrogen-containing functional groups in each of the following structures.

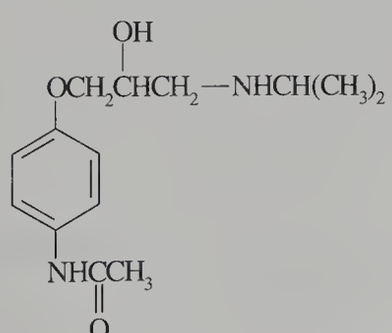
(**a**) phencyclidine, a hallucinogen



(**b**) encainide, an antiarrhythmic drug

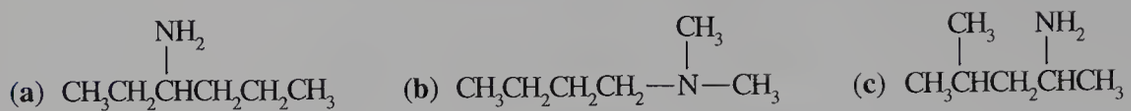


(**c**) practolol, an antihypertensive drug

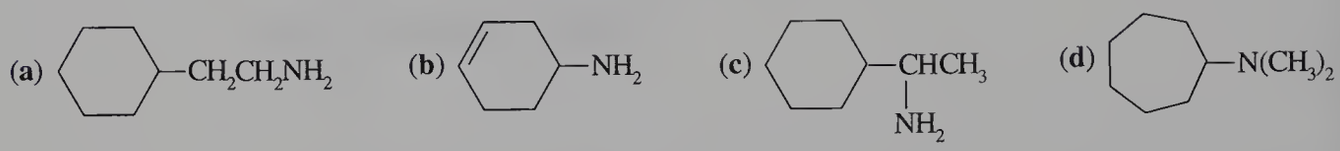


Nomenclature

25.7 Give the IUPAC name for each of the following compounds.



25.8 Give the IUPAC name for each of the following compounds.

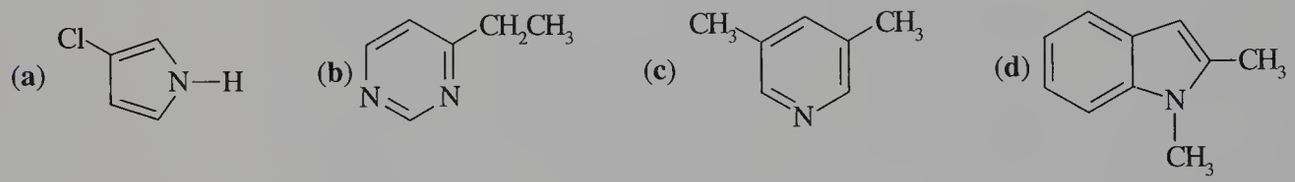


25.9 An antidepressant drug is named *trans*-2-phenylcyclopropylamine. Draw its structure.

25.10 Tranexamic acid is a drug that aids blood clotting. Its IUPAC name is *trans*-4-(aminomethyl)cyclohexanecarboxylic acid. Draw its structure.

25.11 Draw the structure of each of the following compounds.
(a) 2-ethylpyrrole **(b)** 3-bromopyridine **(c)** 2,5-dimethylpyrimidine **(d)** 2,6,8-trimethylpurine

25.12 Name each of the following compounds.



Molecular Formulas of Amines

25.13 What is the general molecular formula for a saturated amine? What is the general molecular formula for a saturated cyclic amine?

25.14 How many isomers are possible for each of the following molecular formulas?
(a) C_2H_7N **(b)** C_3H_9N **(c)** C_3H_7N

25.15 Draw the isomers of the primary amines with molecular formula $C_4H_{11}N$.

25.16 Draw the isomers of the tertiary amines with molecular formula $C_5H_{13}N$.

Properties of Amines

25.17 The boiling points of the isomeric compounds propylamine and trimethylamine are 49 and 3.5 °C, respectively. Explain this large difference.

25.18 The boiling point of 1,2-diaminoethane is 116 °C. Explain why this compound boils at a much higher temperature than propylamine (49 °C).

25.19 The difference between the boiling points of pentane (36 °C) and 1-butanamine (78 °C) is 42 °C. Explain why the difference between the boiling points of nonane (151 °C) and dibutylamine (159 °C) is smaller.

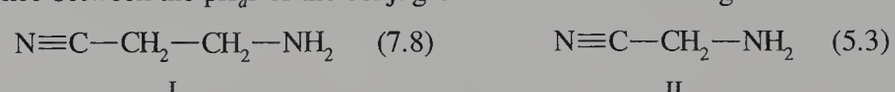
25.20 Explain why the boiling points of tertiary amines are close to the boiling points of the structurally related alkanes.

Basicity of Amines

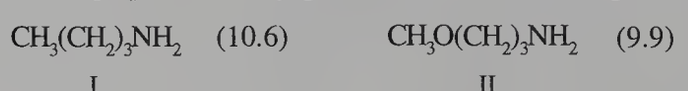
25.21 The pK_b values for cyclohexylamine and triethylamine are 3.34 and 2.99, respectively. Which compound is the stronger base?

25.22 The K_b values for dimethylamine and diethylamine are 4.7×10^{-4} and 3.1×10^{-4}, respectively. Which compound is the stronger base?

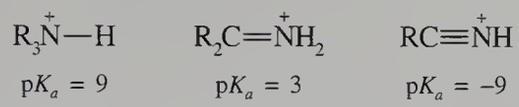
25.23 Explain the difference between the pK_as of the conjugate acids of the following bases.



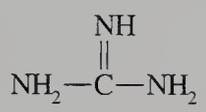
25.24 Explain the difference between the pK_as of the conjugate acids of the following bases.



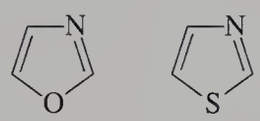
25.25 Explain the order of acidity of the following generalized structures. Why is the difference between the pK_a values of the conjugate acids of an imine and a nitrile twice the difference between those of the conjugate acids of an amine and an imine?



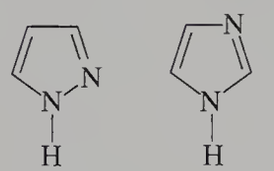
25.26 Explain why the basicity of guanidine is comparable to that of an alkoxide ion. Where does protonation occur?



25.27 Explain why oxazole is a weaker base than thiazole.



25.28 Explain why pyrazole is a weaker base than imidazole.



Synthesis of Amines

25.29 Write the steps required for the synthesis of each of the following compounds starting from 1-pentanol.
(**a**) 1-butanamine (**b**) 1-pentanamine (**c**) 1-hexanamine

25.30 Write the steps required for the synthesis of each of the following compounds starting from 3-methyl-1-butanol.
(**a**) 2-methyl-1-propanamine (**b**) 3-methyl-1-butanamine (**c**) 4-methyl-1-pentanamine

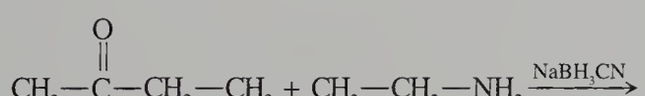
25.31 Suggest a synthesis of *cis*-4-methylcyclohexylamine starting from each of the following compounds.
(**a**) *trans*-4-methylcyclohexanol (**b**) *cis*-4-methylcyclohexanecarboxylic acid
(**c**) *trans*-4-bromomethylcyclohexane (**d**) *cis*-4-methylcyclohexanol

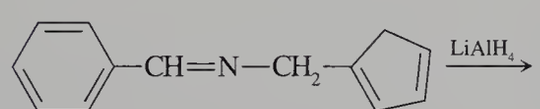
25.32 Outline the steps required to convert each reactant into the indicated product.
(**a**) benzoic acid into *N*-ethylbenzylamine
(**b**) benzyl chloride into 2-phenylethanamine
(**c**) 1,4-dibromobutane into 1,6-diaminohexane

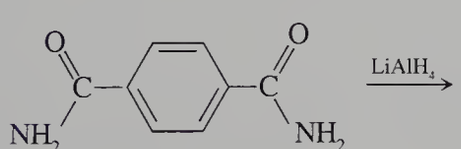
25.33 Reaction of (*R*)-2-butyl tosylate with azide ion gives an alkyl azide. Subsequent reduction by lithium aluminum hydride gives an amine. Write the structure of the product.

25.34 Cyclohexene oxide reacts with azide ion to give an azido alcohol. Subsequent reduction by lithium aluminum hydride gives an amino alcohol. Write the structure of the product showing its stereochemistry.

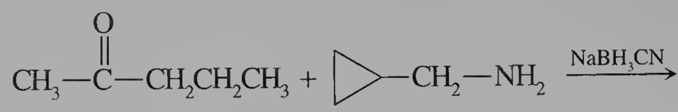
25.35 Write the structure of the product of each of the following

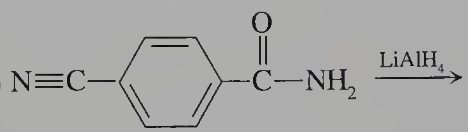
(**a**) 

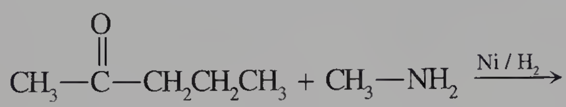
(**b**) 

(**c**) 

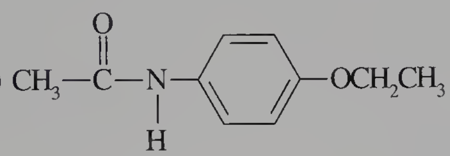
25.36 Write the structure of the product of each of the following reactions.

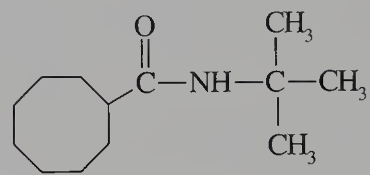
(a) 

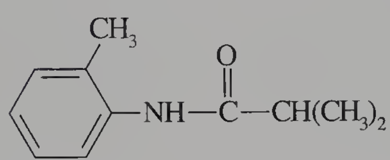
(b) 

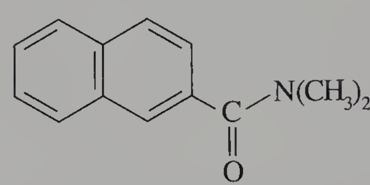
(c) 

25.37 Write the product of reduction of each of the following compounds by lithium aluminum hydride.

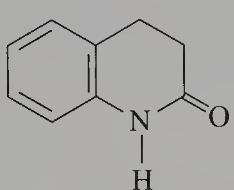
(a) 

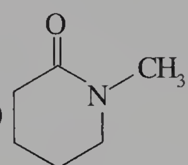
(b) 

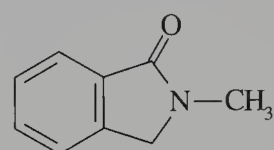
(c) 

(d) 

25.38 Write the product of reduction of the following lactams by lithium aluminum hydride.

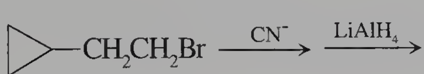
(a) 

(b) 

(c) 

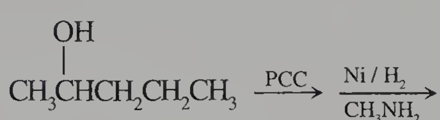
25.39 Write the structure of the final product of each of the following sequences of reactions.

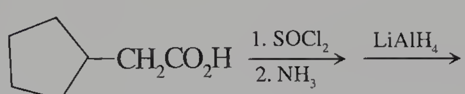
(a) $CH_3(CH_2)_4CO_2H \xrightarrow[2.\ NH_3]{1.\ SOCl_2} \xrightarrow{LiAlH_4}$

(b) 

(c) $CH_3(CH_2)_3CO_2CH_3 \xrightarrow{LiAlH_4} \xrightarrow[2.\ NH_3(excess)]{1.\ PBr_3}$

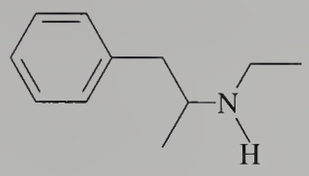
25.40 Write the structure of the final product of each of the following sequences of reactions.

(a) 

(b) 

(c) $HOCH_2(CH_2)_4CH_2OH \xrightarrow[(excess)]{HBr} \xrightarrow[(excess)]{CN^-} \xrightarrow[(excess)]{LiAlH_4}$

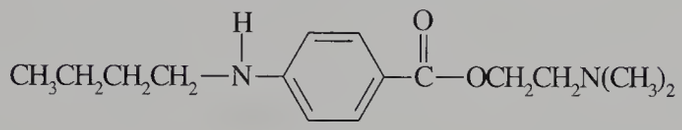
25.41 Devise a synthesis of Apetinil, an appetite suppressant, from each of the following starting materials.



Apetinil

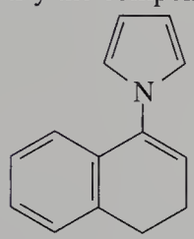
(a) 1-phenyl-2-bromopropane **(b)** 1-phenyl-2-propanone
(c) 1-phenyl-2-propanamine **(d)** 2-methyl-3-phenylpropanoic acid

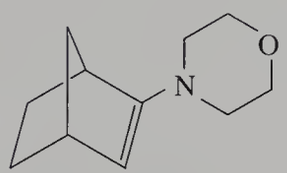
25.42 Devise a synthesis of tetracaine, a spinal anesthetic, from p-nitrobenzoic acid.

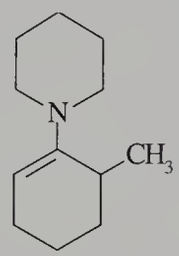


Enamines

25.43 Identify the components used to prepare each of the following enamines.

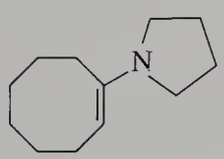
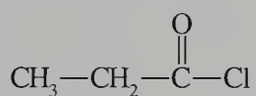
(a) 

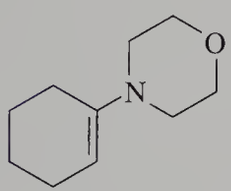
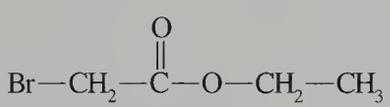
(b) 

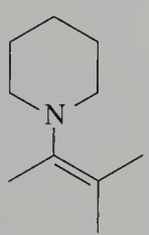
(c) 

25.44 Draw the structure of the enamine prepared from each of the following combinations of reagents.
(a) cyclooctanone and piperidine **(b)** 2-pentanone and pyrrolidine **(c)** butanal and morpholine

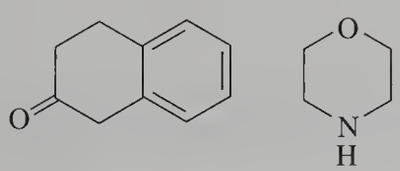
25.45 Draw the structure of the product obtained in the reaction of each of the following combination of reactants.

(a)  and 

(b)  and 

(c)  and 

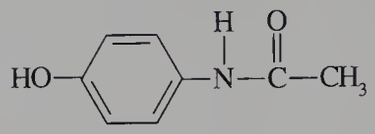
25.46 Explain why a single enamine forms from the following combination of reactants. Draw its structure. Draw the structure of the product of the reaction of this enamine and allyl bromide.



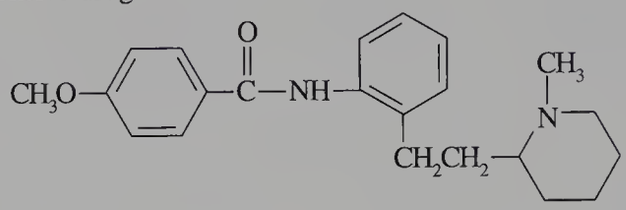
Amides

25.47 What amine and acid derivative are required to form the amides contained in each of the following compounds?

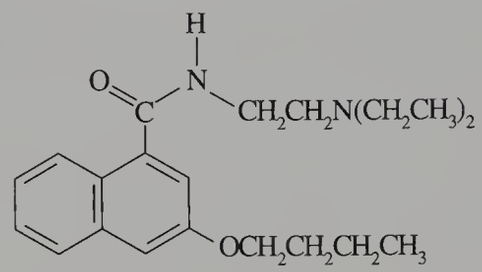
(**a**) acetaminophen, an analgesic



(**b**) practolol, an antihypertensive drug

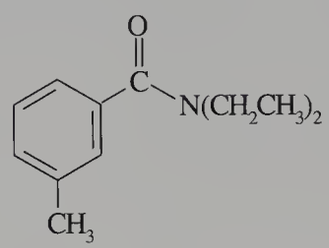


(**c**) nubucaine, a local anesthetic

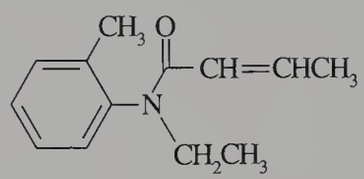


25.48 What amine and acid derivative are required to form the amides contained in each of the following compounds?

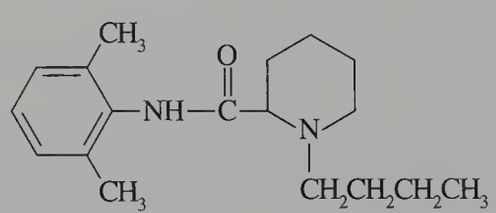
(**a**) DEET, an insect repellent



(**b**) crotamiton, used to treat scabies



(**c**) bupivacaine, a local anesthetic

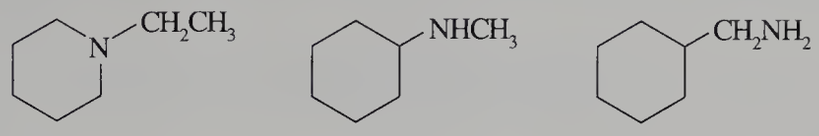


25.49 Nylon is resistant to dilute acids or bases, but polyesters are damaged by acids or bases. Explain this difference.

25.50 Draw a representation of the condensation polymer formed by adipic acid and 1,3-diaminopropane.

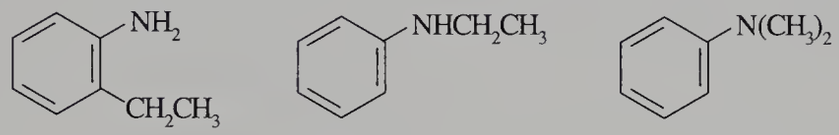
Sulfonamides

25.51 Explain how the following isomeric amines can be distinguished by the Hinsberg test.



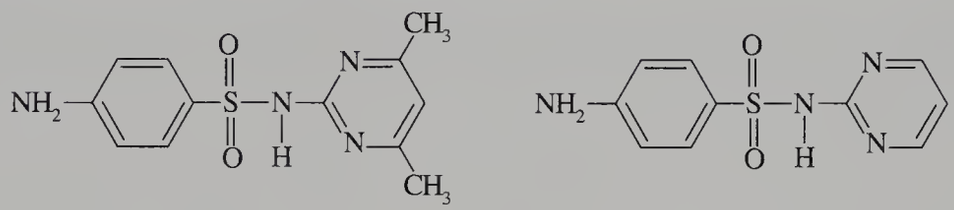
I II III

25.52 What observations would be made if the Hinsberg test were used with each of the following amines?



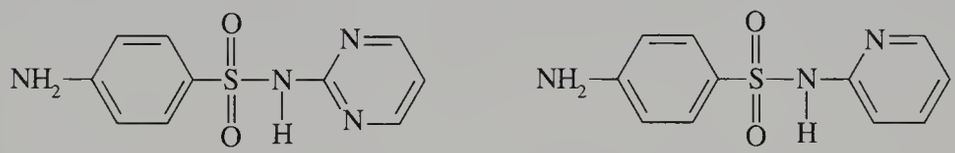
I II III

25.53 Explain why sulfamethazine is a weaker acid than sulfadiazine.



sulfamethazine sulfadiazine

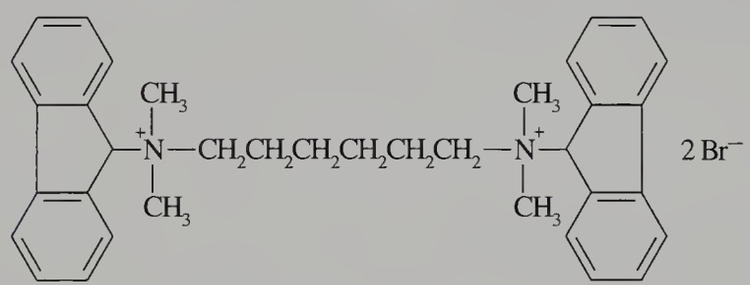
25.54 Explain why sulfadiazine is a stronger acid than sulfapyridine.



sulfadiazine sulfapyridine

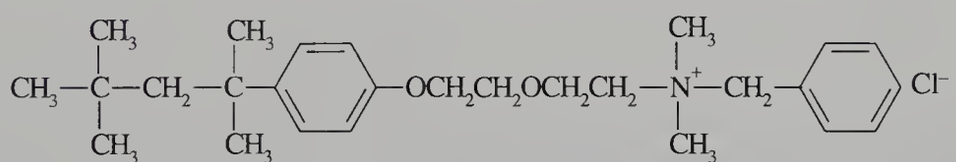
Quaternary Ammonium Salts

25.55 Propose a synthesis of hexafluorenium bromide, a neuromuscular-blocking agent, using 1,6-dibromohexane.



hexafluorenium bromide

25.56 Draw the structure of the primary amine required to synthesize benzethonium chloride.

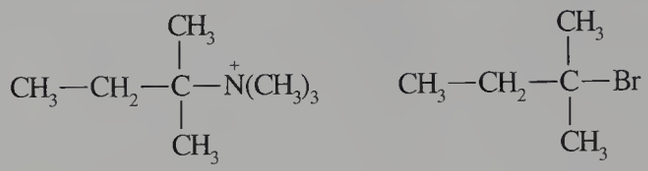


benzethonium chloride

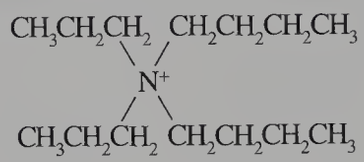
Hofmann Elimination

25.57 The following quaternary ammonium ion undergoes a Hofmann elimination to give a mixture of two products. The structurally related bromoalkane reacts with sodium ethoxide to give a mixture of the same two products. One of

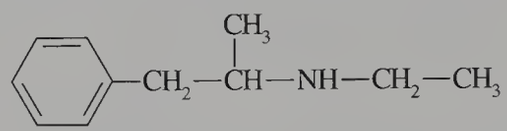
the two reactants gives a 6:4 ratio of the two alkenes. The other gives a 1:12 ratio of the same two alkenes. What are the structures of the two alkenes, and which product ratio corresponds to each reactant?



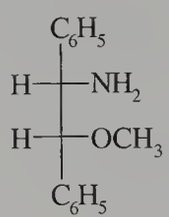
25.58 Explain why the following quaternary ammonium ion undergoes a Hofmann elimination to give propene and 1-butene in a 2:1 ratio.



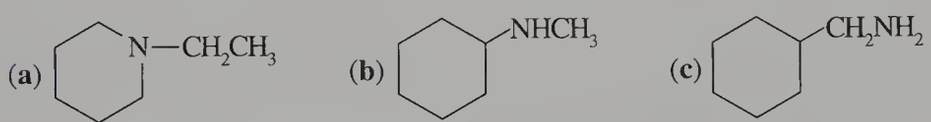
25.59 Exhaustive methylation of Apetinil, the ingredient of a "diet pill," followed by the Hofmann elimination reaction gives a mixture of alkenes. Draw their structures. Which alkene is the major product?



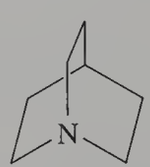
25.60 The following amine is exhaustively methylated and then reacts by the Hofmann elimination reaction. Draw the structure of the product, indicating the stereochemistry around the double bond.



25.61 What unsaturated compound is obtained by exhaustive methylation of each of the following isomeric amines followed by a Hofmann elimination?

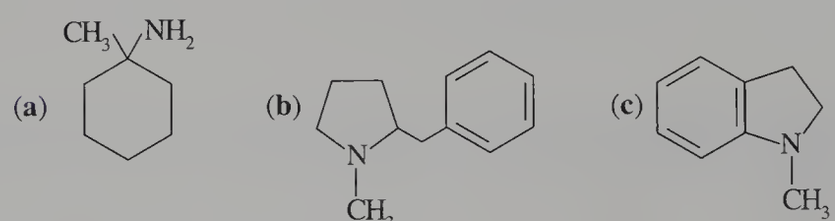


25.62 Draw the structure of the unsaturated compound obtained by a series of exhaustive methylations followed by Hofmann elimination for quinuclidine.

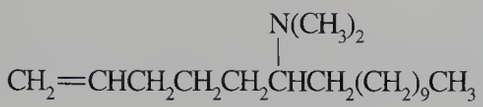


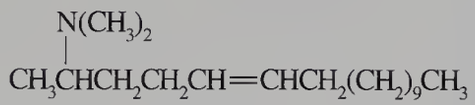
quinuclidine

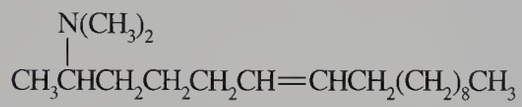
25.63 What unsaturated compound is obtained by successive exhaustive methylations of each of the following isomeric amines followed by Hofmann eliminations?



25.64 A compound found in the venom of the red fire ant has the molecular formula $C_{17}H_{35}N$. It is exhaustively methylated and then reacted to give the following mixture of Hofmann elimination products. Draw the structure of original amine.







Diazotization of Amines

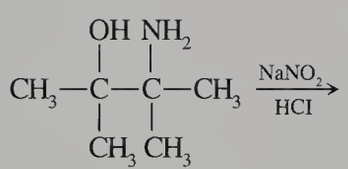
25.65 A compound, $C_4H_{11}N$, reacts with nitrous acid to yield a yellow oil. What structures are possible for $C_4H_{11}N$?

25.66 A compound, $C_4H_{11}N$, reacts with nitrous acid to yield nitrogen gas. What structures are possible for $C_4H_{11}N$?

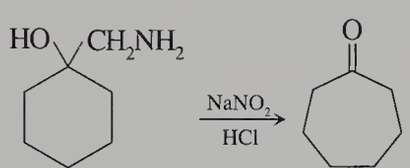
25.67 Cyclohexylamine reacts with nitrous acid in aqueous solution to give both cyclohexanol and cyclohexene. Explain the origin of these products.

25.68 (Cyclopentylmethyl)amine reacts with nitrous acid in aqueous solution to yield cyclohexanol as one of the products. Explain the origin of this product.

25.69 The following reaction yields a ketone with the molecular formula $C_6H_{12}O$. Draw the structure of the product. How does this reaction resemble that of a vicinal diol with acid?

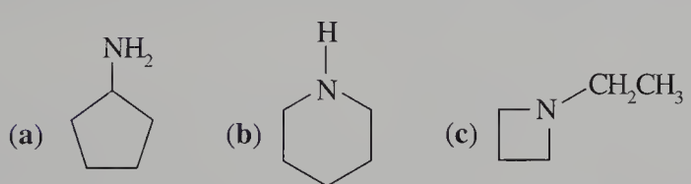


25.70 Write a mechanism for the following reaction that accounts for the formation of the product.



Spectroscopy of Amines

25.71 How can each of the following isomeric amines be distinguished using infrared spectroscopy?



25.72 Which of the isomeric compounds with molecular formula $C_4H_{11}N$ have the following characteristics in their infrared spectrum?

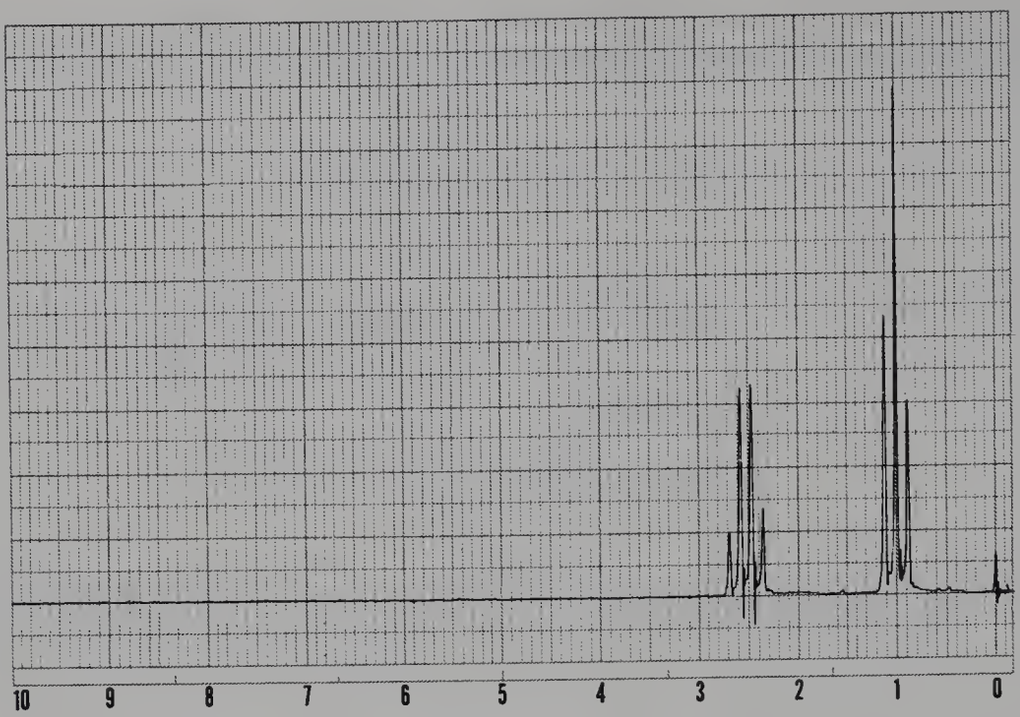
(**a**) no absorption in the 3200–3400 cm^{-1} region

(**b**) single absorption in the 3200–3400 cm^{-1} region

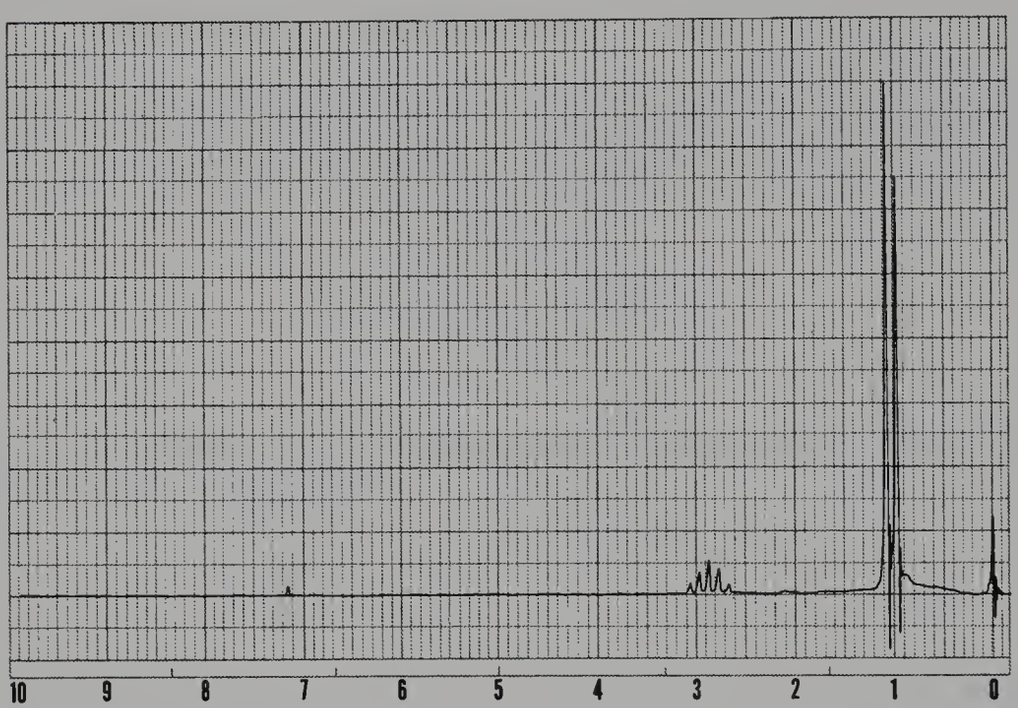
(**c**) two absorptions in the 3200–3400 cm^{-1} region

25.73 Deduce the structure of isomeric amines with molecular formula $C_6H_{15}N$ that have each of the following hydrogen NMR spectra (next page).

(a)



(b)



25.74 Deduce the structure of each of the following diamines with the indicated molecular formulas and hydrogen NMR spectra. The number of hydrogen atoms and the multiplicity of each resonance are given within parentheses.

(**a**) $C_5H_{14}N_2$; 2.25 δ (12, singlet), 2.7 δ (2, singlet)

(**b**) $C_3H_{10}N_2$; 1.1 δ (4, singlet), 1.6 δ (2, singlet), 2.75 δ (4, singlet)

(**c**) $C_4H_{12}N_2$; 1.2 δ (4, singlet), 1.1 δ (6, singlet), 2.5 δ (2, singlet)

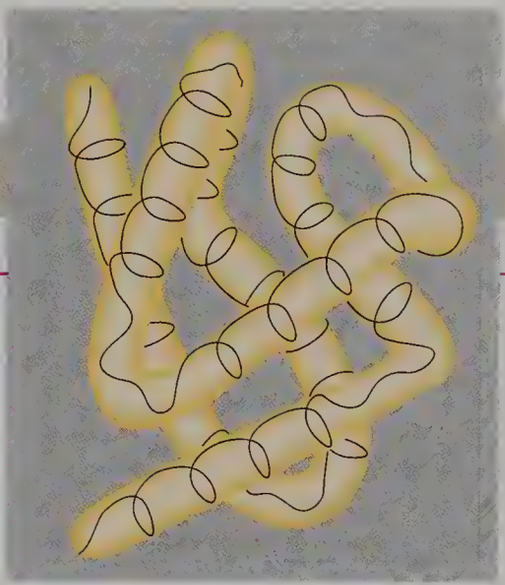
25.75 Using the data from the carbon NMR spectrum, deduce the structure of each of the following amines with the molecular formula $C_6H_{15}N$ that have no absorption in the 3200–3400 cm^{-1} region of the infrared spectrum. The multiplicities are given within parentheses.

(**a**) 12.6 ppm (quartet), 46.9 ppm (triplet) (**b**) 25.6 ppm (quartet), 38.7 ppm (quartet), 53.2 ppm (singlet)

25.76 Using the data from the carbon NMR spectrum, deduce the structure of each of the following amines with the molecular formula $C_6H_{15}N$ that have a single absorption in the 3200–3400 cm^{-1} region of the infrared spectrum. The multiplicities are given within parentheses.

(**a**) 23.7 ppm (quartet), 45.3 ppm (doublet) (**b**) 12.0 ppm (quartet), 23.9 ppm (triplet), 52.3 ppm (triplet)

26



Amino Acids and Proteins

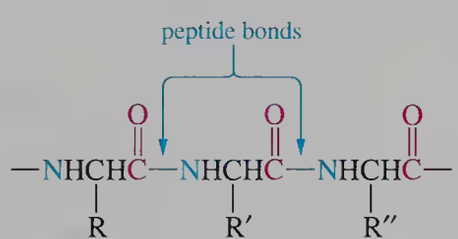
26.1 Proteins and Polypeptides Are Polymers

In Chapter 20, we learned that monosaccharides form polymers in which the units are linked by acetal bonds. The resulting polysaccharides are used for energy storage in animals and plants and for maintaining cellular structure in plants. Amino acids also form polymers, called proteins, which perform a variety of essential functions in all cells.

The name *protein* comes from the Greek *proteios*, meaning preeminent or holding first place. Proteins have an extraordinary range of functions. Proteins called enzymes catalyze nearly all of the chemical reactions of the cell. Proteins are required for the transport of most substances across cell membranes. They are the major structural components of skin, blood, muscle, hair, and other tissues. Immune system proteins, called antibodies, help combat foreign substances that enter the body.

Proteins, and related structures called polypeptides, are polymers of α-amino acids. **Proteins** contain 50 to as many as 8000 α-amino acids. **Polypeptides** are smaller molecules generally containing fewer than 50 amino acids. Some important hormonal polypeptides with physiological functions, such as pain relief and control of blood pressure, contain only a few amino acids.

Amino acids contain both amino and carboxylic acid functional groups. In proteins and polypeptides they are linked by amide bonds, also called **peptide bonds**.

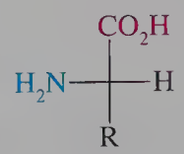


We will begin this chapter by describing the structure and properties of the 20 amino acids isolated from proteins. We will also consider methods for synthesizing amino acids in the laboratory. Then we will consider the structure and properties of

polypeptides and proteins. We will also describe the general method of synthesizing polypeptides and proteins and analytical methods to determine their structure.

26.2 Amino Acids

Amino acids contain both an amino group and a carboxylic acid group. About 250 have been found in natural sources; however, only about 20 of them occur in large amounts in proteins. The amino acids of proteins in all cells are α-amino acids. They have an amino group bonded to the α carbon atom of a carboxylic acid. The Fischer projection formula for an α-amino acid is



(an α-amino acid)

In this structure, the R group is called the side chain. There are 20 different R groups in amino acids isolated from proteins. Of these 20 α-amino acids, 19 are chiral. Glycine, which has a hydrogen rather than an R group, is not chiral.

The naturally occurring amino acids in proteins have the *S* configuration. However, they have traditionally been compared to other chiral substances using the D,L convention. The amino acids have the L configuration in contrast to carbohydrates, which have the D configuration. We recall that the specific rotation is not related to configuration, and the signs of rotation shown in Table 26.1 are both positive and negative.

Table 26.1
Specific Rotation of L-Amino Acids

Amino acid	*Specific rotation*
glycine	0
alanine	8.5
valine	13.9
leucine	−10.8
isoleucine	11.3
proline	−85.0
serine	−6.8
threonine	−28.3
methionine	−8.2
cysteine	6.5
phenylalanine	−35.1
tryptophan	−31.5
tyrosine	−10.6
asparagine	−5.4
glutamine	6.1
aspartic acid	25.0
glutamic acid	31.4
lysine	14.6
arginine	12.5
histidine	−39.7

Classification of Amino Acids

The amino acids in proteins are primary amines, except for the secondary amine proline (Table 26.2). Three-letter abbreviations of the amino acids are used as a shorthand to describe protein structure. (An alternate one-letter shorthand method exists, but will not be used in this text.)

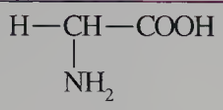
The amino acids are classified by their side chain R groups as neutral, basic, or acidic. **Neutral amino acids** contain one amino group and one carboxyl group and, as we shall see below, have no net charge at physiological pH. The neutral amino acids are further divided according to the polarity of the R group. Three of the neutral amino acids—serine, threonine, and tyrosine—are also alcohols. Phenylalanine, tyrosine, and tryptophan contain aromatic rings. Two of the neutral amino acids, cysteine and methionine, contain a sulfur atom. The remaining neutral amino acids have hydrocarbon side chains.

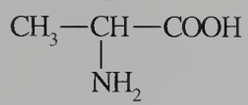
Three **basic amino acids**—lysine, arginine, and histidine—have basic side chains. That is, they ionize at pH 7 to give a conjugate acid and hydroxide ion. Two **acidic amino acids**—aspartic acid and glutamic acid—have carboxylic acid side chains. The side chains of these amino acids exist predominantly as their conjugate bases ($-CO_2^-$) at pH 7. The acidic amino acids also have close relatives that exist as neutral amides—asparagine and glutamine.

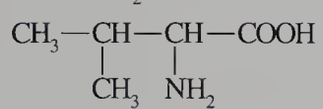
Amino acids can also be classified by the tendency of their side chains to interact favorably or unfavorably with water. Those amino acids with polar side chains are said to be **hydrophilic**, that is, water-loving. Those whose side chains are nonpolar are said to be **hydrophobic**. Hydrophobic amino acids have alkyl or aromatic groups that do not hydrogen bond to water.

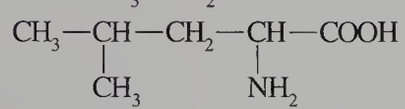
Table 26.2
Nomenclature of Amino Acids

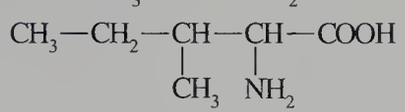
Nonpolar R groups

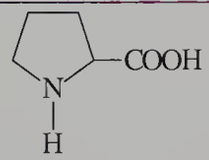
glycine (Gly) 

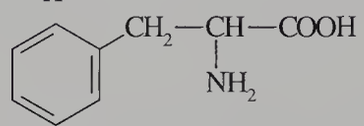
alanine (Ala) 

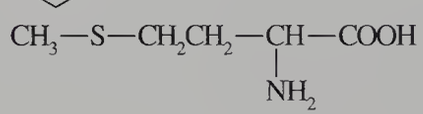
valine (Val) 

leucine (Leu) 

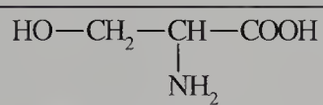
isoleucine (Ile) 

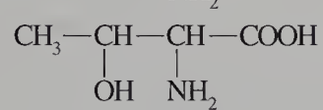
proline (Pro) 

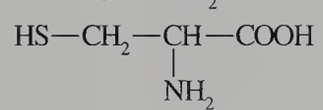
phenylalanine (Phe) 

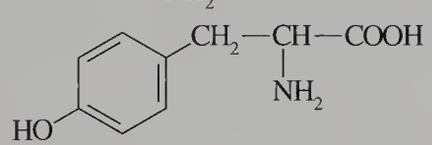
methionine (Met) 

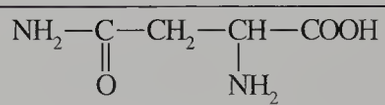
Polar but neutral R groups

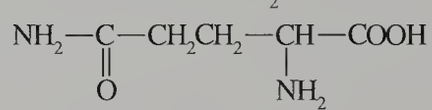
serine (Ser) 

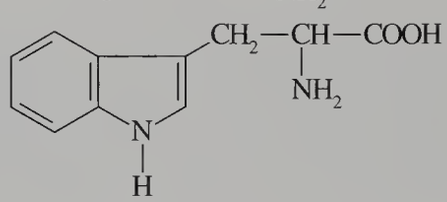
threonine (Thr) 

cysteine (Cys) 

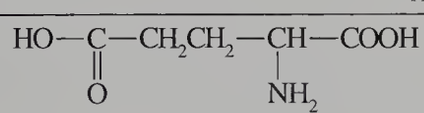
tyrosine (Tyr) 

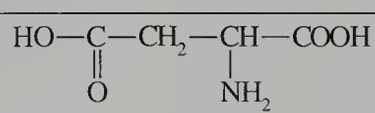
asparagine (Asn) 

glutamine (Gln) 

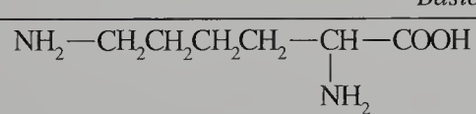
tryptophan (Trp) 

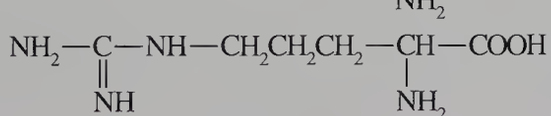
Acidic R groups

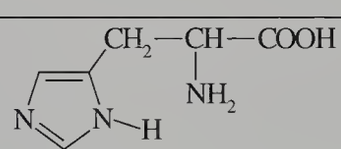
glutamic acid (Glu) 

aspartic acid (Asp) 

Basic R groups

lysine (Lys) 

arginine (Arg) 

histidine (His) 

Commercial Availability

The L enantiomers of common amino acids are commercially available—produced by hydrolysis of proteins—and their prices are relatively low (Table 26.3). Racemic mixtures are prepared commercially by methods described in Section 26.3. The cost of the racemic mixtures depends on the synthetic method used. As a consequence, the price of the racemate may be lower or higher than the price of the L enantiomer. The D enantiomers must be prepared by resolution of the racemic mixtures, and their substantially higher prices reflect the cost of such procedures.

Table 26.3
Prices of Amino Acids

	Price per 100 g ($)		
Amino acid	L *enantiomer*	D *enantiomer*	*Racemate*
glycine			(2)
alanine	28	187	6
valine	26	164	10
leucine	17	270	47
isoleucine	58	21,640	74
methionine	22	103	5
proline	31	1,520	370
phenylalanine	26	124	21
tryptophan	49	182	52
serine	35	192	16
threonine	54	148	32
cysteine	26	3,055	179
tyrosine	16	722	58
asparagine	14	31	20
glutamine	21	1,200	
aspartic acid	6	106	6
glutamic acid	5	169	24
lysine	6	627	35
arginine	13	1,096	159
histidine	25	306	102

Glutamic acid and aspartic acid are the least expensive α-amino acids. Both compounds have important commercial applications. As a result, inexpensive methods to produce them in large quantity have been developed. Glutamic acid is prepared for use as monosodium glutamate (MSG), a flavor enhancer in food. Aspartic acid and phenylalanine are components of a dipeptide used in aspartame, a synthetic sweetener.

Problem 26.1

An amino acid known as β-alanine is one of the component structural units of coenzyme A. What is the IUPAC name of this compound?

$$NH_2CH_2CH_2CO_2H$$

Sample Solution

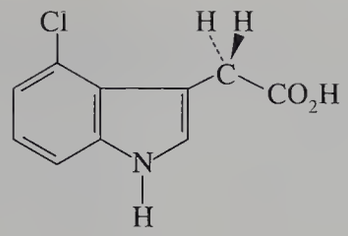
We expect the carboxyl group of the carboxylic acid to take precedence over the amino group, as it does for the hydroxyl group (Section 21.2). The parent name is propanoic acid. We recall that the carboxyl carbon atom is numbered 1 although that number is not used in the IUPAC name. Thus the amino group is located at the 3 position and the name is 3-aminopropanoic acid.

Problem 26.2

Draw the structure of 1-aminocyclopropanecarboxylic acid, an amino acid that is converted to ethylene to aid in the ripening of fruit.

Problem 26.3

The following carboxylic acid and its methyl ester are found in green peas. What amino acid does it resemble?



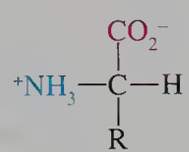
26.3 Acid–Base Properties of Amino Acids

The α-amino acids as shown in Table 26.2 have no net charge. However, the properties of amino acids resemble those of salts rather than uncharged molecules. Amino acids have low solubilities in organic solvents, but are moderately soluble in water, unlike most organic compounds. The physical states of amino acids are also different from those of comparable carboxylic acids and amines. Consider ethylamine, acetic acid, and glycine. Ethylamine is a gas and acetic acid is a liquid at room temperature. In contrast, glycine is a solid.

$CH_3CH_2NH_2$	CH_3CO_2H	$NH_2CH_2CO_2H$
mp −84 °C	mp 16 °C	mp 232 °C

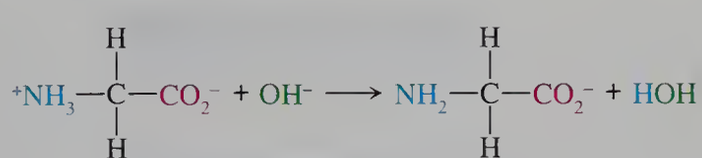
Ionic Forms of Amino Acids

When an amino acid dissolves in an aqueous buffer solution at pH 7, its carboxyl group ionizes to give a conjugate base, and the α-amino group reacts to give a conjugate acid. Thus, the molecule exists as a dipolar ion, sometimes called a **zwitterion**. The dipolar ion has the properties of both an acid and a base. That is, it is amphoteric.



structure of a dipolar ion (zwitterion)

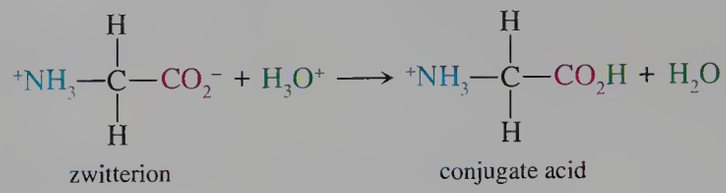
When an amino acid dissolves in basic solution, the carboxyl group exists as a carboxylate anion and the α-amino group exists in its uncharged basic form. This species is the conjugate base of the original amino acid. It has a negative charge because the carboxylate ion has a −1 charge and the amino group is uncharged.



zwitterion conjugate base

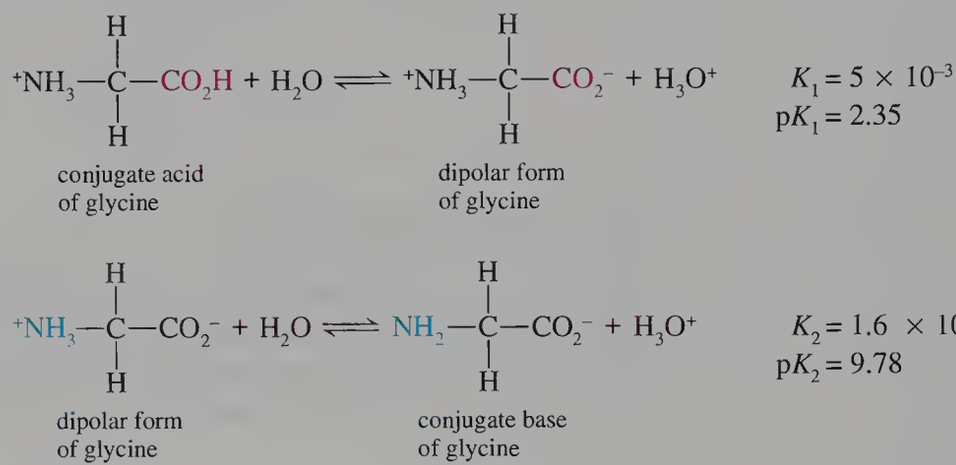
When an amino acid dissolves in acidic solution, the carboxyl group does not ionize, but the α-amino group is protonated. This species is the conjugate acid

of the original amino acid. Because the carboxyl group and the α-amino group are both protonated in acidic solution, the conjugate acid has a net charge of +1.



pK_a Values of α-Amino Acids

The pK_a values of the carboxyl and α-amino groups of amino acids depend on the structure of the amino acid. The pK_a values of the carboxyl groups of amino acids (pK_1) range from 1.81 for histidine to 2.58 for phenylalanine. The pK_a values of the α-ammonium groups (pK_2) range from 8.8 for asparagine to 10.78 for tyrosine (Table 26.4).



When an amino acid dissolves in an aqueous solution, several species usually exist. When the pH of the solution equals the pK_a of the ionizing group, the concentrations of the acid form and its conjugate base are equal. For example, the pK_as of the $-CO_2H$ and $-NH_3^+$ groups of glycine are 2.35 and 9.78, respectively. When the pH of a dilute solution is 2.3, the concentrations of the dipolar ion and the conjugate acid of glycine are equal. When the pH of the glycine solution is increased to 9.8, the concentrations of the conjugate base of glycine and the dipolar ion are equal. At pH values between 2.35 and 9.78 , the dipolar ion is the major ionic form of the amino acid in solution.

Problem 26.4

Write the structure of the dipolar ion and the conjugate base of alanine.

Problem 26.5

In what form does serine exist in 0.1 M HCl?

Table 26.4
pK_as of Amino Acids at 25 °C

Amino acid	pK_1 (—CO_2H)	pK_2 (—NH_3^+)	pK_a *(side chain)*
glycine	2.35	9.78	
alanine	2.35	9.87	
valine	2.29	9.72	
leucine	2.33	9.74	
isoleucine	2.32	9.76	
methionine	2.17	9.27	
proline	1.95	10.64	
phenylalanine	2.58	9.24	
tryptophan	2.43	9.44	
serine	2.19	9.44	
threonine	2.09	9.10	
cysteine	1.89	10.78	8.33
tyrosine	2.20	9.11	10.07
asparagine	2.02	8.80	
glutamine	2.17	9.13	
aspartic acid	1.99	10.0	3.96
glutamic acid	2.13	9.95	4.32
lysine	2.16	9.20	10.80
arginine	1.82	8.99	12.48
histidine	1.81	9.15	6.00

26.4 Isoionic Point

Table 26.5
Isoionic Points

Amino acid	pH_i
glycine	5.97
alanine	6.10
valine	5.96
leucine	5.98
isoleucine	6.02
methionine	5.74
proline	6.30
phenylalanine	5.48
tryptophan	5.89
serine	5.68
threonine	5.60
cysteine	5.07
tyrosine	5.66
asparagine	5.41
glutamine	5.65
aspartic acid	2.77
glutamic acid	3.22
lysine	9.74
arginine	10.76
histidine	7.59

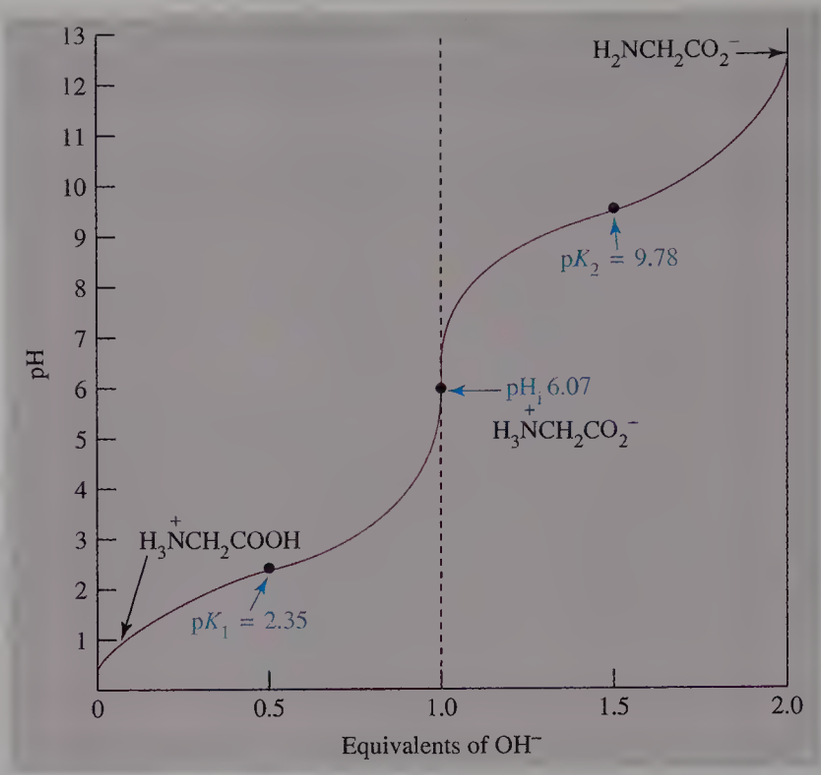
The **isoionic point**, pH_i, is the pH at which the concentration of the zwitterion reaches a maximum When the pH equals the pH_i, an amino acid has no *net* charge. When the pH is greater than the pH_i, the net charge of the predominant ionic form of the amino acid is negative. When the pH is less than the pH_i, the net charge of the predominant ionic form of the amino acid is positive. Table 26.5 shows the isoionic points of some amino acids. The isoionic point of an amino acid equals one half of the sum of the pK_a values of the carboxyl group and the α-amino group if it does not have an ionizing side chain. For example, the pK_a of the carboxyl group of alanine is 2.4 and the pK_a value of the α-ammonium ion is 9.9. The isoionic point of alanine is 6.1.

The isoionic points of acidic and basic amino acids are calculated as follows. The isoionic point of an acidic amino acid is one half of the sum of the pK_a of the α-CO_2H and the pK_a of the side chain. Similarly, the isoionic point of a basic amino acid is one half of the sum of the pK_a of the α-NH_3^+ and the pK_a of the basic group of the side chain. In general, acidic amino acids have pH_i values less than 7 and basic amino acids have pH_i values greater than 7.

Titration Curves of Amino Acids

The pK_a of the carboxyl and ammonium groups of an amino acid, as well as the pH_i, can be determined by titrating the conjugate acid with base. Figure 26.1 shows a typical titration curve for glycine. As base is added, some of the conjugate acid is converted to the zwitterion, and the pH increases. The pH at which the —CO_2H group is one-half neutralized is equal to pK_1. After one equivalent of base has been added, the zwitterion is the major form in solution, and the pH at this point is pH_i. Addition of a second equivalent of base starts to convert the —NH_3^+ group to the conjugate base of the amino acid. The pH at which half-neutralization has occurred is equal to pK_2.

FIGURE 26.1 Titration Curve of an Amino Acid



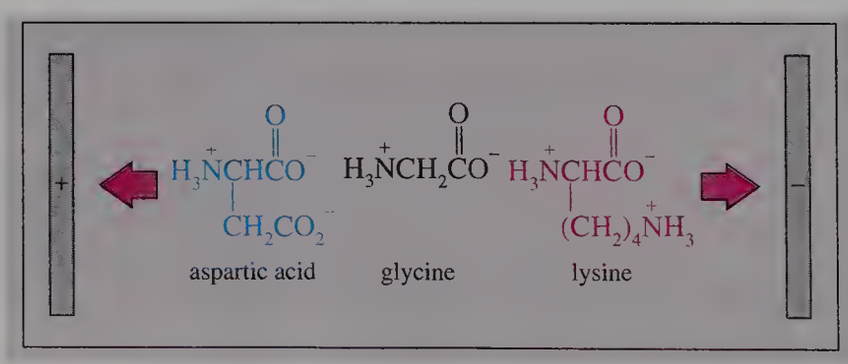
Isoionic Points of Proteins

The isoionic point of a protein depends upon its amino acid composition. At its isoionic point, a protein carries no net charge, and its solubility is at a minimum. As a consequence, a protein tends to precipitate from solution at its isoionic pH. For example, casein, a protein in milk, carries a net negative charge at pH 6.3. Casein has many glutamic acid and aspartic acid residues. If milk is made more acidic, the glutamate and aspartate side chains of casein become protonated, and casein precipitates. Casein, used in making cheese, is obtained by adding an acid to milk or by adding bacteria that produce lactic acid.

Separation of Amino Acids and Proteins

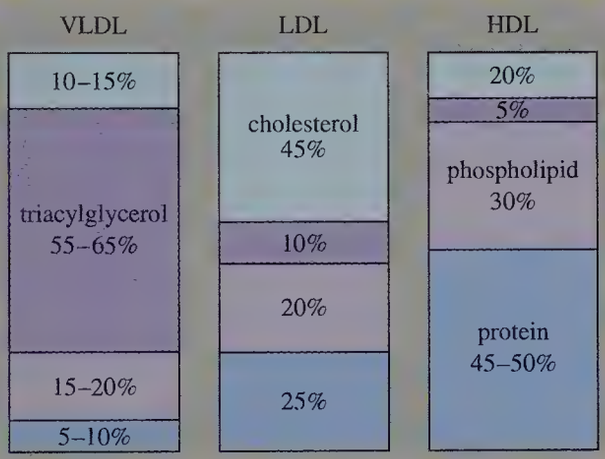
Mixtures of amino acids can be separated and identified by a technique called **electrophoresis** (Figure 26.2). In this technique, a paper strip saturated with a buffer solution at a selected pH bridges two vessels containing the buffer. A sample of the amino acid mixture is placed at the center of the paper as a "spot," and an electric potential is applied between the two vessels. If the buffer pH equals the isoionic point of an amino acid, the dipolar ion predominates, and the amino acid does not migrate. An amino acid with a negative charge at that pH migrates toward the positive electrode, whereas an amino acid with a positive charge at that pH migrates

FIGURE 26.2 Electrophoresis of Amino Acids



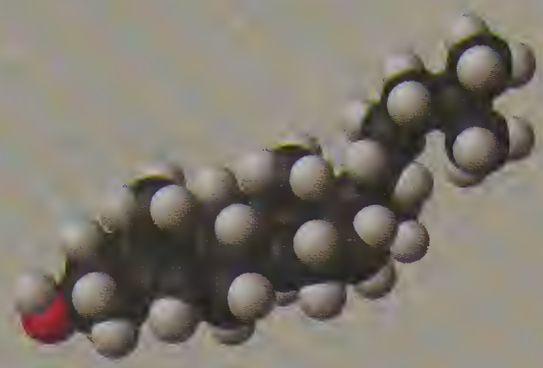
Cholesterol and Lipoproteins

Lipoproteins are complexes of several types of proteins and lipids, including triacylglycerols, cholesterol, and phospholipids. Lipoproteins transport lipids in human plasma and regulate the cholesterol level in the blood. These compounds account for about 0.5–1.0% of blood serum. Plasma lipoproteins share a common structure. They have a hydrophobic core of triacylglycerols and cholesterol esters surrounded by a shell of phospholipids, cholesterol, and proteins. Lipoproteins are divided into three classes according to their density: high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL). The density of a lipoprotein complex depends upon the lipid/protein ratio (see figure). Because proteins are more dense than lipids, increasing the protein component of a lipoprotein complex increases its density.



The densities of VLDLs, which consist of about 90% lipid and 10% protein, range from 0.95 to 1.006 g/mL. LDLs have densities of 1.006–1.063 g/mL, and consist of about 75% lipid and 25% protein. HDLs have densities of 1.063–1.21 g/mL. They are about 50% lipid and 50% protein.

The VLDLs are the principal carriers of triacylgycerols, whereas LDLs carry 80% of the blood serum



cholesterol

cholesterol. HDLs carry the remaining cholesterol. The functions of LDLs and HDLs in cholesterol transport are quite different. LDLs carry cholesterol to cells, where it is incorporated in cell membranes or used for the synthesis of other molecules. HDLs carry excess cholesterol away from cells to the liver for processing and excretion from the body. Individuals with high HDL levels have an efficient means of removing excess cholesterol from blood serum. This is an important function because the accumulation of cholesterol ester deposits in arteries results in atherosclerosis, hardening of the arteries. If the HDL level is too low, excess cholesterol accumulates on the walls of the arteries. One consequence of this condition is coronary heart disease. So high concentrations of HDLs tend to diminish the risk of heart disease.

The average concentration of HDLs in blood is 45 mg/100 mL for men and 55 mg/100 mL for women prior to menopause. This difference in HDL concentration may partly explain why proportionately fewer younger women have heart attacks than men at the same age. The concentration of HDLs appears to increase if a person exercises. For example, the HDL concentration in long-distance runners may be as high as 75 mg HDL/100 mL

toward the negative electrode. After a while, the original "spot" of the amino acid sample separates into two or more spots, each corresponding to an amino acid present in the original mixture.

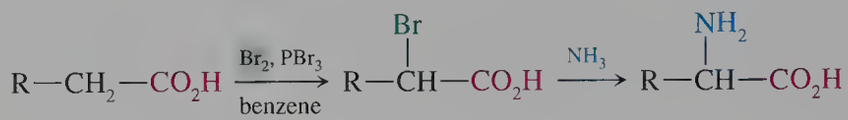
Proteins can also be separated by electrophoresis. Electrophoretic separation of proteins is an important tool in research and in clinical laboratories. Because proteins have different charges and molecular weights, they move at different rates in the electrophoresis apparatus. Electrophoresis is commonly used to analyze blood serum. For example, the identification of certain enzymes in the blood is used as a diagnostic tool for myocardial infarction.

26.5 Synthesis of Amino Acids

Protein hydrolysis can provide naturally occurring amino acids in the laboratory, but they must be individually separated from the reaction mixture. Thus, it is important to have synthetic methods to prepare these amino acids and other amino acids not found in natural sources. Each of the synthetic methods described in this section uses reactions that we have studied in earlier chapters of this text.

Amination of α-Halocarboxylic Acids

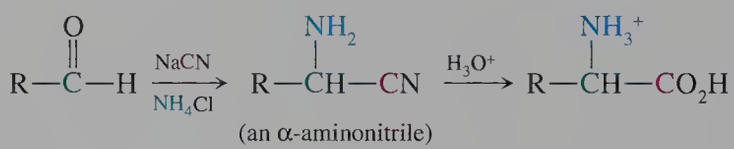
The oldest method of synthesizing amino acids is the nucleophilic substitution of the halogen of an α-halocarboxylic acid by ammonia. The α-halocarboxylic acid is prepared by treating a carboxylic acid with Br_2 and PBr_3. This reaction, known as the Hell–Volhard–Zelinsky reaction, produces a carboxylic acid with a bromine atom at the α position. The α-bromo acid is a useful synthetic intermediate. For example, it reacts with ammonia in an S_N2 substitution reaction to give an α-amino acid.



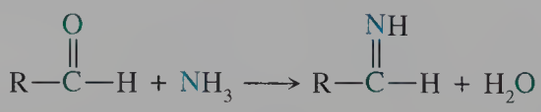
We recall that direct substitution of alkyl halides by ammonia is often complicated by multiple alkylation of the nitrogen (Section 25.7). However, multiple alkylation does not occur in the synthesis of amino acids. The nitrogen atom in the amino acid is less nucleophilic than in ammonia because the carbonyl group inductively withdraws electrons from the nitrogen atom.

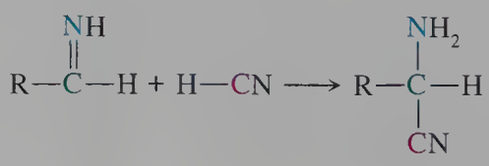
The Strecker Synthesis

A second early method to synthesize amino acids starts with an aldehyde having one less carbon atom than the desired amino acid. In the first step, an α-aminonitrile is prepared by reaction with CN^- and ammonia or an ammonium salt. Then, the nitrile is hydrolyzed to a carboxylic acid.



The first step of this reaction sequence is formation of an imine, which is in equilibrium with the aldehyde (Section 19.10). Then the imine undergoes an addition reaction with HCN similar to the reaction we discussed for the addition of HCN to a carbonyl group (Section 19.2).

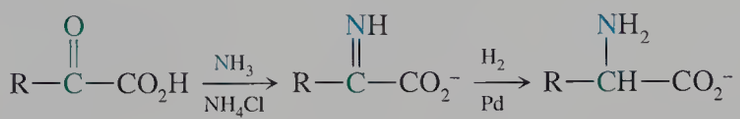




Reductive Amination

Reductive amination of aldehydes or ketones is an excellent method of synthesizing amines, particularly on an industrial scale. To form amino acids by this method, laboratories start with an α-keto acid. We recall that the biosynthesis of amino acids by transamination also requires an α-keto acid (Section 19.10). In transamination, the amino group that replaces the keto oxygen atom is provided by pyridoxamine. (In a sense the process is a reductive amination reaction.)

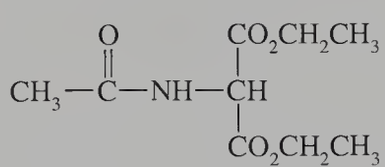
In the reductive amination method for the synthesis of amino acids, ammonia reacts with the keto group to yield an imine, which is directly reduced by hydrogen in the presence of a palladium catalyst.



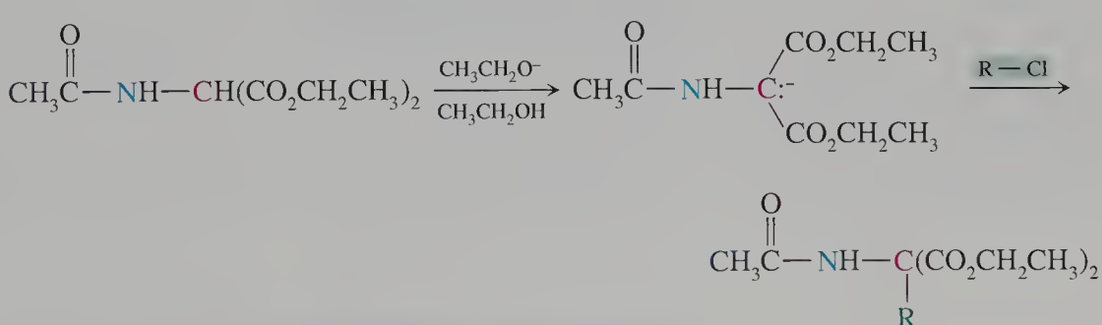
The entire reaction is carried out in a single step with all reagents present. Although a carbonyl group can be reduced under a high pressure of hydrogen gas, the imine is more easily reduced, and the conditions are selected to prevent reduction of the starting material.

Acetamidomalonate Synthesis

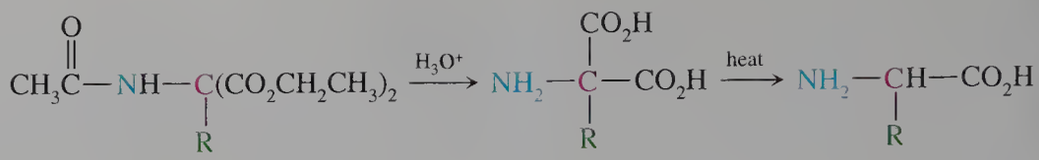
One of the best methods for synthesizing amino acids is based on the chemistry of malonate esters (Section 23.17) and a modification of the Gabriel synthesis of amines. Diethyl acetamidomalonate has a nitrogen atom bonded to the α carbon atom of the malonate ester. This nitrogen atom eventually becomes the amino nitrogen atom of the final amino acid product.



We recall that the α hydrogen atom of a malonate can be removed by an alkoxide base, and the resulting ester enolate can be alkylated (Section 23.17). These steps provide a way to synthesize amino acids using diethyl acetamidomalonate. The alkyl halide has the same R group as the desired amino acid.



Acid-catalyzed hydrolysis of the product cleaves both the carbonyl carbon–nitrogen bond of the amide and the two carbon–oxygen bonds of the malonate ester. The resulting substituted malonic acid spontaneously decarboxylates to give an amino acid.

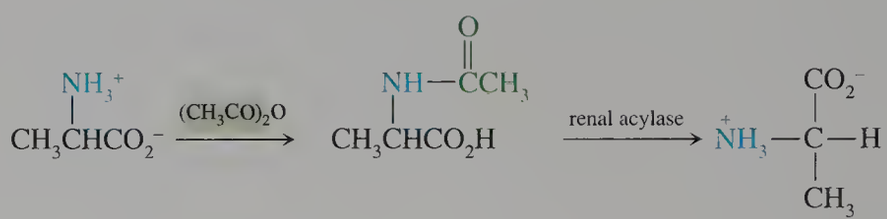


Resolution of Amino Acids

All of the methods described in this section yield racemic mixtures of amino acids. However, to obtain amino acids of the *S* configuration (L-amino acids,) it is necessary to resolve the mixture. Although the process is conceptually straightforward, in practice resolution is time consuming and expensive and gives a poor yield because we throw away more than 50% of the product.

We can admire the efficiency of enzymes, which generate amino acids with the *S* configuration by the transamination reaction starting from an α-keto acid. Chemists have taken advantage of the efficiency of enzymes to prepare amino acids with the *S* configuration and also to obtain amino acids with the *R* configuration. The method is called **kinetic resolution**. It takes advantage of the stereoselectivity of enzymes.

The enzyme hog renal acylase, isolated from hog kidneys, stereospecifically catalyzes the hydrolysis of amide linkages of compounds with the *S* configuration. If a racemic mixture of an amino acid is acetylated and the *N*-acyl amino acid is then hydrolyzed by the enzyme, only the free *S* amino acid is produced. The method is illustrated using a racemic mixture of alanine.



(*R*,*S*)-alanine (*R*,*S*)-*N*-ethanoylalanine (*S*)-alanine

The (*S*)-alanine produced in the reaction is precipitated by adding ethanol to the aqueous solution of the renal acylase. The (*R*)-*N*-ethanoylalanine remaining in solution can be chemically hydrolyzed to obtain the (*R*)-alanine.

Problem 26.6

What carboxylic acid is required to synthesize leucine using the amination of an α-halo carboxylic acid method?

Sample Solution

The synthesis substitutes a bromine atom at the α position followed by displacement of bromide by ammonia. Thus, the required starting material is a carboxylic acid having the same carbon skeleton as leucine—4-methylpentanoic acid.

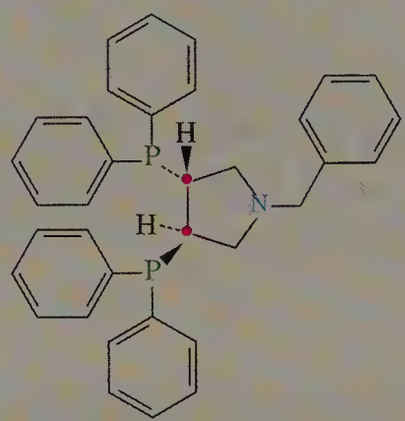
Problem 26.7

What reagents are required for the Strecker synthesis of phenylalanine?

Asymmetric Synthesis of Amino Acids

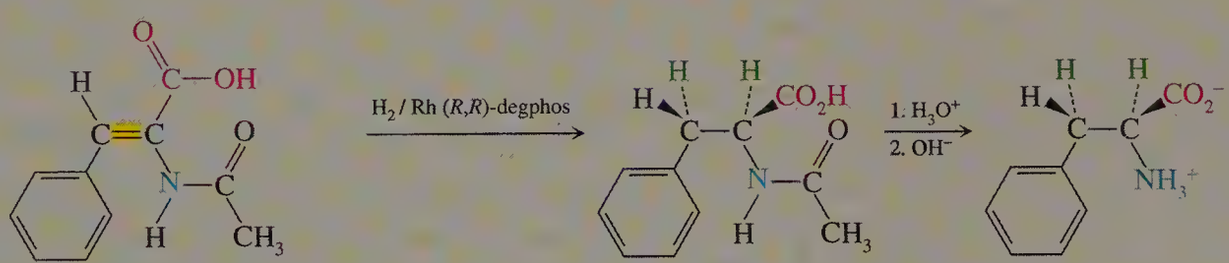
The synthetic methods outlined in this section to form amino acids give racemic mixtures. For example, the reduction of an imine using achiral reagents gives a racemic mixture of amines. However, nature carries out similar reductions with high stereoselectivity. As outlined in Section 18.5, coenzymes such as NADH can stereoselectively reduce a carbonyl group to an alcohol by catalyzing the addition of hydrogen to just one face of the C=O bond. Chemists are developing synthetic catalysts to accomplish similar goals. The procedure, called **asymmetric synthesis**, uses chiral reagents—or better yet, chiral catalysts—to convert achiral starting materials into chiral products. Some important processes have been developed that use transition metal catalysts coordinated with chiral ligands. Because the ligand is chiral, the transition states incorporating the catalyst and the achiral starting material can give two possible diastereomeric transition states as either of two chiral centers for the two enantiomeric products is generated. Thus, the transition state energies are different and the rate of formation of one enantiomer is favored over another.

The synthesis of some amino acids in industry by the reduction of the carbon–carbon double bond of enamides has been accomplished using chiral hydrogenation catalysts. For example, the chiral ligand "degphos" when coordinated to rhodium gives a homogeneous catalyst that stereoselectively directs hydrogen to one face of an alkene, giving one enantiomer.



(*R*,*R*)-degphos

The hydrogenation of (*Z*)-2-acetamido-3-phenylpropenoic acid using (*R*,*R*)-degphos, followed by hydrolysis of the amide, gives (*S*)-phenylalanine. This amino acid is a component of the dipeptide used in the manufacture of aspartame, an artificial sweetener produced in large quantities. The process is over 99% stereoselective.



(*Z*)-2-acetamido-3-phenylpropenoic acid

(*S*)-*N*-acetylphenylalanine

(*S*)-phenylalanine

Problem 26.8

What keto acid is required to produce glutamic acid by reductive amination?

Problem 26.9

What reagents are required to synthesize methionine by the acetamidomalonate method?

Sample Solution

The α carbon atom and its attached amino group as well as the carboxyl group are derived from the diethyl acetamidomalonate. The remaining portion of the amino acid, the R group, is derived from an alkyl halide. Attach a halogen atom such as chlorine to the R group that starts at the β carbon atom of the amino acid. In this case the R group contains a thiomethyl group.

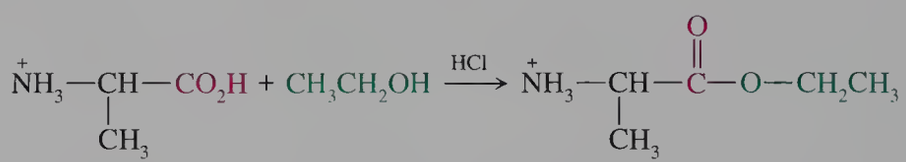
$$CH_3—S—CH_2—CH_2—Cl$$

26.6 Reactions of Amino Acids

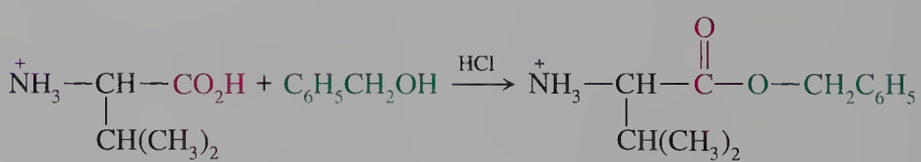
Each functional group of amino acids can undergo characteristic reactions if conditions are selected to prevent simultaneous reaction of the other functional group. In this section, we consider only selected reactions of the carboxyl group and amino group that are used to prepare amino acids for combination into peptides. These reactions are the esterification of the carboxyl group and the acylation of the amino group.

Esterification of the Carboxyl Group

The carboxyl group of an amino acid can be esterified by reaction with an excess of an alcohol using gaseous HCl. Under these conditions, the $—NH_2$ group is protonated and therefore unreactive. Ethyl or benzyl esters are commonly prepared to protect the carboxyl group against other reactions to be subsequently carried out at the amino group.

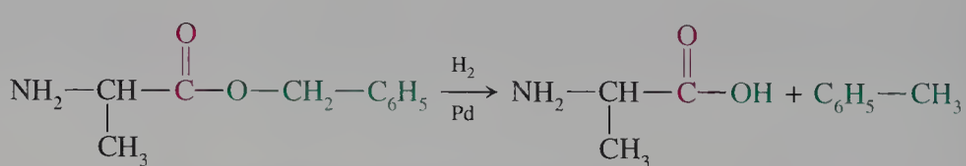


alanine ethanol ethyl ester of alanine



valine benzyl alcohol benzyl ester of valine

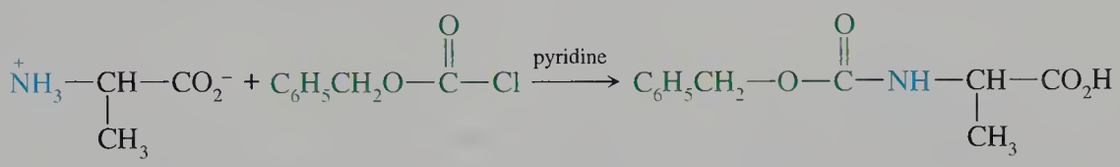
After the $—CO_2H$ group has been protected, the amino group can be modified. Then the ethyl group can be removed by acid hydrolysis. Benzyl esters can be similarly hydrolyzed, but these esters can be cleaved by catalytic hydrogenation, which removes the benzyl group as toluene. The process is called **hydrogenolysis**. It occurs under neutral conditions with no competing side reactions.



Acylation of the Amino Group

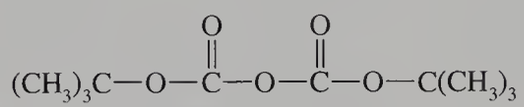
The amino group of an amino acid is converted to an amide by acylation with an anhydride or an acyl chloride. When the amino group is thus protected, it is possi-

ble to carry out reactions at the carboxyl group. We recall that acetic anhydride is a common reagent for acetylating amines. However, amides are difficult to hydrolyze, and the deprotection of an amino group contained in an *N*-acetyl derivative may well also affect other functional groups, including other amide linkages in a peptide. For this reason, two special reagents are used that provide a protecting group that can be more easily removed. Benzyl chloroformate acylates the amino group of an amino acid to yield a benzyloxycarbonyl (Cbz) derivative. Pyridine is required to convert the α-NH_2 group to the neutral nucleophilic form.



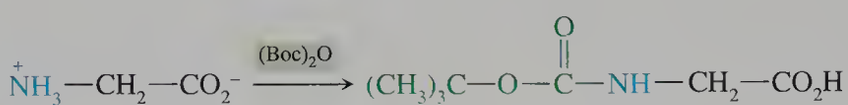
alanine benzyl chloroformate *N*-benzyloxycarbonyl alanine (Cbz-alanine)

The second protective group is *tert*-butoxycarbonyl (commonly abbreviated Boc). *tert*-Butoxycarbonyl chloride is very unstable, so the Boc protective group is provided from an anhydride.



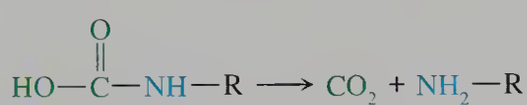
di-*tert*-butyldicarbonate $(Boc)_2O$

The Boc group is functionally similar to the benzyloxycarbonyl group, but it has a *tert*-butyl group in place of a benzyl group.



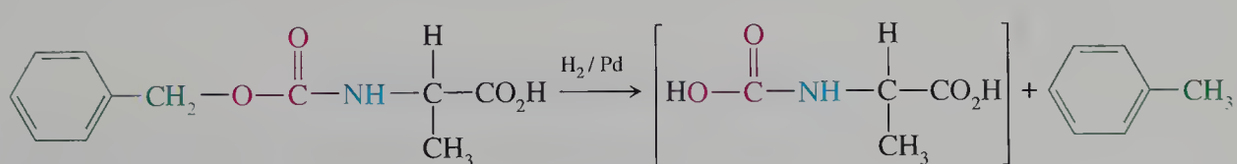
glycine *N*-*tert*-butoxycarbonyl glycine (Boc-glycine)

Both oxycarbonyl derivatives are carbamate esters. A carbamic acid is an unstable compound that easily decarboxylates to give an amine. Therefore, when a carbamate ester is converted into a carbamic aeid, it decomposes.



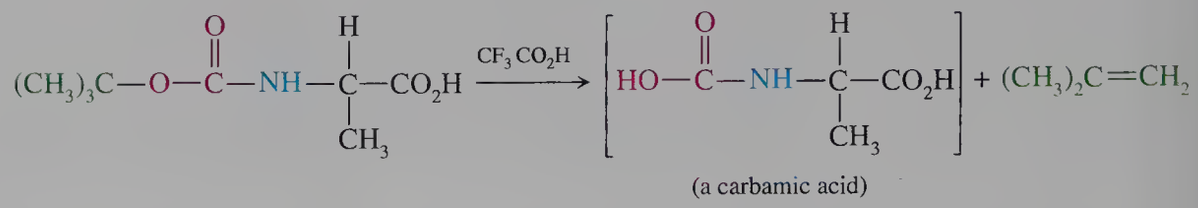
(a carbamic acid)

Hydrogenolysis of the carbamate ester of the *N*-benzyloxycarbonyl derivative of an amino acid yields a carbamic acid, which then decomposes to yield the deprotected amino acid.



(a carbamic acid)

The Boc group is very acid sensitive and is easily cleaved by trifluoroacetic acid. The resulting carbamic acid readily decarboxylates to give a deprotected amine group. The *tert*-butyl group is released as isobutylene.

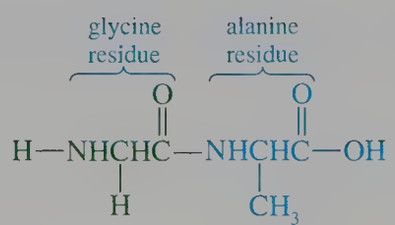


(a carbamic acid)

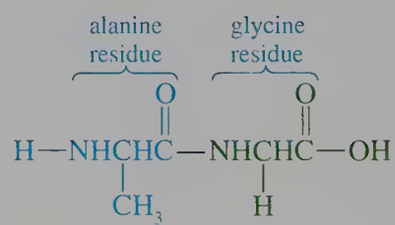
26.7 Peptides

When the α-amino group of one amino acid is linked to the carboxyl group of a second amino acid by an amide bond, the product is called a **peptide**. Each amino acid in a peptide is called an amino acid residue. If the peptide contains two amino acid units, it is a **dipeptide**; if three amino acids, a **tripeptide**. A prefix, *di-*, *tri-*, etc., indicates the number of amino acids in a peptide. But a peptide that contains, say, 14 amino acids is more likely called a 14-peptide than a tetradecapeptide. Peptides that contain only a "few" amino acids are called **oligopeptides**.

A peptide has two ends: the end with a free α-amino group is called the **N-terminal amino acid residue**. The end with the free carboxyl group is called the **C-terminal amino acid residue**. Peptides are named from the N-terminal amino acid to the C-terminal amino acid. Two examples of this nomenclature for isomeric dipeptides containing glycine and alanine are shown below.



glycylalanine (Gly-Ala)



alanylglycine (Ala-Gly)

The number of possible isomeric peptides containing one each of n different amino acid residues is equal to $n!$, where

$$n! = 1 \times 2 \times 3 \times \cdots \times (n-1) \times n$$

Thus there are six possible isomers of a tripeptide with three different amino acids. The isomeric tripeptides with the amino acids glycine, alanine, and valine are Gly-Ala-Val, Gly-Val-Ala, Val-Gly-Ala, Val-Ala-Gly, Ala-Gly-Val, and Ala-Val-Gly. For a peptide with one each of 20 different amino acid residues there are 2,432,902,008,176,640,000 isomers! Polypeptides and proteins may contain two or more residues of the same amino acid, in which case the above formula does not apply. However, the number of isomers is still astronomically large.

Biological Functions of Peptides

Cells contain many relatively small peptides that have diverse functions. Some act as hormones with physiological functions, such as pain relief and control of blood

pressure. These oligopeptides are produced and released in small amounts. They are rapidly metabolized, but their physiological action is necessary for only a short time. For example, the 14-peptide somatostatin, which inhibits the release of other hormones such as insulin, glucagon, and secretin, has a biological half-life of less than 4 minutes. Table 26.6 shows examples of some of hormonal peptides.

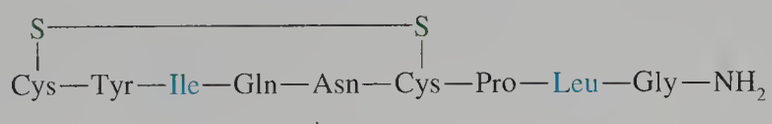
Table 26.6
Peptide Hormones

Hormone	*Amino acid residues*	*Molecular weight*	*Function*
tuftsin	4	501	stimulates phagocytosis
met-enkephalin	5	645	analgesic activity
angiotensin II	8	1031	affects blood pressure
oxytocin	8	986	affects uterine contractions
vasopressin	8	1029	an antidiuretic
bradykinin	9	1069	produces pain
somatostatin	14	1876	inhibits release of other hormones
gastrin	17	2110	promotes pepsin secretion
secretin	27	2876	stimulates pancreatic secretions
glucagon	29	3374	stimulates glucose production from glycogen
calcitonin	32	3415	decreases calcium level in blood
relaxin	48	5500	relaxation of pubic joints
insulin	51	5700	affects blood sugar level

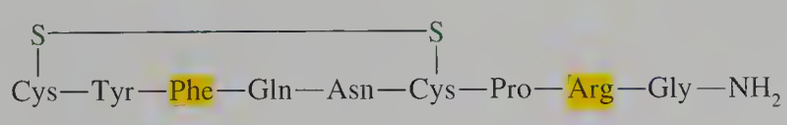
Enkephalins are peptides that bind specific receptor sites in brain cells to reduce pain. The enkephalin receptor sites have a high affinity for opiates, including morphine, heroin, and other structurally similar substances. Hence, enkephalin receptors are commonly called *opiate receptors*. Opiates mimic the enkephalins normally present in the body to mitigate pain.

Peptides are produced in many tissues. For example, kidney cells secrete angiotensin II, which increases blood pressure by constricting blood vessels. Angiotensin II is the most potent vasoconstrictor known, and the production of excess angiotensin II is responsible for some forms of hypertension.

Oxytocin, a peptide hormone produced in the pituitary, causes the contraction of smooth muscle, such as that of the uterus. It is used clinically to induce labor or to increase the effectiveness of uterine contractions. Vasopressin, another pituitary peptide hormone, regulates the excretion of water by the kidneys and affects blood pressure. The structures of oxytocin and vasopressin differ by only two amino acids. They are both cyclic peptides that result from a disulfide bond (—S—S—) between what would otherwise be the N-terminal amino acid cysteine and another cysteine five amino acid residues away. The C-terminal amino acid exists as an amide in both compounds.



oxytocin

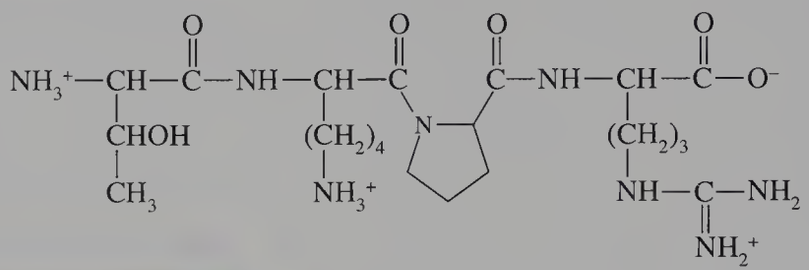


vasopressin

The structural difference between oxytocin and vasopressin may seem small at first glance. When we compare oxytocin and vasopressin, we see that residue 3 in oxytocin is isoleucine and that residue 3 in vasopressin is phenylalanine. This change has relatively little effect: both residues are nonpolar and about the same size. However, residue 8 in oxytocin is leucine, a nonpolar amino acid with a *sec*-butyl side chain, whereas residue 8 in vasopressin is arginine, an amino acid with a strongly basic side chain and a positive charge at pH 7. Because of this difference in charge, the receptor for oxytocin has a weak affinity for vasopressin, and the receptor for vasopressin has a very low affinity for oxytocin. These peptides therefore bind different receptors and have different functions.

Problem 26.10

Identify the terminal amino acids of tuftsin, a tetrapeptide that stimulates and promotes the destruction of tumor cells. Write the amino acid sequence using three-letter abbreviations for the amino acids. Also write the complete name without abbreviations.



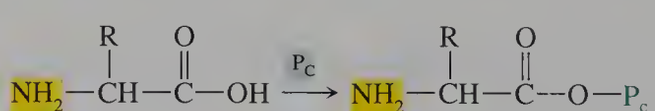
Problem 26.11

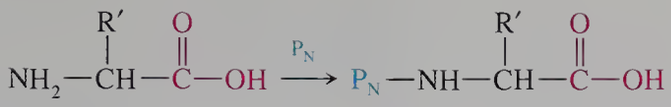
Determine the number of isomeric tripeptides containing one alanine and two glycine residues. Write representations of the isomers using the three-letter abbreviations.

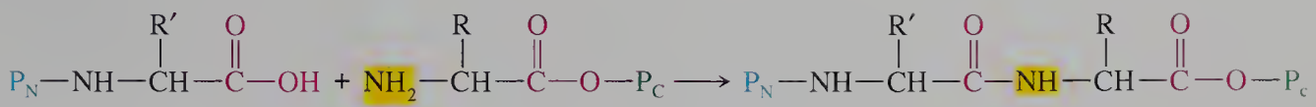
26.8 Synthesis of Peptides

The synthesis of peptides and polypeptides is an important aspect of research in biochemistry and is a lucrative part of the biotechnology industry. A highly specialized set of reagents is required for this process. We cannot simply react two amino acids under conditions that lead to the formation of amide bonds if we wish to synthesize a particular dipeptide. Two amino acids, such as alanine and glycine, yield a mixture of dipeptides. Each amino acid has two reactive ends. Therefore, each amino acid could randomly form bonds with its own kind to form Gly-Gly and Ala-Ala or the other kind to give Gly-Ala and Ala-Gly. Also, the amino acids in the reaction mixture can continue to react in an uncontrolled manner with the dipeptide products to yield oligopeptides.

The synthesis of a dipeptide having a specific sequence requires modification of both amino acids. One amino acid is protected at its carboxyl group—by a reagent we will call P_C—leaving the amino group available for peptide bond formation. The second amino acid is protected at the amino group—by a reagent we will call P_N—leaving the carboxyl group available for peptide bond formation. Only one condensation reaction is then possible.





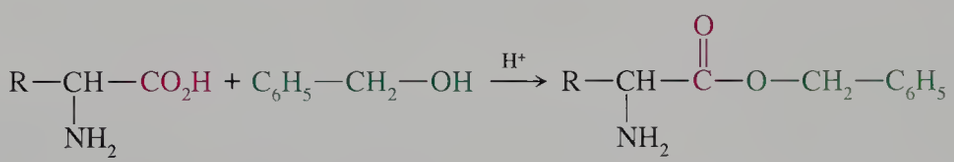


This method of peptide synthesis has several requirements.

1. The carboxyl group of one amino acid must be protected.
2. The amino group of the other amino acid must be protected.
3. A reagent must be chosen to form the amide bond.
4. Conditions must be chosen that selectively free one protecting group so that the sequence can be repeated.

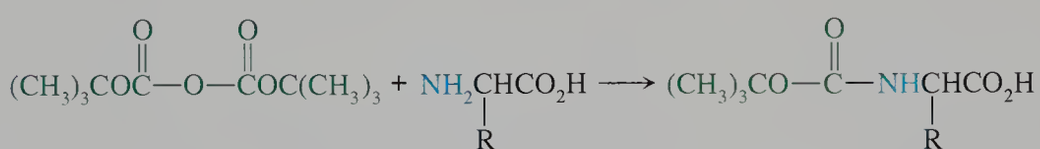
Protection of the Carboxyl Group

The carboxyl group is protected by converting it to a benzyl (Bz) ester. We saw in Section 26.6 that benzyl esters can be specifically cleaved by catalytic hydrogenation. Hence, the carboxyl terminus is easily "deprotected" at the end of the synthesis.



Protection of the Amino Group

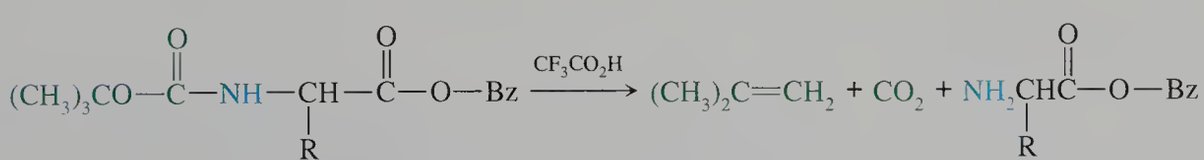
We also recall that several protecting groups have been developed to protect the amino terminus of an amino acid; the *tert*-butoxycarbonyl (Boc) derivative is typical. Reaction of an amino acid with di-*tert*-butyl dicarbonate gives a Boc-amino acid.



di-*tert*-butyl dicarbonate

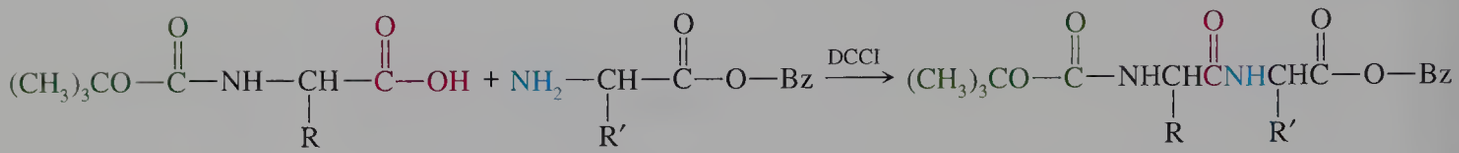
(a Boc-amino acid)

Note that the carbonyl group of the Boc group is bonded to both an oxygen atom and a nitrogen atom. This functional group is a carbamate, which is more easily hydrolyzed than amides and even esters. The Boc group can be removed with trifluoroacetic acid. Both the amide bonds and the ester of a protected carboxyl group are unaffected by the reaction conditions. The by-products of the reaction, CO_2 and 2-methylpropene, are gases.



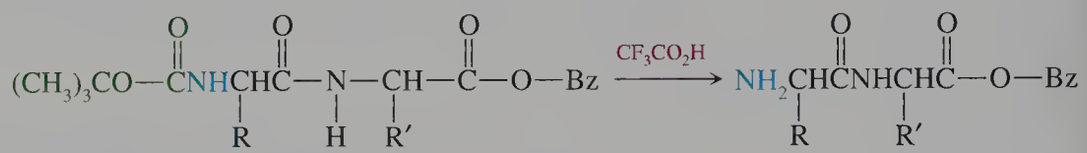
Condensation of the Amino and Carboxyl Groups

The protecting groups of both the amino and the carboxyl groups are sensitive to acid and base. Therefore, the condensation reaction to produce a dipeptide bond must be carried out under neutral conditions. A special reagent, dicyclohexylcarbodiimide (DCCI), causes condensation of two amino acids by removing the elements of water. The reaction has a very high yield, and no other functional groups on the amino acids are affected. The by-product of the reaction is dicyclohexylurea.



Formation of a Polypeptide

The dipeptide that is protected at both the carboxyl and the amino groups is deprotected by hydrolysis of the Boc group at the *N*-terminal amino acid. The ester linkage of the carboxyl group is unaffected.



This dipeptide can only react at the free amino group. Reaction with another Boc-amino acid and DCCI yields a tripeptide. Ultimately, after the proper number of reaction sequences, the final polypeptide is liberated by hydrolysis with base.

Experimental Limitations

One of the limitations of any synthetic method is the mechanical losses that result from the isolation and purification using distillation or recrystallization. The product—in this case a peptide—must be separated from remnants of protecting groups, coupling reagents, and by-products. Thus, even reactions that regiospecifically yield a single product may not produce a high isolated yield. The problem is compounded when a large number of consecutive reactions is required in peptide synthesis. Consider, for example, a synthetic sequence to prepare a peptide containing 25 amino acids. A total of four steps is required for each amino acid joined to the peptide chain. Thus, 100 separate steps are required altogether. If the product of each step were isolated in 90% yield, the final yield would be extremely small because the amount of each product formed is controlled by the product formed in the previous reaction. We obtain the fraction of product obtained relative to the original reactant by multiplying the decimal equivalent of the yield for each reaction. The yield for the described peptide synthesis is 0.0026%.

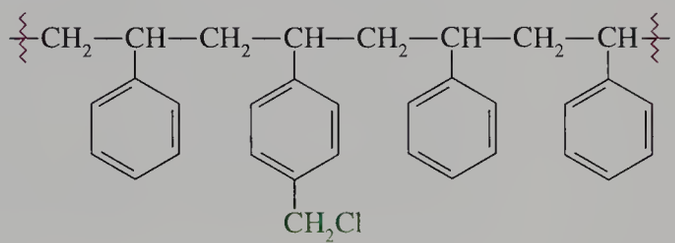
$$(0.90)^{100} = 0.000026$$

The problem becomes worse as the number of amino acids in a protein increases. Synthesis of even a "small" enzyme such as ribonuclease, with 124 amino acids, by conventional means is clearly out of the question.

26.9 Solid Phase Synthesis

R. B. Merrifield of Rockefeller University developed a **solid phase synthesis** of peptides, which uses a polymer with reactive sites that chemically bind to the developing peptide chain. This technique circumvents the problems associated with low yields due to separation and purification. Because the polymer is very insoluble, it can be filtered and washed without mechanical losses. The developing protein chain attached to the polymer is "dangling" off the polymer and is in contact with any reagents added in solution. As a result, a large number of steps can be carried out on the peptide, and the product remains linked to a solid that can be separated from impurities in solution.

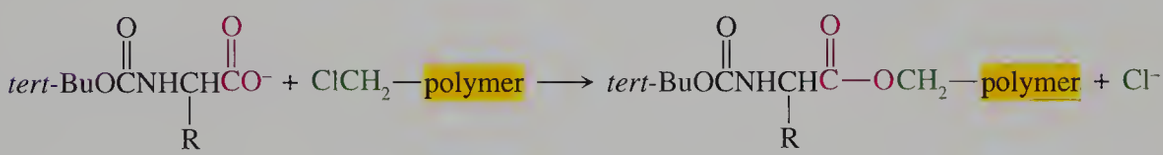
The polymer used in solid phase synthesis is an addition polymer of styrene in which some of the benzene rings have a $-CH_2Cl$ group. As few as one out of 10 rings are so substituted. The general structure of the polymer is



chloromethylated polystyrene

We recall that benzyl halides are reactive in substitution reactions. Even relatively weak nucleophiles such as carboxylate salts react with benzyl halides to yield benzyl esters. Thus, a solution of a carboxylate salt of an N-protected amino acid in an aprotic solvent such as DMF readily gives an ester. This first step, using a shorthand representation of the polymer, is

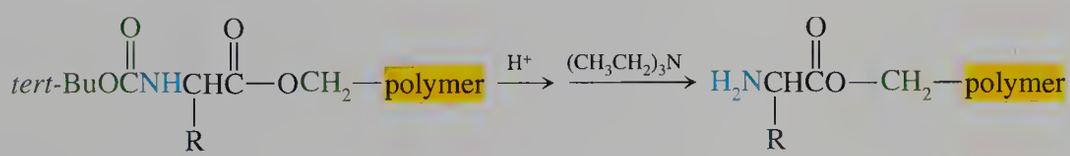
Step 1



N-protected amino acid — polymer-bound N-protected amino acid

The polymer-bound N-protected amino acid is filtered and then washed with solvent. The "pure" product is then treated with CF_3CO_2H to deprotect the amino group by removing the Boc group in step 2. Subsequent treatment with an amine base neutralizes the ammonium group of the amino acid and yields a "pure" polymer-bound amino acid.

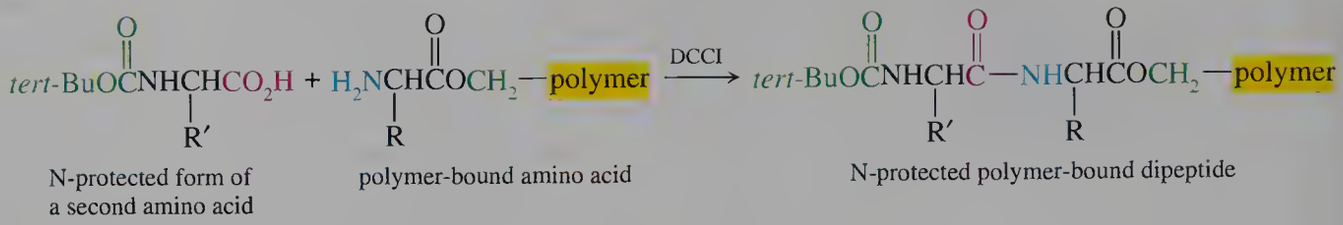
Step 2



polymer-bound amino acid

The polymer-bound amino acid is then reacted with a solution of an N-protected amino acid and DCCI in step 3, yielding a polymer-bound N-protected dipeptide.

Step 3



After washing away excess reagent and the *N,N'*-dicyclohexylurea by-product, the N-protected polymer bound dipeptide is available for a repeat of steps 2 and 3 to yield a polymer-bound N-protected tripeptide. A number of cycles yields a polypeptide.

At the end of the synthesis, the peptide is released from the polymer by treatment with anhydrous hydrogen fluoride. The Boc group is simultaneously hydrolyzed. Because the sequence of reactions is repetitive and a limited number of reagents are used, the entire synthesis has been automated using a "peptide synthesizer." The individual steps were initially carried out in about 99% yield. Bradykinin, a nonapeptide, was synthesized by this method in an 85% yield. The synthesis of ribonuclease, which contains 124 amino acid residues, required a total of 11,391 steps. Only by improving the yields of each cycle to higher than 99% was it possible to obtain an 18% yield of the enzyme.

26.10 Determination of Amino Acid Composition in Proteins

The first item of business when analyzing the structure of a protein is determination of its amino acid composition, which requires two steps. First the protein is hydrolyzed. Then the hydrolysis products are separated by chromatography. The order of elution from the chromatography column is a characteristic of each amino acid (Figure 26.3). The determination of both the identity of the amino acids and the number of each is possible using well-established techniques with automated instruments. The numbers of amino acid residues in some proteins are given in Table 26.7.

A protein or polypeptide is hydrolyzed by heating it for 24 hours in 6 M HCl at 100 °C. Complete hydrolysis produces the constituent amino acids of the polypeptide or protein. For example, hydrolysis of the pentapeptide leucine enkephalin gives two molar equivalents of glycine and one each of

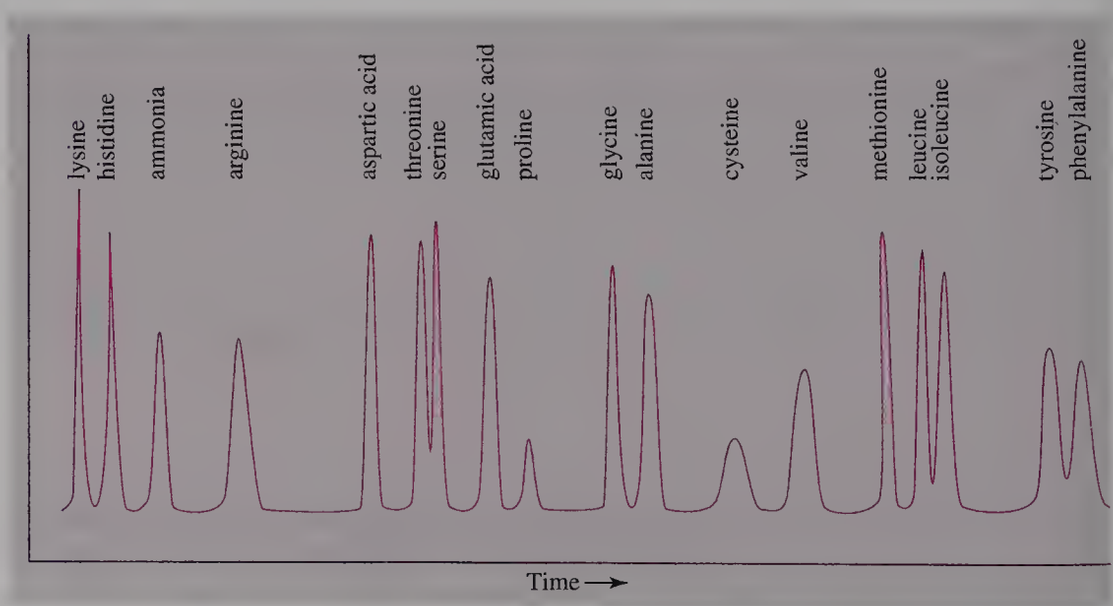


FIGURE 26.3 Chromatographic Separation of Amino Acids

Table 26.7
Amino Acid Composition of Proteins

	Number of residues per molecule		
Amino acid	*Cytochrome c*	*Insulin*	*Hemoglobin (α chain)*
Nonpolar			
Ala	6	3	21
Val	3	5	13
Leu	6	6	18
Ile	8	1	0
Pro	4	1	7
Met	3	0	2
Phe	3	3	7
Trp	1	0	1
Polar, neutral			
Cys	2	6	1
Gly	13	4	7
Ser	2	3	11
Thr	7	1	9
Tyr	5	4	3
Asn	5	3	4
Gln	2	3	1
Polar, acidic			
Asp	3	0	8
Glu	8	4	4
Polar, basic			
Lys	18	1	11
Arg	2	1	3
His	3	2	10
Total residues	104	51	141

leucine, tyrosine, and phenylalanine. The composition is represented as Gly_2,Leu,Tyr,Phe.

$$\text{leucine enkephalin} \longrightarrow 2\ \text{Gly} + \text{Leu} + \text{Tyr} + \text{Phe}$$

26.11 Determination of Amino Acid Sequences in Proteins

The linear sequence of amino acid residues in a polypeptide or protein is called the **primary structure**. This structure is "primary" for two reasons. First, the sequence of amino acid residues in a protein is specified by its gene. Second, all higher ordered structures of the protein automatically result from the primary structure.

The amino acid sequence is determined by a combination of methods.

1. Partial hydrolysis and fragment overlap analysis.
2. Selective enzymatic hydrolysis.
3. End group analysis.

Partial Hydrolysis

When a peptide is heated with HCl for short time intervals, hydrolysis reactions yield oligopeptides of random sizes. For example, heating leucine enkephalin in HCl might yield the tripeptides Phe-Leu-Gly and Gly-Phe-Leu and the dipeptide

Ala-Gly. The amino acid sequence can be obtained by aligning the common partial sequences.

Ala-Gly
Gly-Phe-Leu
Phe-Leu-Gly

Ala-Gly-Phe-Leu-Gly

Enzymatic Hydrolysis

Enzymes called **proteases** can specifically cleave a protein or polypeptide. These enzymes are used in the laboratory to determine the structure of polypeptides and proteins. Two common proteolytic enzymes are chymotrypsin and trypsin. Chymotrypsin hydrolyzes peptide bonds on the C-terminal side of the aromatic amino acids phenylalanine, tyrosine, and tryptophan. Trypsin hydrolyzes peptide bonds on the C-terminal side of the basic amino acids lysine and arginine.

$$\text{Lys-Glu-Tyr-Leu} \xrightarrow{\text{chymotrypsin}} \text{Lys-Glu-Tyr} + \text{Leu}$$

$$\text{Lys-Glu-Tyr-Leu} \xrightarrow{\text{trypsin}} \text{Lys} + \text{Glu-Tyr-Leu}$$

Let us see how we can use enzymatic hydrolysis to determine the structure of leucine enkephalin. We know from the total hydrolysis that the compound contains phenylalanine, an aromatic amino acid. The structure of leucine enkephalin can be partially established by hydrolysis with chymotrypsin. The pentapeptide cleaves to give a tripeptide with a C-terminal phenylalanine residue and a dipeptide with an N-terminal leucine residue.

$$\text{leucine enkephalin} \xrightarrow{\text{chymotrypsin}} \text{Ala-Gly-Phe} + \text{Leu-Gly}$$

Phenylalanine must have been bonded to leucine, the N-terminal amino acid of the other fragment. Considering the structures of the two fragments, the overall structure must be Ala-Gly-Phe-Leu-Gly.

End Group Analysis

Partial hydrolysis of a polypeptide chain, either by HCl or by specific enzymes, produces peptides of varying lengths. The sequence of these peptides must be determined in order to determine the overall sequence. The sequence of the peptide fragments produced by partial hydrolysis can often be deduced by end group analysis. Consider a tripeptide, which may have six isomeric structures. If the identity of the N-terminal amino acid is known, then only two isomeric arrangements are possible for the other two amino acid residues. Subsequent identification of the C-terminal amino acid provides the complete structure.

Enzymatic End Group Analysis

Some enzymes hydrolyze the peptide bond of a terminal amino acid and "nibble" their way down the chain until they have digested the entire molecule. For example, **carboxypeptidases** sequentially remove peptides from the C-terminal end of a polypeptide chain. In contrast, **aminopeptidases** sequentially hydrolyze peptides from the N-terminal amino acid. By identifying the amino acids produced by a carboxypeptidase or an aminopeptidase at various time intervals, the sequence of amino acids can be determined. For example, hydrolysis of the pentapeptide leucine enkephalin catalyzed by carboxypeptidase first liberates glycine. The

tetrapeptide remaining in solution and in contact with the enzyme then yields leucine, followed by phenylalanine, and so on.

$$\text{leucine enkephalin} \xrightarrow{\text{carboxypeptidase}} \text{tetrapeptide} + \text{Gly}$$

$$\text{tetrapeptide} \xrightarrow{\text{carboxypeptidase}} \text{tripeptide} + \text{Leu}$$

When an aminopeptidase hydrolyzes leucine enkephalin, it first releases alanine, then glycine, phenylalanine, and so on.

$$\text{leucine enkephalin} \xrightarrow{\text{aminopeptidase}} \text{Ala} + \text{tetrapeptide}$$

$$\text{tetrapeptide} \xrightarrow{\text{aminopeptidase}} \text{Gly} + \text{tripeptide}$$

Carboxypeptidase and aminopeptidase can only be used to determine a few residues in a polypeptide chain. Because these enzymes hydrolyze peptide bonds continuously and at different rates, the reaction mixture rapidly becomes too difficult to analyze.

Chemical End Group Analysis

The identity of the N-terminal amino acid of a polypeptide can be determined by a method invented by Pehr Edman called the **Edman degradation**. In the Edman degradation, the polypeptide is treated with phenyl isothiocyanate—the Edman reagent—which reacts with the N-terminal amino acid to give an *N*-phenylthiourea derivative. This derivative forms by addition of the terminal N—H bond across the C=N of the phenyl isothiocyanate. After the adduct has formed, anhydrous trifluoroacetic acid is added to the reaction mixture. This reagent cleaves the polypeptide at the N-terminal residue. Under these conditions, the peptide bonds in the protein do not break (Figure 26.4). A complex cyclization reaction occurs to give a substituted phenylthiohydantoin. This ring contains the carbonyl carbon atom, the α-carbon atom, and the amino nitrogen atom. The R group of the amino acid is attached to the ring. Comparison with the phenylthiohydantoin of known amino acids establishes the identity of the amino acid. This entire process can be carried out automatically by an instrument called an automatic sequenator.

Because the Edman degradation does not cleave the peptide bonds in the protein, it can be repeated to sequentially identify the amino acids from the N-terminal amino acid of the molecule. The yield of the Edman degradation approaches 100%, and sequences of 30 residues of a polypeptide can be determined from 5-picomole (5×10^{-12} mole) samples. This means that the sequence of a peptide with 30 amino acid residues, with a molecular weight of about 3000, can be determined from a 15-nanogram sample!

Problem 26.12

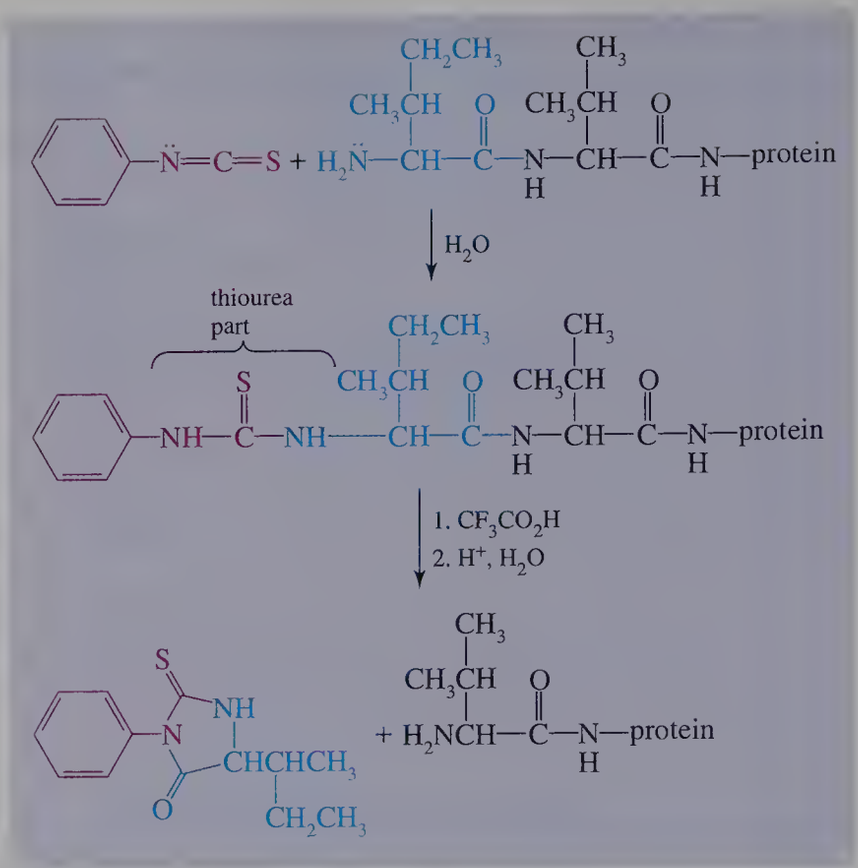
Predict the products of the chymotrypsin-catalyzed hydrolysis of the following enkephalin.

Tyr-Gly-Gly-Phe-Leu

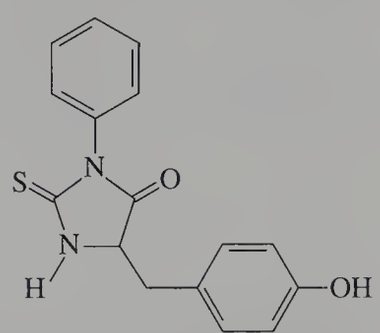
Problem 26.13

β-Endorphin, a 31-peptide, has analgesic effects and promotes the release of growth hormone and prolactin. Treating β-endorphin with phenyl isothiocyanate followed by

FIGURE 26.4 Use of the Edman Reagent in End Group Analysis



hydrolysis with anhydrous trifluoroacetic acid yields the following phenylthiohydantoin. What does this information reveal about the structure of the peptide?

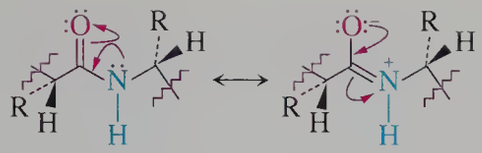


26.12 Bonding in Proteins

In this section we will consider the major types of bonds that occur in proteins. These include peptide bonds, disulfide bonds, hydrogen bonds, ionic bonds, and hydrophobic interactions.

The Peptide Bond

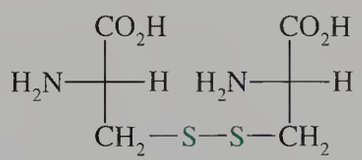
The peptide bond is the strongest and most important bond in a protein. A peptide bond is pictured as a resonance hybrid of two contributing structures. These resonance hybrids result from delocalization of the unshared electron pair of the amide nitrogen atom. Hence, the carbon–nitrogen bond has partial double bond character. The peptide bond is planar, and there is restricted rotation around the carbon–nitrogen bond. As a result, peptides exist almost exclusively in trans conformations around the carbon–nitrogen bond.



Although free rotation does not occur around the peptide bond, the bond between the α carbon atom and the carbonyl carbon atom is a rotationally free single bond. Similarly, the single bond between the nitrogen atom and the α carbon atom of the next amino acid is also rotationally free. Free rotation also occurs around the bonds between the α carbon atoms and the R groups. Thus, a protein chain consists of rigid peptide units connected to one another by freely rotating single bonds.

The Disulfide Bond

Many proteins—especially relatively small ones containing fewer than 100 amino acid residues—have a high cysteine content. Each of these cysteine residues has a sulfhydryl group (—SH) that can be oxidized to form a disulfide bond, as in cystine.



cystine

Disulfide bonds form after a protein has folded into its biologically active conformation. Once they have formed, the protein conformation is much less flexible. Intrachain disulfide bonds occur in small peptides such as oxytocin and vasopressin, as we saw in Section 26.7. Disulfide bonds can also link a cysteine residue in one polypeptide chain with a cysteine residue in another polypeptide chain as in the polypeptide insulin.

Hydrogen Bonds

Proteins contain many functional groups that can form hydrogen bonds. Although hydrogen bonds are much weaker than peptide and disulfide bonds, they help stabilize the folded conformation of proteins. Intramolecular hydrogen bonding between the amide hydrogen atom of one peptide group and the carbonyl oxygen atom of another peptide unit is very common. Hydrogen bonds also form between various amino acid side chains.

Ionic Bonds

At physiological pH, some of the R groups attached to the polypeptide chain are charged. Ionic attractive forces between the carboxylate groups and the ammonium groups pull portions of chains together. An intrachain ionic bond is called a **salt bridge**. Ionic bonds occur between acidic and basic amino acids.

Hydrophobic Interactions

Proteins contain many nonpolar side chains. These side chains are repelled by water and tend to associate with one another on the "inside" of a folded protein molecule,

out of contact with water. The tendency of nonpolar side chains to collect out of contact with the solvent is called the **hydrophobic effect**. The hydrophobic interactions in proteins are similar to those in the micelle of a soap (Section 21.5) or the bilayer of lipids in membranes (Section 24.7). Hydrophobic interactions among nonpolar side chains in proteins are weak, but abundant, and are primarily responsible for maintaining the folded conformation of a protein.

26.13 Protein Structure

The biological activity of a protein depends on the three-dimensional shape or conformation of the molecule. The overall shape and structure of a protein constitute its **native state** or **native conformation**. Protein structure is divided into four levels: primary, secondary, tertiary, and quaternary. These divisions are somewhat arbitrary because the total structure of the protein controls its function. Nevertheless, it is useful to consider the levels of structure one by one.

Primary Structure

The linear sequence of amino acids in a protein and the location of disulfide bonds constitute its **primary structure**. For example, insulin consists of two peptide chains, called the A chain and the B chain, linked by two disulfide bonds. The A chain has 21 amino acids, and the B chain has 30 amino acids (Figure 26.5). There is also an intrachain disulfide bond within the A chain. Insulins from different animals have slightly different amino acid sequences, as noted in Figure 26.5. Because the sequence within the cyclic portion of the shorter chain does not affect the physiological function of the insulin, diabetic individuals who became allergic to one type of insulin were often given insulin from another animal source. However, this

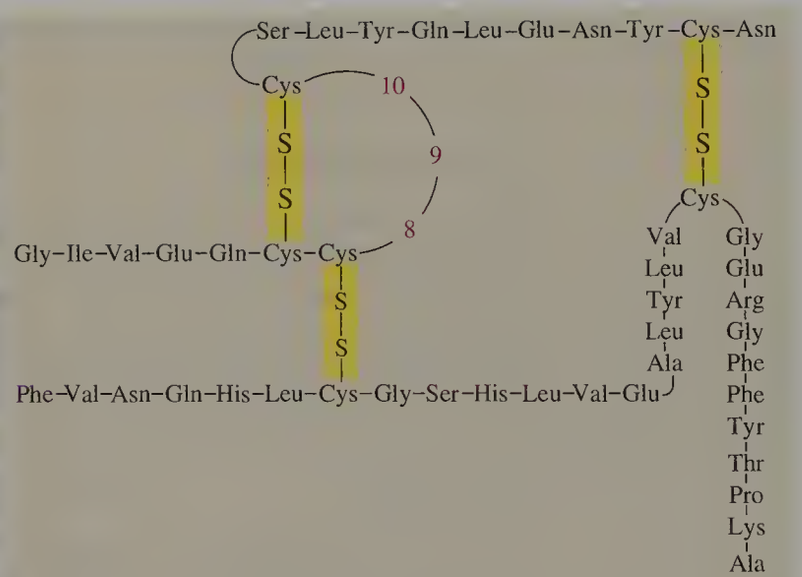


FIGURE 26.5
Primary Structure of Insulin
The insulin varies according to species but the majority of the amino acids are identical.

	Positions		
Animal	8	9	10
Sheep	Ala	Gly	Val
Cow	Ala	Ser	Val
Pig	Thr	Ser	Ile
Horse	Thr	Gly	Ile

problem has been eliminated by the synthesis of insulin using recombinant DNA technology in which bacteria produce human insulin with virtually no allergens.

Secondary Structure

Many proteins contain regularly repeating conformations of the polypeptide backbone. These conformations are stabilized by hydrogen bonds between residues that are relatively close to one another in the sequence. These regularly repeating conformations constitute the **secondary structure** of the protein (Figure 26.6). Many proteins consist of chains coiled into a spiral known as an α helix. Like a screw, such a helix may be either right- or left-handed. The right-handed (or α) helix is more stable than the left-handed helix, which rarely occurs in proteins. The helix is held together by hydrogen bonds between the proton of the N—H group of one amino acid and the oxygen atom of the C=O group of an amino acid in the next turn of the helix.

Some proteins have interchain hydrogen bonds and form pleated-sheet structures (Figure 26.6). Proteins with interchain hydrogen bonding include fibrin (the blood-clotting protein), myosin (a protein of muscle), and keratin (the protein of hair).

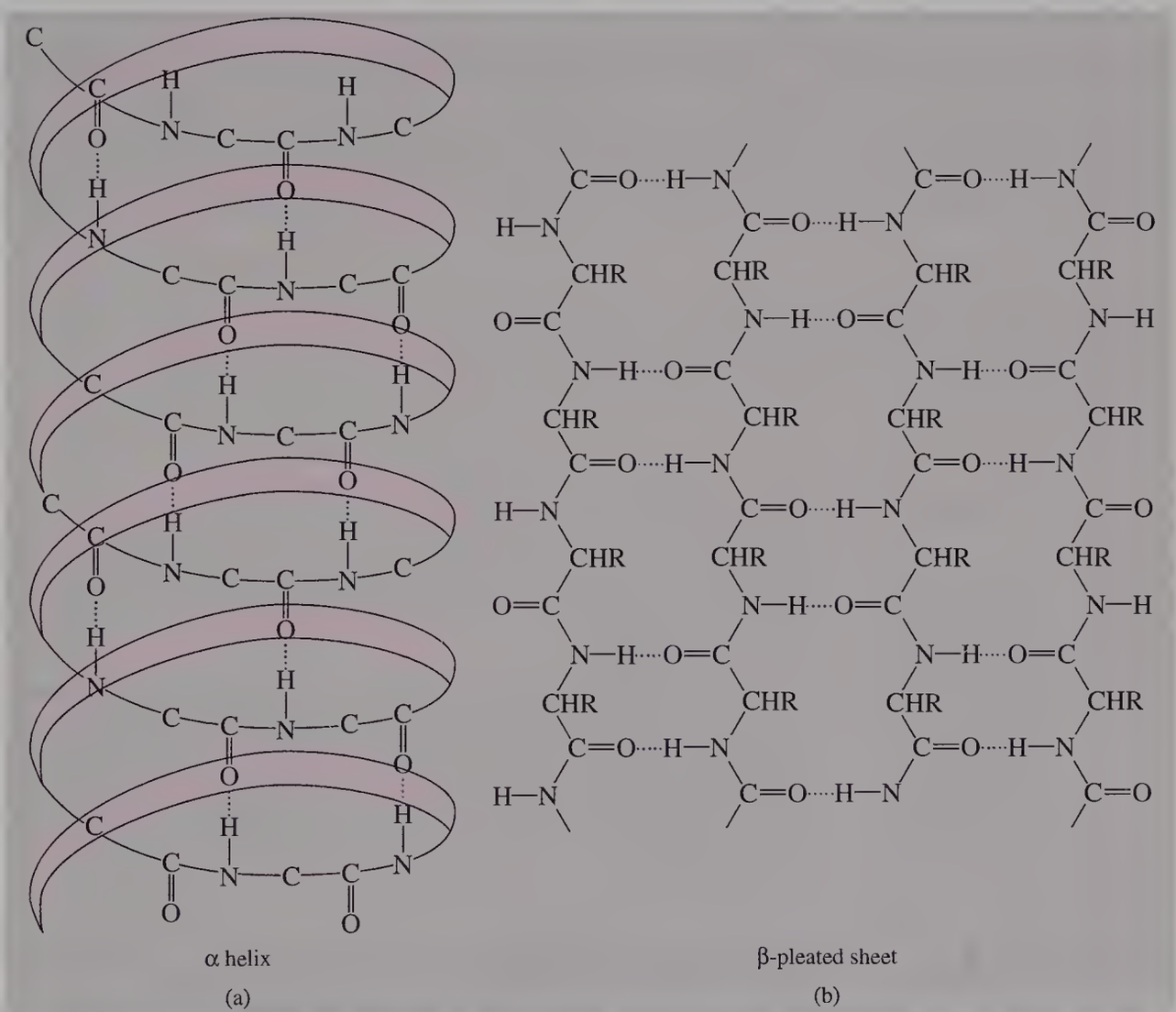


FIGURE 26.6 Hydrogen Bonding and Secondary Structure in Proteins
(a) The intramolecular hydrogen bonds between coils of the helix are shown only on the "front". This structure is found in a large variety of proteins. (b) The intramolecular hydrogen bonds between the chains of proteins cause a regular pleated or partially folded structure. This type of structure is found in the proteins of silk, fibrin, myosin, and keratin.

Tertiary Structure

The folded three-dimensional conformation of a protein constitutes its **tertiary structure**. The tertiary structure of a protein results from noncovalent interactions among the side chains of amino acid residues that are far apart in the polypeptide chain. Two amino acid residues separated by many intervening amino acids in the primary structure may actually lie close together in the folded structure. The proximity of amino acids in the tertiary structure determines the activity of many enzymes. The three-dimensional folded shape of proteins (Figure 26.7) is entirely determined by the primary structure.

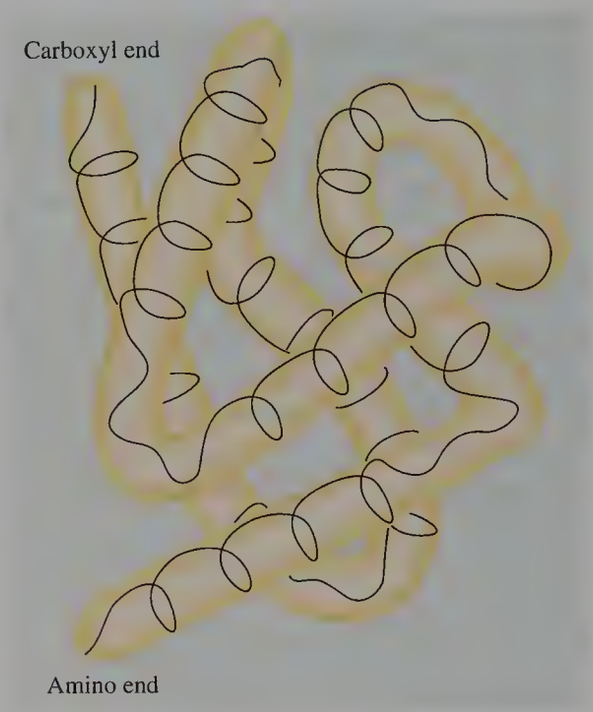


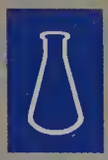
FIGURE 26.7
Tertiary Structure of a Protein
The helix is shown as a coil within the volume occupied by the protein.

When a protein assumes its native tertiary structure, hydrophobic residues tend to associate within the interior of the folded structure. Polar or charged (hydrophilic) groups tend to be located at the surface near water molecules. Thus, the conformation of a protein results from a balance among the different kinds of noncovalent bonds.

Because the tertiary structure of a protein depends upon its primary structure, any changes in the primary structure can disrupt the tertiary structure and destroy biological activity. Changes in the primary structure result from changes in the gene coding for the protein. Several genetic diseases are caused by a mutation that changes a single amino acid residue in a protein that contains hundreds of amino acids.

Quaternary Structure

Some proteins exist as assemblies of two or more polypeptide chains that interact only by noncovalent forces. These proteins, called oligomers, are said to have a **quaternary structure**. Thus, the quaternary structure of a protein is the organization or the association of several protein chains or subunits into a closely packed arrangement. Each subunit has its own primary, secondary, and tertiary structure.



Hemoglobin Structure and Function

There are 141 and 146 amino acids in the α and β chains of hemoglobin, respectively. In some people the sixth amino acid from the N-terminal end of the β chain is valine rather than glutamic acid. This difference of a single amino acid out of 146 in the chain changes the hemoglobin and leads to abnormally shaped red blood cells. The cells tend to be sickle-shaped, and as a result their passage through the blood vessels is restricted. The associated circulatory problems are known as sickle cell anemia. Other single residue mutations cause related milder diseases.

The four protein subunits of hemoglobin do not behave independently. When one heme molecule binds with one O_2 molecule, the conformation of the surrounding protein chain is slightly altered. When a change in conformation at one site of an oligomeric protein is caused by a change in a spatially separated site of the oligomer, the change is called an **allosteric effect**, and the protein is called an **allosteric protein**. Hemoglobin is an allosteric protein. When one heme group in hemoglobin binds oxygen, it is easier for successive oxygen molecules to bind at the remaining three sites. Thus, once oxygenation occurs at one heme, there is cooperation at all other sites in hemoglobin, which can then carry four oxygen molecules.

Differences in hemoglobin between species do not affect its oxygen-carrying capacity. The β chains of the gorilla and human hemoglobins are identical except for position 104. In gorillas, lysine replaces another basic amino acid, arginine, found in human hemoglobin. The pig β chain differs from human hemoglobin at 17 sites, and that of the horse at 26 sites. However, nine positions contain the same amino acids in all hemoglobin molecules. These positions are important to the oxygen-binding function of hemoglobin.

The subunits in a quaternary structure must be specifically arranged for the entire protein to function properly. Any alteration in the structure of the subunits or the way in which the subunits are associated results in marked changes in biological activity. A list of some proteins that have quaternary structure is given in Table 26.8.

Table 26.8
Proteins with Quaternary Structure

Protein	*Molecular weight*	*Number of subunits*	*Function*
alcohol dehydrogenase	80,000	4	enzyme of alcohol fermentaion
aldolase	150,000	4	enzyme for glycolysis
fumarase	194,000	4	enzyme in the citric acid cycle
hemoglobin	65,000	4	oxygen transport in blood
insulin	11,500	2	hormone regulating metabolism of glucose

One example of a protein with a quaternary structure is hemoglobin. Hemoglobin consists of two pairs of different proteins, designated the α and the β chains. Each is linked covalently to a molecule of heme. Heme is the site in hemoglobin at which a single O_2 molecule binds. The two identical α chains and the two identical β chains are arranged tetrahedrally in a three-dimensional structure (Figure 26.8). These units are held together by hydrophobic interactions, hydrogen bonding, and salt bridges between oppositely charged amino acid side chains.

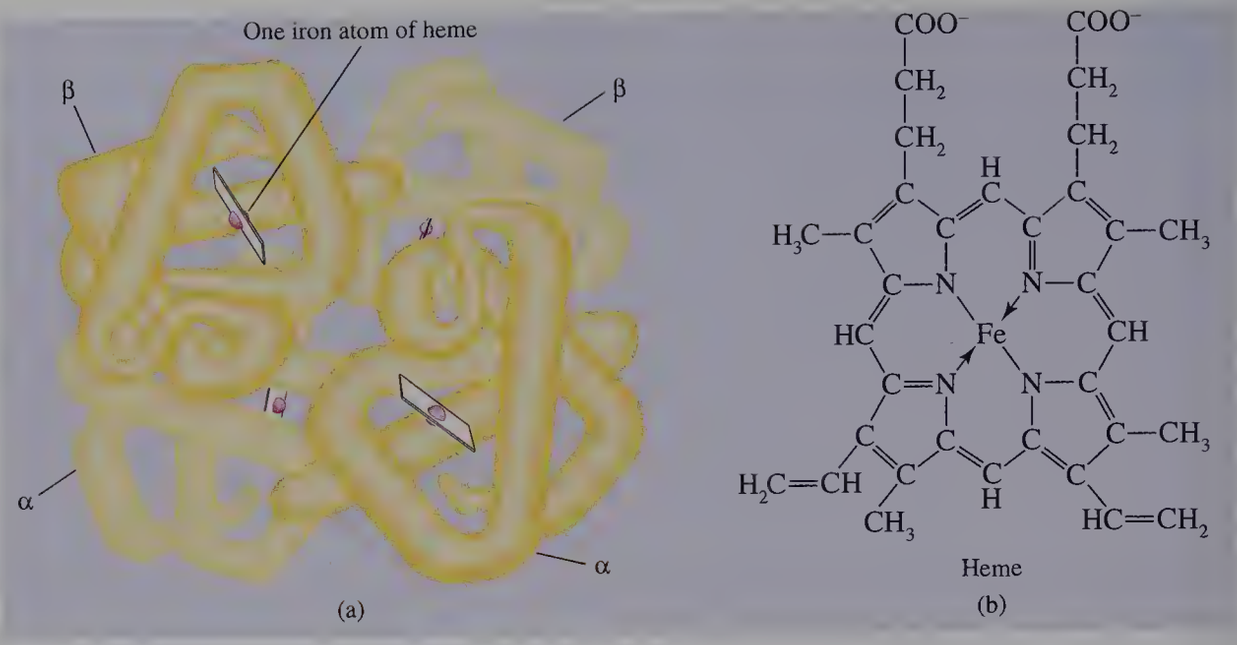


FIGURE 26.8 Quaternary Structure of Hemoglobin
(a) The iron atoms of the heme are shown as spheres within the folds of the four protein chains. Heme is shown by the plane around the iron atom.
(b) The structure of heme.

EXERCISES

Amino Acids

26.1 D-Glutamic acid is found in bacterial cell walls. Draw its projection formula.

26.2 Gramicidin S is a cyclic peptide antibiotic that contains D-phenylalanine. Draw the projection formula of D-phenylalanine.

26.3 The following compound is an amino acid found in collagen. From what amino acid could this compound be derived?

$$NH_2—CH_2—\underset{\displaystyle OH}{\underset{|}{CH}}—CH_2—CH_2—\underset{\displaystyle NH_2}{\underset{|}{CH}}—CO_2H$$

26.4 The following antibacterial agent is contained in garlic. From what amino acid might it be derived?

$$CH_2{=}CH—CH_2—\overset{\displaystyle O}{\overset{\|}{S}}—CH_2—\underset{\displaystyle NH_2}{\underset{|}{CH}}—CO_2H$$

26.5 The following compound is an unusual amino acid that functions as a neurotransmitter. Classify this amino acid, and determine its IUPAC name.

$$NH_2—CH_2—CH_2—CH_2—CO_2H$$

26.6 The following compound is one of the amino acids formed in the biosynthesis of penicillin. Classify this amino acid, and determine its common name.

$$HO_2C—\underset{\displaystyle NH_2}{\underset{|}{CH}}—CH_2—CH_2—CH_2—CO_2H$$

Acid–Base Properties

26.7 Draw the structures of alanine and glutamic acid at pH = 1 and pH = 12.

26.8 Draw the structures for the zwitterions of serine and valine.

26.9 How could you distinguish between aqueous solutions of asparagine and aspartic acid?

26.10 Would you expect an aqueous solution of lysine to be neutral, acidic, or basic? Explain.

26.11 One of the pK_a values of tyrosine is 9.11. What functional group is responsible for this acidic hydrogen atom?

26.12 One of the pK_a values of cysteine is 8.33. What functional group is responsible for this acidic hydrogen atom?

26.13 Explain why the pK_a for the $-NH_3^+$ group of tyrosine is slightly smaller than the corresponding pK_a of phenylalanine.

26.14 Explain why the pK_a for the side chain $-CO_2H$ group of aspartic acid is smaller than the corresponding pK_a of glutamic acid.

26.15 Explain why the difference between the pK_a values of aspartic acid and asparagine is larger than the difference between the pK_a values of glutamic acid and glutamine.

26.16 Consider the amino and imino nitrogen atoms of the side chain of arginine. Which one would be protonated in acid solution? How can resonance stabilization account for the site of protonation.

Isoionic Points

26.17 Estimate the isoionic points of the following tripeptides.
(**a**) Ala-Val-Gly (**b**) Ser-Val-Asp (**c**) Lys-Ala-Val

26.18 Estimate the isoionic points of the following tripeptides.
(**a**) Glu-Val-Ala (**b**) Arg-Val-Gly (**c**) His-Ala-Val

26.19 Examine the structures of oxytocin and vasopressin in Section 26.7. Which should have the higher isoionic point?

26.20 Examine the structure of the enkephalin given in Section 26.11 and estimate its isoionic point.

26.21 The isoionic point of chymotrypsin is 9.5. What does this value indicate about the composition of chymotrypsin?

26.22 The isoionic point of pepsin is 1.1. What does this value indicate about the composition of pepsin?

Synthesis of Amino Acids

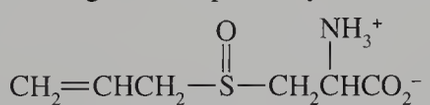
26.23 What haloalkane is required to synthesize isoleucine by the acetamidomalonate method? What side reaction might decrease the yield?

26.24 What reactants are required to synthesize phenylalanine by reductive amination?

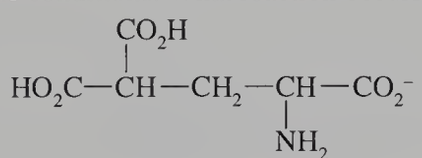
26.25 Alanine can be prepared by a conjugate addition reaction using acrylonitrile ($CH_2{=}CH{-}C{\equiv}N$). What other reactant is required? What other type of reaction could compete with this process? Why is the indicated reaction favored?

26.26 Methionine can be prepared from propenal in a multistep sequence. Explain how the thiomethyl group is introduced and how the carbon chain is increased by one additional carbon atom.

26.27 Alliin is an unusual amino acid contained in garlic. Propose a synthesis of alliin starting from an amino acid.



26.28 One of the amino acids in the blood-clotting protein prothrombin is shown below. It was difficult to detect because it decomposes under hydrolysis conditions. What reaction occurs and what is the product?



Polypeptides

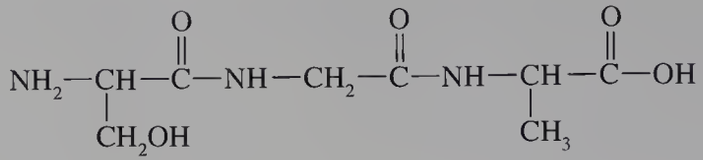
26.29 Write the complete formula and the condensed formula for alanylserine.

26.30 How does glycylserine differ from serylglycine?

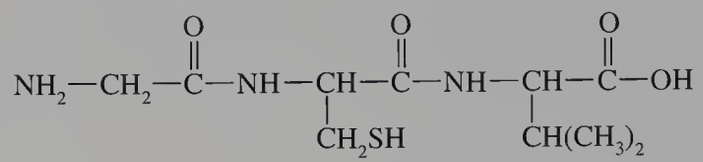
26.31 Which amino acids can form peptides with carboxyl groups or carboxylate groups at internal positions in the peptide chain?

26.32 Which amino acids can form peptides with amino groups or ammonium groups at internal positions in the peptide chain?

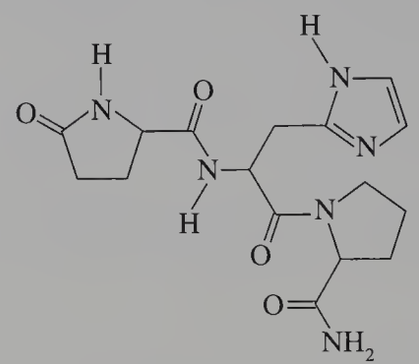
26.33 Identify the amino acids contained in the following tripeptide. Name the compound.



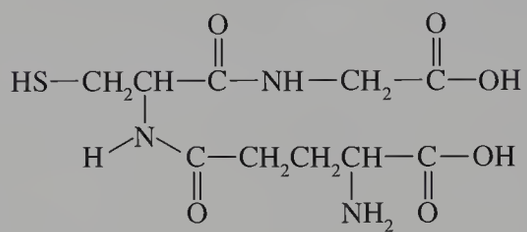
26.34 Identify the amino acids contained in the following tripeptide. Name the compound.



26.35 Thyrotropin-releasing hormone (TRH) causes the release of thyrotropin from the pituitary gland, which then stimulates the thyroid gland. Examine its structure and comment on one unusual structural feature.



26.36 The tripeptide glutathione, which is important in detoxifying metabolites, has an unusual structural feature. Identify it.



26.37 How many isomeric compounds with the composition Gly_2,Ala_2 exist?

26.38 How many isomeric compounds with the composition Gly_2,Ala,Leu exist?

Hydrolysis and Structure Determination

26.39 Assuming that only dipeptides are formed by partial hydrolysis, what is the minimum number that must be identified to establish the structure of a pentapeptide?

26.40 Assuming that only tripeptides are formed by partial hydrolysis, what is the minimum number that must be identified to establish the structure of an octapeptide?

26.41 The tetrapeptide tuftsin is hydrolyzed to produce Pro-Arg and Thr-Lys. Does this information establish the structure of tuftsin?

26.42 Assume that the octapeptide angiotensin II is hydrolyzed to produce Pro-Phe, Val-Tyr-Ile, Asp-Arg-Val, and Ile-His-Pro. What is its structure?

26.43 Treatment of somatostatin with the Edman reagent gives a derivative of alanine. Partial hydrolysis of the polypeptide gives the following oligopeptides. Write the structure of the polypeptide.

I: Phe-Trp II: Lys-Thr III: Thr-Ser-Cys IV: Thr-Phe-Thr-Ser-Cys

V: Asn-Phe-Phe-Trp-Lys VI: Ala-Gly-Cys-Lys-Asn-Phe

26.44 Treatment of bradykinin with an aminopeptidase yields arginine. The composition of the peptide is (Arg_2,Gly,Phe_2,Pro_3,Ser). Partial hydrolysis yields several fragments that include the following oligopeptides. Write the structure of bradykinin.

I: Gly-Phe-Ser II: Arg-Pro-Pro-Gly III: Phe-Arg-Ser-Pro-Phe

Enzymatic Hydrolysis

26.45 Which of the following tripeptides will be cleaved by trypsin? If cleavage occurs, name the products.

(**a**) Arg-Gly-Tyr (**b**) Glu-Asp-Gly (**c**) Phe-Trp-Ser (**d**) Ser-Phe-Asp

26.46 Which of the following tripeptides will be cleaved by trypsin? If cleavage occurs, name the products.

(**a**) Asp-Lys-Ser (**b**) Lys-Tyr-Cys (**c**) Asp-Gly-Lys (**d**) Arg-Glu-Ser

26.47 Indicate which of the tripeptides in Exercise 26.45 will be cleaved by chymotrypsin and name the products.

26.48 Indicate which of the tripeptides in Exercise 26.46 will be cleaved by chymotrypsin and name the products.

26.49 The tetrapeptide tuftsin is hydrolyzed by trypsin to produce Pro-Arg and Thr-Lys. Does this information establish the structure of tuftsin?

26.50 The pentapeptide met-enkephalin is hydrolyzed by chymotrypsin to give Met, Tyr, and Gly-Gly-Phe. Does this information establish the structure of met-enkephalin?

26.51 The nonapeptide known as the sleep peptide is hydrolyzed by chymotrypsin to produce Ala-Ser-Gly-Glu and Ala-Arg-Gly-Tyr and Trp. What two structures are possible for the sleep peptide?

26.52 The sleep peptide is hydrolyzed by trypsin to produce Gly-Tyr-Ala-Ser-Gly-Glu and Trp-Ala-Arg. What is the structure of the sleep peptide?

26.53 Feline gastrin, a hormone that stimulates secretion of gastric juice in cats, has the amino acid composition (Ala_2,Asp,Gly_2,Glu_5,Leu,Met,Phe,Pro,Trp_2,Tyr). End group analysis shows that the C-terminal and N-terminal amino acids are Phe and Glu, respectively. Hydrolysis with chymotrypsin yields the following four peptides. Write two possible structures of feline gastrin.

I: Gly-Trp II: Met-Asp-Phe III: Glu-Gly-Pro-Trp IV: Leu-Glu-Glu-Glu-Glu-Ala-Ala-Tyr

26.54 Corticotropin, a pituitary hormone, stimulates the adrenal cortex. Hydrolysis by chymotrypsin yields six peptides:

I: Arg-Trp II: Ser-Tyr III: Ser-Met-Glu-His-Phe IV: Pro-Leu-Glu-Phe

V: Pro-Asp-Ala-Gly-Glu-Asp-Gln-Ser-Ala-Glu-Ala-Phe

VI: Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Pro-Val-Lys-Val-Tyr

Hydrolysis by trypsin produces lysine, arginine, and five peptides:

I: Trp-Gly-Lys II: Pro-Val-Gly

III: Pro-Val-Gly-Lys IV: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg

V: Val-Tyr-Pro-Asp-Ala-Gly-Glu-Asp-Gln-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe

Write the structure of corticotropin.

End Group Analysis

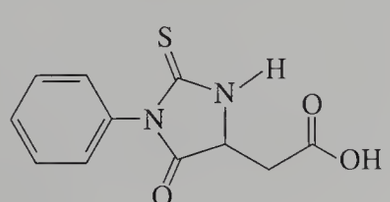
26.55 Hydrolysis of tuftsin with an aminopeptidase yields Thr. Using the information in Exercise 26.49, what is the structure of tuftsin?

26.56 Hydrolysis of met-enkephalin with a carboxypeptidase yields Met. Using the information in Exercise 26.50, what is the structure of met-enkephalin?

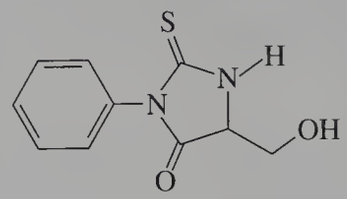
26.57 A structure determination of insulin using the Edman method yields two phenylthiohydantoin products. Why?

26.58 Cholecystokinin, a 33-peptide, plays a role in reducing the desire for food, and its production is stimulated by food intake. Its N-terminal amino acid is lysine. Draw the structure of the phenylthiohydantoin product.

26.59 Reaction of angiotensin II with the Edman reagent yields the following product. What information has been established?



26.60 Corticotropin is released when the blood level of corticosteroids is diminished. Reaction of corticotropin with the Edman reagent yields the following product. What information has been established?



Proteins

26.61 Which of the following amino acids are likely to exist in the interior of a protein dissolved in an aqueous solution?
(**a**) glycine (**b**) phenylalanine (**c**) glutamic acid (**d**) arginine

26.62 Which of the following amino acids are likely to exist in the interior of a protein dissolved in an aqueous solution?
(**a**) proline (**b**) cysteine (**c**) glutamine (**d**) aspartic acid

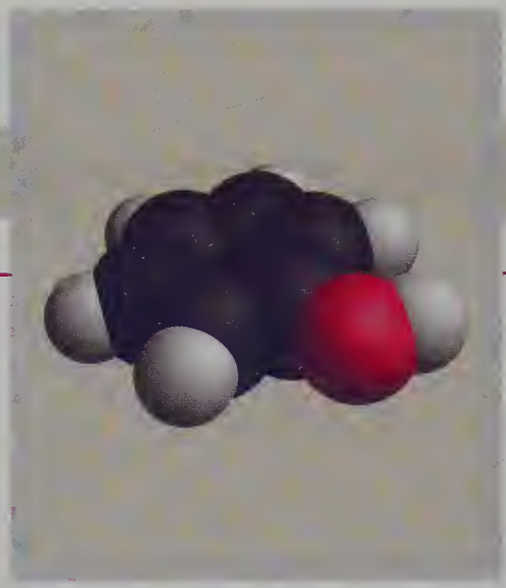
26.63 If a protein is embedded in a lipid bilayer, which of the amino acids listed in Exercise 26.61 will be in contact with the interior of the bilayer?

26.64 If a protein is embedded in a lipid bilayer, which of the amino acids listed in Exercise 26.62 will be in contact with the interior of the bilayer?

26.65 Noting that proline is a secondary amine, explain how proline can disrupt the α helix of a protein.

26.66 Examine the structures of valine and glutamic acid and suggest a reason why human hemoglobin is affected by the substitution of valine for glutamic acid at position 6 in the β chain.

27



Aryl Halides, Phenols, and Anilines

27.1 Properties of Aromatic Compounds

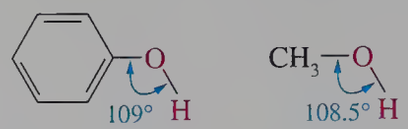
In Chapter 8 we considered alcohols and haloalkanes (alkyl halides). The chemistry of these compounds, which includes nucleophilic substitution and elimination reactions, is governed by a C—O or C—X bond of an sp^3-hybridized carbon atom. In Chapter 25, we presented the chemistry of alkylamines. These compounds undergo substitution reactions at the nitrogen atom rather than the carbon atom. They undergo elimination reactions with difficulty.

Substituents, such as a halogen atom, hydroxyl group, or amino group bonded to an sp^2-hybridized carbon atom, have very different chemistry than they do in alkyl halides, alcohol, and alkylamines. We recall that nonbonded electron pairs of electronegative atoms bonded directly to aromatic rings affect the rate of electrophilic aromatic substitution reactions (Section 14.5). The second period elements nitrogen and oxygen can donate nonbonded electron pairs to the aromatic ring. Chlorine, a third period element, is a far less effective donor of electrons by resonance. And so, if we now change our focus from the aromatic ring to the substituent itself, we should expect to see some modification of the properties of C—X, C—O, and C—N bonds. In this chapter, we examine the special chemical reactivity that results from bonding between an aryl carbon atom and a halogen atom, hydroxyl group, or amino group.

Bonding and Structure

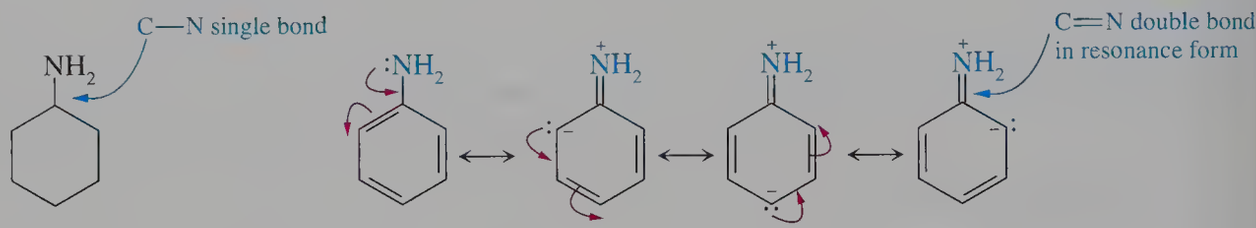
The carbon–halogen bond of an aryl halide is slightly shorter than the carbon–halogen bond of an alkyl halide. This decrease in bond length results from a larger percent *s* character in the sp^2 hybrid orbital of the aryl carbon atom compared to the sp^3 hybrid orbital of an alkyl carbon atom. The aryl–chlorine bond dissociation energy (407 kJ $mole^{-1}$ for carbon–chlorine) is substantially larger than the bond dissociation energy for a typical alkyl–chlorine bond (340 kJ $mole^{-1}$). This very high bond energy accounts in part for the different reactivities of aryl and alkyl halides.

The carbon–oxygen bond lengths of phenols and alcohols are 136 and 142 pm, respectively. Again, the C—O bond of a phenol is shorter because of the increased *s* character of the sp^2-hybridized carbon atom, which draws electrons closer to the carbon nucleus. The geometry around the oxygen atom of phenols is essentially the same as that in alcohols. The C—O—H angle has the tetrahedral angle of 109°.

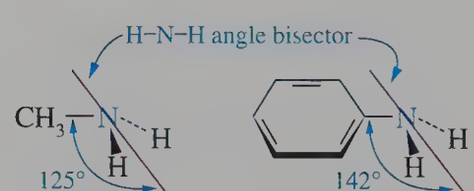


phenol methanol

The groups around nitrogen in arylamines form a shallower pyramid than do the groups in alkylamines. Also, the carbon–nitrogen bond in arylamines (140 pm) is shorter than that in alkylamines (147 pm). The shortened bond length results from the double bond character of the carbon–nitrogen bond, depicted in the resonance forms of aniline. In these resonance forms, the lone pair electrons of nitrogen are delocalized into the benzene ring.



In this molecule two opposing forces balance, producing a stable structural compromise. The most effective overlap between the nitrogen orbital and those of the aromatic ring would occur if the lone pair electrons occupied a pure *p* orbital. This would maximize resonance stabilization. The bonded pairs would then occupy sp^2 hybrid orbitals, and all atoms bonded to the nitrogen atom would be in a plane. However, nitrogen would pay a price to adopt this hybridization. The lone pair electrons in a *p* orbital would move farther from the nitrogen nucleus as a result of resonance stabilization. Nitrogen is very electronegative, and it attracts electrons toward its nucleus most effectively by using an sp^3 hybrid orbital. An sp^3 hybrid orbital allows nitrogen to best keep its electrons close, but it can contribute little in resonance stabilization. The compromise is a hybridization for the nitrogen orbital with somewhat more *p* character than the 75% of an sp^3 hybrid orbital. The angle between the C—N bond and a line bisecting the H—N—H bond angle provides evidence of this compromise.



methylamine aniline

The angle is larger for aniline, resulting in a flattened pyramid. If the unshared pair of electrons of nitrogen occupied a *p* orbital, the atoms bonded to nitrogen would lie in a plane and the angle would be 180°.

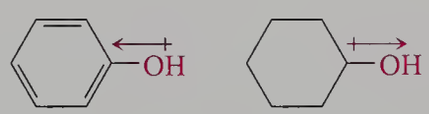
Bond Polarity

The bond polarities of aryl–halogen and aryl–oxygen bonds compared to those in alkyl halides and alcohols provides a measure of the effect of the sp^2 hybrid orbital on the σ bond and of the resonance interactions between the nonbonded electrons of the substituent and the aromatic ring. The dipole moment of chlorobenzene is smaller than the dipole moment of chlorocyclohexane.

chlorobenzene (1.7 D) chlorocyclohexane (2.2 D)

This difference indicates that electron density in the σ bond is not "pulled" as strongly toward the chlorine atom in chlorobenzene as in chlorocyclohexane. The higher *s* character of the sp^2-hybridized carbon atom of chlorobenzene makes it more electron attracting than an sp^3-hybridized carbon atom. Thus, the electronegativity difference between carbon and chlorine is smaller for an sp^2-hybridized carbon atom than for an sp^3-hybridized carbon atom.

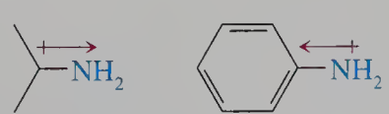
The magnitude of the dipole moment of phenol is also slightly less than that of cyclohexanol, its cycloalkyl counterpart, but in the opposite direction. The oxygen atom is the positive end of this dipole.



phenol (1.5 D) cyclohexanol (1.7 D)

The sp^2-hybridized carbon atom of a phenol also pulls the bonding electrons of the C—O bond toward the ring, an effect similar to that which accounts for the decreased polarity of chlorobenzene compared to chlorocyclohexane. However, the reversal of net polarity results from donation of nonbonded electrons of oxygen by resonance to the aromatic ring.

The dipole moments of alkylamines are in the expected direction—that is, the negative end of the dipole is toward the more electronegative nitrogen atom. However, again as in the case of phenols, the dipole moments of arylamines are opposite in direction. The nitrogen atom is the positive end of the dipole.



isopropylamine (1.3 D) aniline (1.3 D)

The electrons in the C—N σ bond are pulled closer to the sp^2-hybridized carbon of aniline than to the sp^3-hybridized carbon atom of methylamine. But the effective π donation of lone pair electrons of nitrogen to the aromatic ring decreases the electron density at the nitrogen atom.

Problem 27.1

The dipole moment of toluene is 0.4 D. Predict the direction of this dipole. The dipole moment of *p*-fluorotoluene is 2.0 D. Predict the dipole moment of fluorobenzene.

27.2 Acid–Base Properties

We have discussed the effect of structure on the acidity of alcohols and on the basicity of amines. The acid–base properties of their aromatic cousins, phenols and anilines, are affected by the aromatic ring. Both the pK_a values of phenols and the pK_b values of anilines illustrate this effect.

Phenols

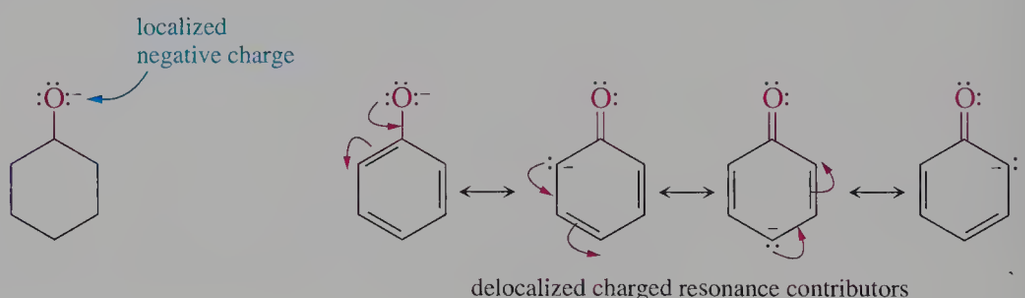
Phenols have pK_a values between those of alcohols and carboxylic acids. The pK_a value of phenol is 10.

$$R{-}O{-}H + H_2O \rightleftharpoons R{-}O^- + H_3O^+ \qquad pK_a = 17$$

$$Ar{-}O{-}H + H_2O \rightleftharpoons Ar{-}O^- + H_3O^+ \qquad pK_a = 10$$

$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O{-}H + H_2O \rightleftharpoons R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O^- + H_3O^+ \qquad pK_a = 5$$

Phenol is more acidic than cyclohexanol and acyclic alcohols because the phenoxide ion is more stable than the alkoxide ion. In an alkoxide ion, the negative charge is localized at the oxygen atom. But in a phenoxide ion, the negative charge is delocalized over the benzene ring. Phenoxide ion is therefore resonance stabilized.



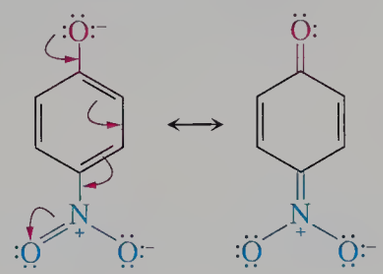
Phenols are weaker acids than carboxylic acids even though there is delocalization of charge over the aromatic ring of the phenoxide ion. The carboxylate ion is more stabilized relative to the phenoxide ion because the negative charge is located on the oxygen atoms of the carboxylate ion. In the phenoxide ion some of the charge is located on the less electronegative carbon atom. Therefore, the resonance stabilization of a carboxylate ion is more effective, and carboxylic acids are stronger acids than phenols.

The pK_a values of substituted phenols are listed in Table 27.1. Although the pK_a values increase for electron-donating groups such as *p*-methyl or *p*-methoxy, the decrease in acidity is less than a factor of 2 in K_a. Electron-withdrawing groups cause a substantial increase in the K_a of phenols.

Table 27.1
pK_a of Substituted Phenols

Substituent	*Ortho*	*Meta*	*Para*
H	10.00	10.00	10.00
bromo	8.42	8.87	9.26
chloro	8.48	9.02	9.38
cyano			7.95
methoxy	9.98	9.65	10.21
methyl	10.29	10.09	10.26
nitro	7.22	8.39	7.15

The nitro group causes the largest increase in K_a; *p*-nitrophenol is almost 1000 times as acidic as phenol. The acidity increases because delocalization of the negative charge onto the oxygen atoms of the nitro group stabilizes the conjugate base.



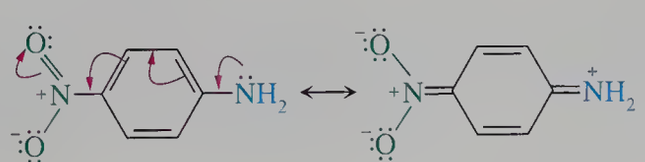
Anilines

Aryl-substituted amines are much weaker bases than ammonia and alkyl-substituted amines. Their K_b values are less than 10^{-9}. For example, the K_b value of aniline is 10^{-6} times smaller than the K_b value for cyclohexylamine. Aryl-substituted amines are weaker bases than ammonia because the unshared pair of electrons of the nitrogen atom is resonance delocalized over the π orbital system of the benzene ring. As a result, the unshared electron pair of nitrogen is less available for bonding with a proton. (The pK_b values of substituted anilines are given in Table 27.2.)

Table 27.2
pK_b of Substituted Anilines

Substituent	*Ortho*	*Meta*	*Para*
H	9.40	9.40	9.40
bromo	11.47	10.42	10.14
chloro	11.35	10.48	10.02
cyano	13.05	11.25	12.26
methoxy	9.48	9.77	8.66
methyl	9.56	9.28	8.90
nitro	14.26	11.53	13.00
trifluoromethyl		10.80	11.25

Electron-donating groups increase the basicity of aniline by a small amount. Electron-withdrawing groups, such as nitro and cyano, decrease the basicity by substantially larger amounts because the lone pair electrons of the amine can be delocalized into the substituent group.



Problem 27.2

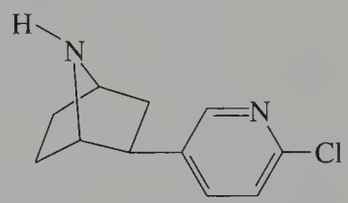
Explain why *m*-nitrophenol is a weaker acid than *p*-nitrophenol but is still a stronger acid than phenol.

Sample Solution

As a result of the formal positive charge of the nitrogen atom, the nitro group is inductively electron withdrawing. In the meta position, the nitro group stabilizes the phenoxide ion by withdrawal of electron density. The stabilization of the conjugate base increases the acidity of the phenol. Although located at a greater distance, the para nitro group is even more effective in stabilizing the conjugate base but not as a result of an inductive effect. In the para position, the nitro group can delocalize the negative charge of the phenoxide ion to the two oxygen atoms. Resonance stabilization of the phenoxide ion by a meta nitro group is not possible.

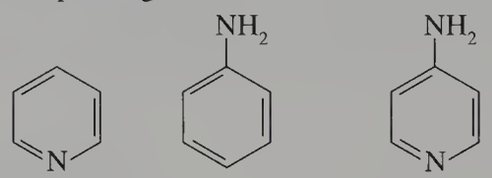
Problem 27.3

Estimate the pK_b values for both basic sites in the following compound, which is a poison secreted by an Ecuadoran frog.



Problem 27.4

The pK_b values of pyridine and aniline are similar, but the pK_b of 4-aminopyridine is much smaller. Which of the two nitrogen atoms of 4-aminopyridine is more basic? Why is it more basic that the corresponding site in one of the reference compounds?



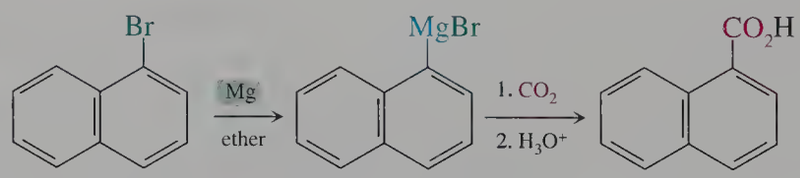
pyridine
$pK_b = 8.7$

aniline
$pK_b = 9.4$

4-aminopyridine
$pK_b = 4.9$

27.3 Formation of Organometallic Reagents

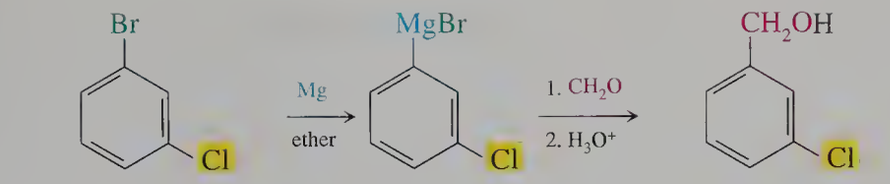
Aryl bromides react with magnesium to form Grignard reagents, which undergo the same reactions with carbonyl compounds as alkyl Grignard reagents.



1-bromonaphthalene

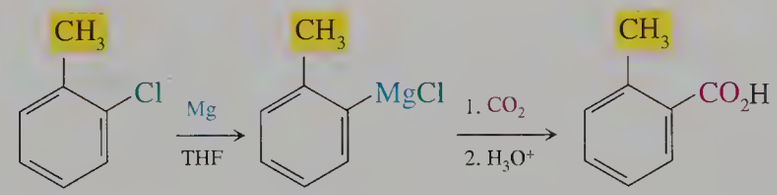
1-naphthoic acid

Aryl chlorides do not form Grignard reagents when ether is the solvent. As a result, an aromatic compound substituted with both bromine and chlorine can be selectively converted into a Grignard reagent at the site of the bromine atom.



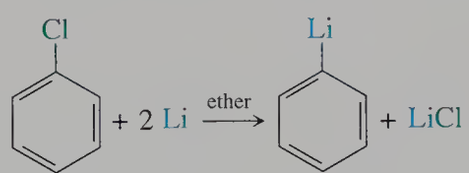
1-bromo-3-chlorobenzene — 3-chlorobenzyl alcohol

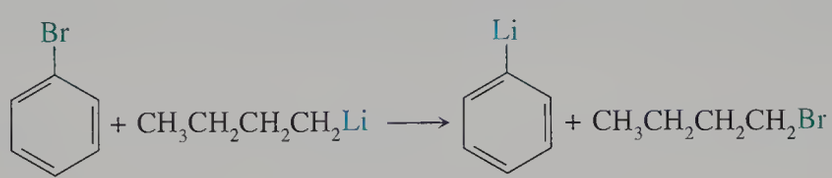
Aryl chlorides are converted into Grignard reagents when tetrahydrofuran is the solvent. Once formed, the Grignard reagents show normal reactivity toward compounds such as carbon dioxide.



2-chlorotoluene — 2-methylbenzoic acid

Aryllithium reagents can be prepared by direct reaction of an aryl chloride or bromide with lithium metal. These reagents may also be prepared by a transmetallation reaction of an aryl bromide or iodide with an alkyllithium reagent such as butyllithium.





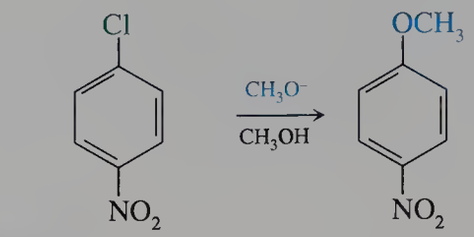
27.4 Nucleophilic Aromatic Substitution

We recall that nucleophilic substitution reactions at sp^3-hybridized centers are easily classified using S_N2 and S_N1 mechanisms. These two mechanisms encompass a wide range of substrate structures, nucleophiles, and leaving groups. Nucleophilic substitution of aryl halides can occur, but only on a limited number of aromatic compounds. Also, neither S_N1 nor S_N2 mechanisms account for the characteristics of the reactions. The S_N2 process does not occur because the aromatic ring prevents the approach of a nucleophile from the side opposite that of the carbon–halogen bond. The S_N1 process is not favored because the formation of an sp^2-hybridized carbocation requires more energy than formation of an sp^3-hybridized carbocation.

Nucleophilic substitution of aromatic compounds occurs by two different, multiple-step mechanisms, termed **addition–elimination** and **elimination–addition**. Although similarly named, the mechanisms are different and result from different reactant structures and reaction conditions.

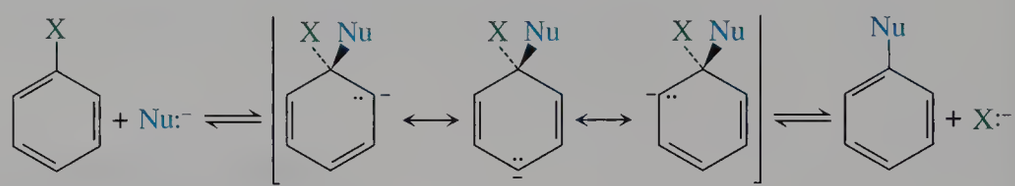
Addition–Elimination

Aryl halides with a strong electron-attracting group ortho or para to the halogen are substituted by nucleophiles such as hydroxide, alkoxides, ammonia, and amines. Suitable groups that facilitate the reaction and their effect on reactivity are nitro > cyano > carbonyl. The reactions occur under relatively mild conditions.

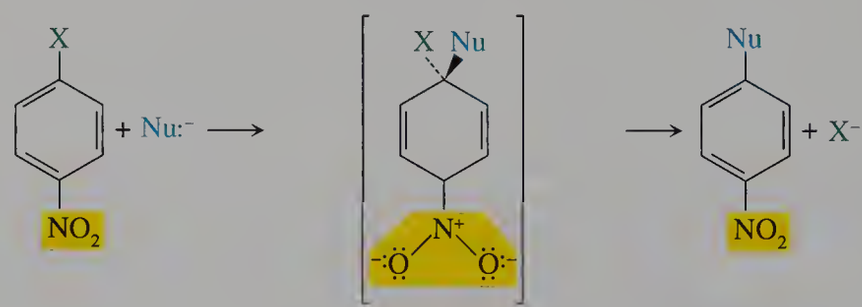


p-nitrochlorobenzene *p*-nitroanisole

The mechanism is similar to the addition–elimination mechanism of acyl derivatives in which a tetrahedral intermediate forms. The addition step is a nucleophilic attack that yields a resonance-stabilized cyclohexadienyl anion. The anion can then eject the nucleophile or a leaving group in the elimination step.



The initial addition step occurs only if the ring has a substituent that can stabilize the negative charge of the intermediate. The substituent must be ortho or para to the site of the reaction. For example, a *p*-nitro group is effective because the negative charge can be distributed to its two oxygen atoms.



resonance-stabilized intermediate

Because the electron-withdrawing nitro group anion stabilizes the anion intermediate, we say that the nitro group activates the aromatic ring toward nucleophilic aromatic substitution. This statement may appear inconsistent with the properties of the nitro group in electrophilic aromatic substitution. We recall that the nitro group deactivates the aromatic ring toward attack by electrophiles. The characteristics of the nitro group have not changed. It attracts electrons from the aromatic ring in both reactions. However, its effect on the stability of the resonance-stabilized intermediate depends on the charge of the intermediate. In nucleophilic aromatic substitution, a negatively charged intermediate forms, so the nitro group stabilizes the charge. In electrophilic aromatic substitution, a positively charged intermediate forms, and the

nitro group destabilizes it. These two examples remind us that the terms "activating group" or "deactivating group" cannot be attributed to a substituent without reference to the reaction type.

The reaction rate profile for the addition–elimination mechanism is shown in Figure 27.1. The first step is rate determining. This fact is established by the order of reactivity of *p*-halonitrobenzenes: F > Cl > Br > I. We recall that the order of leaving group abilities of the halide ions is $I^- > Br^- > Cl^- > F^-$. Therefore, the second step, in which the halide ion is a leaving group, cannot be rate determining. In the elimination step, the carbon–halogen bond breaks. This step is faster than the rate-determining first step in which addition occurs.

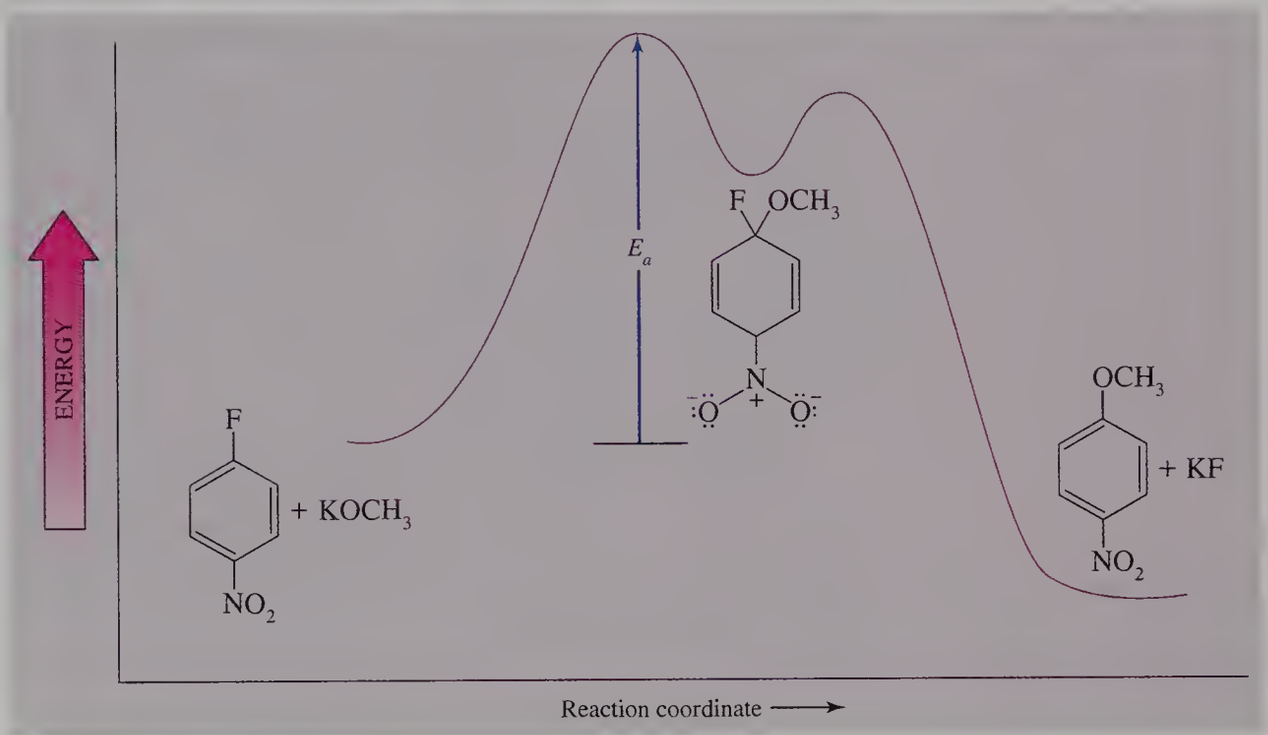
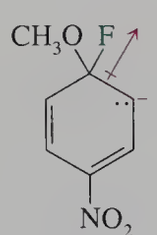


FIGURE 27.1 Addition–Elimination Reaction
The rate-determining step is the addition of the nucleophile to give a tetrahedral intermediate that then reacts in a faster second step to eliminate the leaving group.

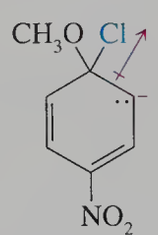
The effect of the halogen atom on the first step of the addition–elimination reaction reflects the stability of the cyclohexadienyl anion intermediate. The electronegativity of the halogen atom explains the order of reactivity of the halogen compounds. Fluorine is the most electronegative halogen, and it is most effective in stabilizing the cyclohexadienyl anion by inductive electron withdrawal.

Fluorine is very effective in withdrawing electrons.



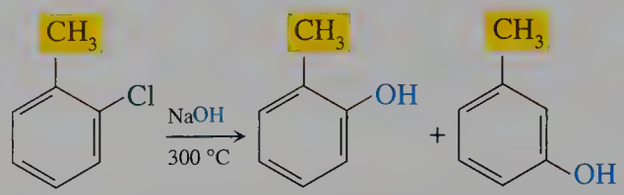
stabilized cyclohexadienyl anion

Chlorine is less effective in withdrawing electrons.

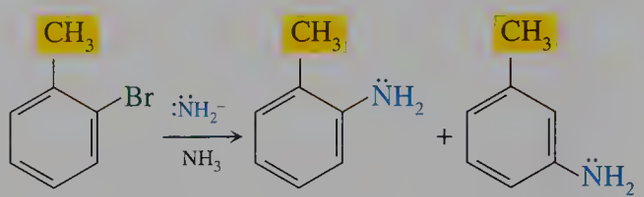


Elimination–Addition Mechanism

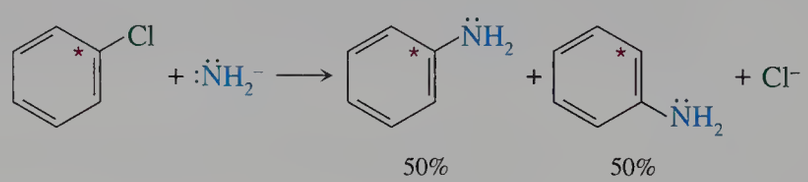
Aryl halides without strongly electron-withdrawing ring substituents undergo substitution reactions. However, the mechanism is an elimination–addition process that occurs only at high temperatures or if the nucleophile is a very strong base. For example, *o*-chlorotoluene reacts with sodium hydroxide at temperatures of about 300 °C to yield a mixture of equal amounts of *o*- and *m*-methylphenols.



Under milder conditions, a strong amide base in liquid ammonia at −33 °C yields similar products. The entering group substitutes at the position originally occupied by the halogen and at the adjacent ring position.

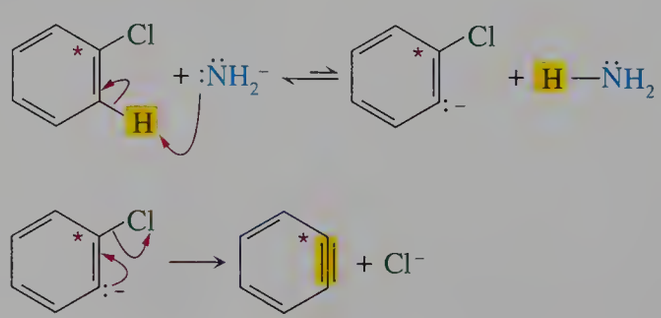


An intermediate known as benzyne, which has a triple bond, accounts for the equivalence of two carbon atoms toward the nucleophile. This intermediate was proposed on the basis of isotopic labeling studies using chlorobenzene labeled with ^{14}C at the C-1 atom. Reaction with amide ion gives a mixture of two differently labeled anilines in equal amounts. The location of the ^{14}C is shown with an asterisk in the following equation.



Half of the product has the radioactive isotope at the same carbon atom substituted in the original reactant. The other half of the product has the radioactive isotope at the carbon adjacent to the substituted carbon atom of the reactant. To account for this distribution of products, the C-1 and C-2 atoms must be equivalent in the reaction intermediate.

The first two steps in the elimination–addition mechanism generate benzyne by a deprotonation followed by loss of chloride ion. The two steps constitute the elimination part of the mechanism.



The base deprotonates a C—H bond at a position adjacent to the C—X bond because the electronegative atom slightly increases the acidity at that site by inductive withdrawal of electrons.

Benzyne is a very reactive intermediate because the "triple bond" is strained (Figure 27.2). The two atoms of an ordinary alkyne, as well as the directly bonded atoms, should be colinear. This is geometrically impossible for benzyne. Only one of the two π bonds can be accommodated by the geometry of the benzene ring. The first π bond results from the overlap of *p* orbitals perpendicular to the plane of the ring. The second π bond forms from overlap of sp^2 hybrid orbitals that are in the same plane as that of the benzene ring. The orbitals that contribute this π bond are not parallel, so less overlap exists in this bond compared to the overlap of 2*p* atomic orbitals of most multiple bonds.

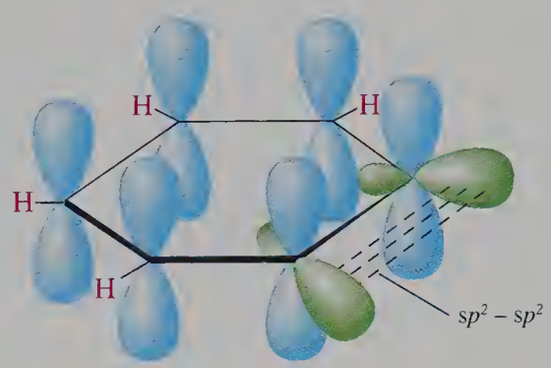
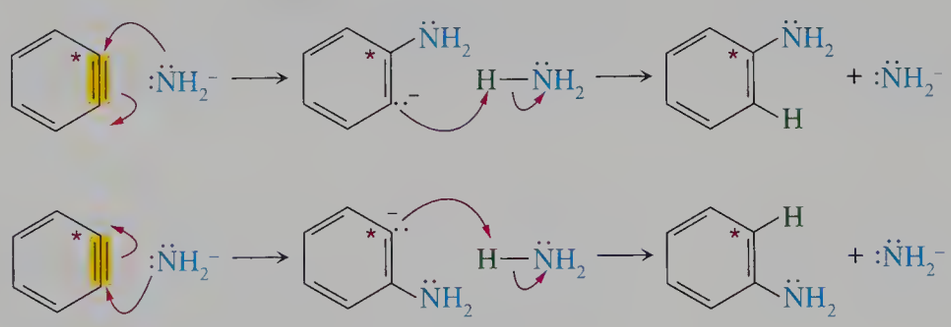


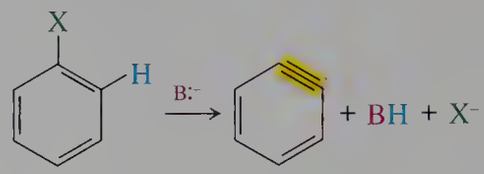
FIGURE 27.2
Structure of Benzyne
The overlap of two sp^2 hybrid orbitals to form a bond is not as efficient as the overlap of two *p* orbitals because the hybrid orbitals are not parallel.

Because of the inefficient overlap of the hybrid orbitals in the second π bond of benzyne, the bond is very reactive toward nucleophiles. Attack of a nucleophile such as amide ion can occur at either carbon atom of the triple bond. Subsequent protonation of both of the two possible anions yields the product mixture. These two steps constitute the addition portion of the mechanism.



The elimination–addition mechanism accounts for the substantial difference in the rates of reaction for hydroxide ion compared to amide ion. The reaction with hydroxide ion requires a very high temperature. The reaction with amide ion occurs at the temperature of liquid ammonia. The amide ion is a better nucleophile than hydroxide ion. However, the difference in nucleophilicities cannot explain the very large difference between their rates. The difference between the basicities of the amide ion and hydroxide ion accounts for the different rates. (The pK_a values of

NH_3 and H_2O are 35 and 15.7, respectively.) The rate of the reaction therefore depends on the elimination step.

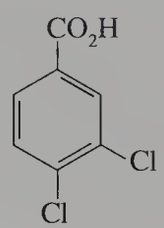


When the C—H bonds ortho to the halogen are nonequivalent, two isomeric benzyne structures form. In general, the formation of the benzynes is not regioselective. However, there may be a small preference for formation of the benzyne that results from deprotonation of the more acidic C—H bond. Note that the acidity of these bonds is affected only by the inductive effect of substituents. The electron pair of the anion occupies an sp^2 hybrid orbital. The pair cannot be delocalized in the π system because it is perpendicular to the $2p$ orbitals that form the aromatic system.

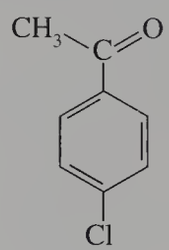
Once formed, a benzyne reacts very rapidly, and with very little regioselectivity, to give a 50:50 mixture of the two possible addition products. The only structural feature that may give a small regioselectivity is the relative stability of the two possible anions. For example, inductive electron-withdrawing substituents can stabilize the charge.

Problem 27.5

Name each of the following two compounds, which were detected in the ash from the 1980 eruption of Mt. St. Helens.



I



II

Problem 27.6

3,4-Dichloronitrobenzene reacts with only one equivalent of sodium methoxide to give an anisole derivative. What is the structure of the product? Explain why only one equivalent of sodium methoxide readily reacts.

Sample Solution

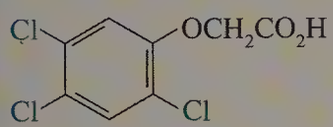
Only the 4-chloro group is replaced because the negative charge of the intermediate formed by addition of methoxide ion can be delocalized to the oxygen atoms of the nitro group. No such stabilization is possible if attack occurs at the 3 position. Thus, the 3-chloro group cannot be displaced in an addition–elimination mechanism. The product is 2-chloro-4-nitroanisole.

Problem 27.7

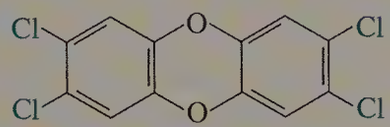
p-Bromotoluene reacts with sodium amide in liquid ammonia to give a mixture of two aniline derivatives. Draw their structures and explain the origin of the two products. Estimate the relative amounts of the two products formed.

Halogenated Aromatic Compounds—Synthetic and Naturally Occurring

Until relatively recently it was generally thought that the majority of the halogenated compounds found in the environment were the products of chemical industry. In many cases, such as the infamous dioxin, the presence of these compounds in nature was used to indict the chemical industry as a major source of the pollution of the environment with undesirable chlorinated aromatic compounds. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin) is a by-product in the production of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) from 2,4,5-trichlorophenol if the reaction is not carefully controlled.



2,4,5-trichlorophenoxyacetic acid

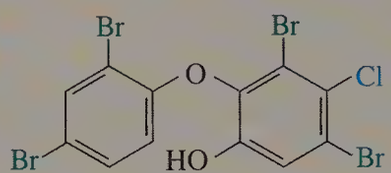


2,3,7,8-tetrachlorodibenzo-*p*-dioxin

In 1976 an industrial accident in Sevesco, Italy, led to the release of an estimated 100 pounds of dioxin into the atmosphere, and it was deposited in the local environment. Dioxin is a poison to some animals but apparently not to humans.

In the last decade it has become increasingly apparent that chlorinated aromatic compounds are very prevalent in nature and were there prior to the development of industrial processes. Dioxins have been found in soil samples collected over a century ago. It now appears that dioxins and structurally similar chlorinated aromatic hydrocarbons are formed by natural processes in amounts far exceeding industrial production. For example, chlorinated phenols are classified by the Environmental Protection Agency (EPA) as Priority Pollutants. However, chlorinated phenols are produced by a wide range of species. 2,4-Dichlorophenol is produced by the soil fungus of the genus *Penicillium*. Grasshoppers secrete 2,5-dichlorophenol, which is a repellant to ants. The female Lone Star tick releases 2,6-dichlorophenol as a sex attractant.

Even the infamous dioxin is more natural than once thought. A closely related "predioxin", a bromochlorodiphenyl ether, is produced by a marine sponge. These types of compounds may well turn out to be more widely distributed once more research is done on the chemistry of aquatic species. In 1987, only 500 compounds had been isolated from the approximately 500,000 marine bacteria, animals, and plants.



The largest source of dioxins in the environment is from the incomplete combustion of damp vegetation in environments containing high concentrations of chloride ion. By one estimate, the amount of dioxin released annually in forest fires in Canada alone is about 130 pounds, an amount comparable to that released in the accident in Sevesco. Worldwide, this natural process is the major source of dioxin in the environment.

27.5 Reactions of Phenols—A Review

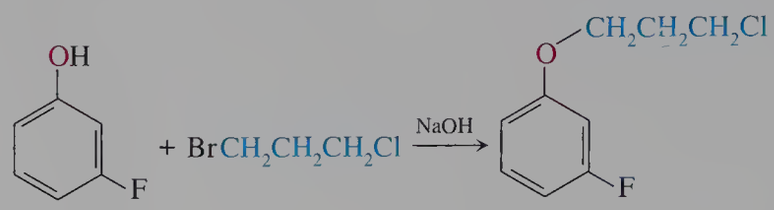
Reaction of phenols can be separated into those at the hydroxyl oxygen and those at the carbon atoms of the aromatic ring. For reactions at the oxygen atom, phenols behave as nucleophiles reacting with electrophiles. Reactions at the carbon atoms of the aromatic ring also involve electrophiles, but the mechanism for electrophilic aromatic substitution differs from substitution reactions at oxygen.

Ether Formation

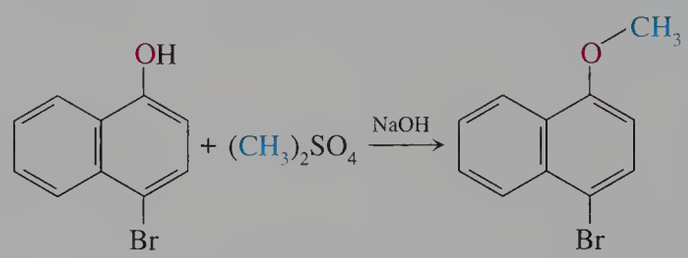
Alkyl phenyl ethers are prepared by the Williamson synthesis (Section 17.6), in which a phenoxide ion displaces a halide ion from an alkyl halide. Because alcohols are weak acids, an alkoxide ion must be prepared using a strong base such as

sodium hydride. Phenols are sufficiently acidic that phenoxides can be obtained by adding hydroxide ion to the phenol.

We recall that the Williamson method works best with primary alkyl halides; secondary and especially tertiary alkyl halides undergo elimination reactions rather than the S_N2 mechanism that gives the ether. The reaction may be carried out in protic solvents such ethyl alcohol or aprotic solvents such as acetone or dimethylformamide.



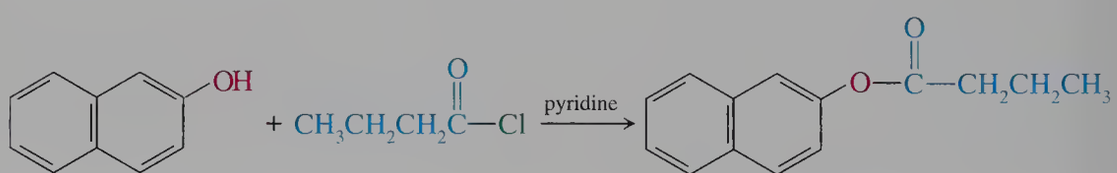
Aryl methyl ethers can be prepared using methyl iodide, but dimethyl sulfate is also widely used.



Ester Formation

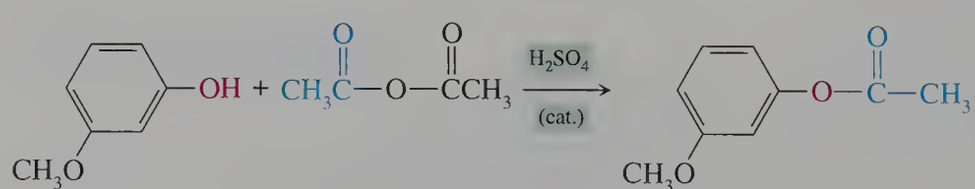
Phenols cannot be converted to esters by the Fischer esterification method because the position of equilibrium is not as favorable as for alcohols. The enthalpy of reaction for ester formation from a phenol and a carboxylic acid is positive.

Esters of phenols are synthesized with acyl halides using the same reaction conditions required to prepare esters of alcohols.

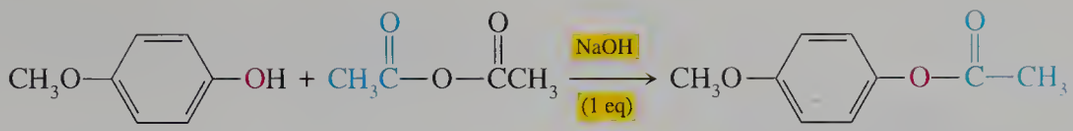


2-naphthol — 2-naphthyl butanoate

When available, acid anhydrides can also be used to form esters of phenols. Acetic anhydride is a readily available inexpensive reagent that is used to prepare acetate esters. The reaction can be done using a catalytic quantity of sulfuric acid to protonate the carbonyl oxygen atom of the anhydride. The reaction can also be done by adding a stoichiometric amount of base to convert the phenol to the more nucleophilic phenoxide ion.



m-methoxyphenol — *m*-methoxyphenyl ethanoate

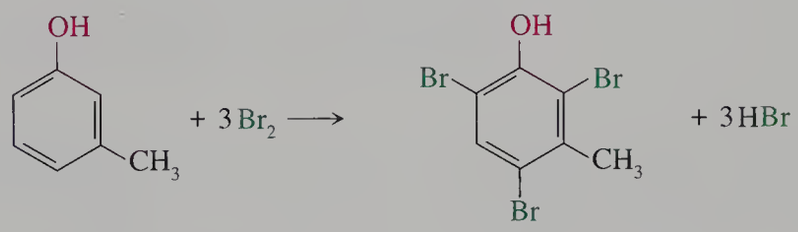


p-methoxyphenol

p-methoxyphenyl ethanoate

Electrophilic Substitution

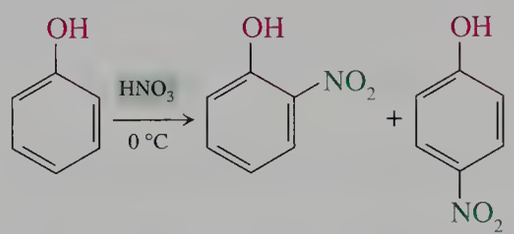
The hydroxyl group is a strongly activating group. Therefore, substitution reactions with many electrophiles occur so rapidly that it is sometimes difficult to avoid multiple substitution by the electrophile. Bromination is one such reaction.



m-methylphenol

2,4,6-tribromo-3-methylphenol

Reactions that introduce a deactivating group decrease the reactivity of the product sufficiently to yield monosubstituted products. The nitration of phenol using dilute nitric acid at room temperature illustrates both the activating influence of the hydroxyl group and the deactivation by a nitro group that permits the formation of a mononitrated product.

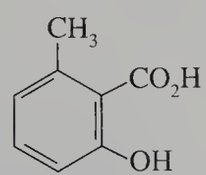


Problem 27.8

2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) is a herbicide. Propose a synthesis of the compound using the Williamson ether synthesis.

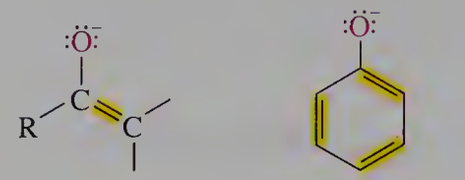
Problem 27.9

The structure of 6-methylsalicylic acid is shown below. What ring carbon atom is selected as C-1 to give this name? What is the structure of the dibrominated product of 6-methylsalicylic acid?



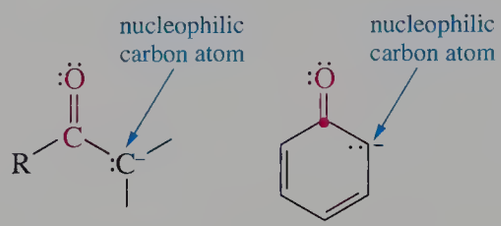
27.6 Reactions of Phenoxide Ions

Phenoxide ions are structurally related to enolates. In both ions the negative charge is largely located on the oxygen atom.



enolate ion (major contributor) phenoxide ion (major contributor)

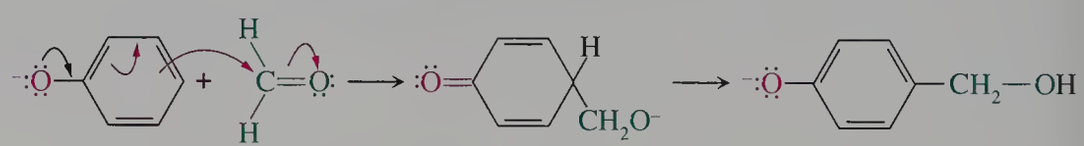
However, we have learned that reaction of electrophiles occurs at carbon rather than oxygen. Therefore, enolates most often behave as carbanions.



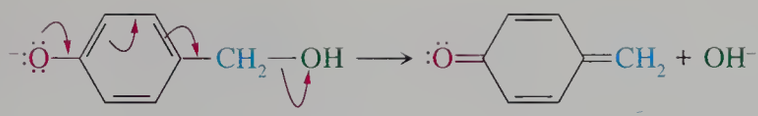
This feature explains several reactions of phenolates. For example, in basic solution phenols react rapidly with bromine. The reaction resembles the bromination of ketones under basic conditions. We recall that multiple bromination of ketones occurs under basic conditions because the enol form of the product is more acidic than the starting ketone. For much the same reason, multiple bromination of phenols occurs in basic solution at all available ortho and para positions.

Addition to Formaldehyde

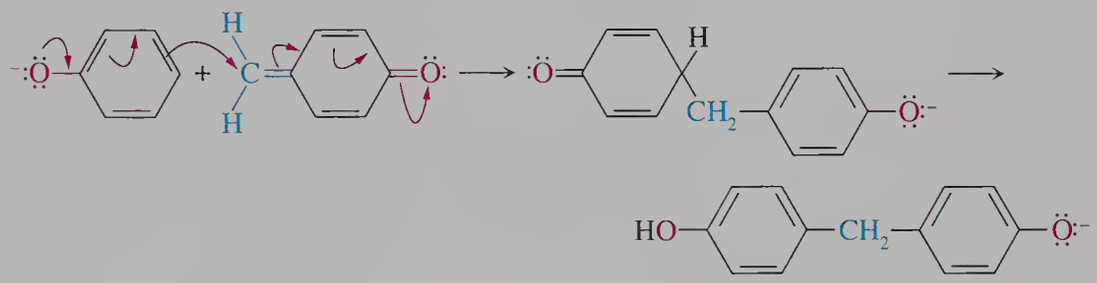
We recall that enolates undergo condensation reactions with the carbonyl carbon atom of aldehydes (Section 23.7). Enolates tend to react to give alkylation at carbon. A similar reaction occurs between the phenolate ion and formaldehyde. Because both the C-2 and C-4 carbon atoms are nucleophilic, two possible condensation products may result. The following reaction shows condensation at C-4, producing a conjugation-extended enolate. Subsequent tautomerization generates the enol form, which is a phenol. Solvent-mediated proton transfer also occurs, giving a phenoxide rather than the more basic (and less stable) alkoxide ion.



Like the aldol condensation product, the product of condensation of phenol with formaldehyde easily dehydrates. Dehydration is shown for the para condensation product. An isomeric condensation product at the ortho position can also form.



The dehydration products are unsaturated conjugated compounds that can act as Michael acceptors. Attack of the phenolate ion results in an addition product. Subsequent tautomerization generates the enol form, a phenol.



This product in turn can undergo another aldol-type condensation at positions either ortho or para to the hydroxyl group, followed by another Michael condensation. Ultimately, a polymer known as Bakelite results. Bakelite has methylene bridges between aromatic rings at ortho and para positions (Figure 27.3). These polymers are also called phenol–formaldehyde resins.

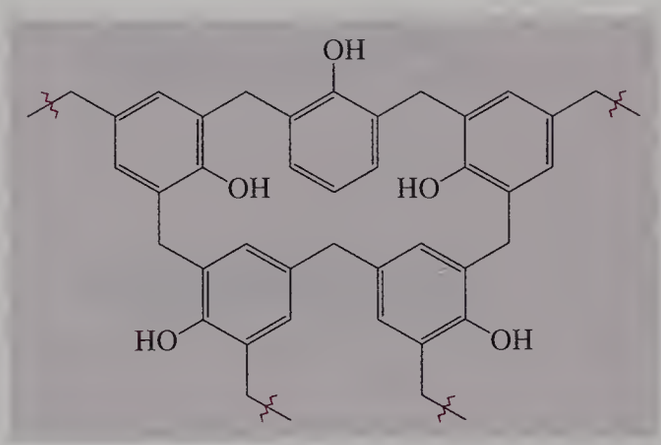
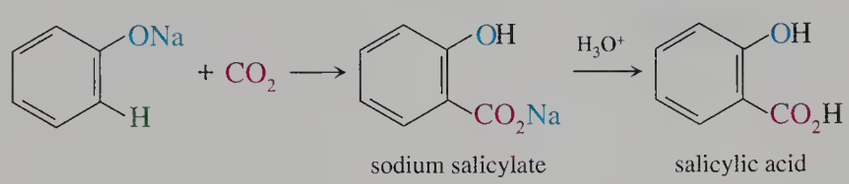


FIGURE 27.3
Structure of Phenol–Formaldehyde Polymer
Methylene units bridge aromatic rings at positions that are ortho and para to the hydroxyl group.

Kolbe Synthesis

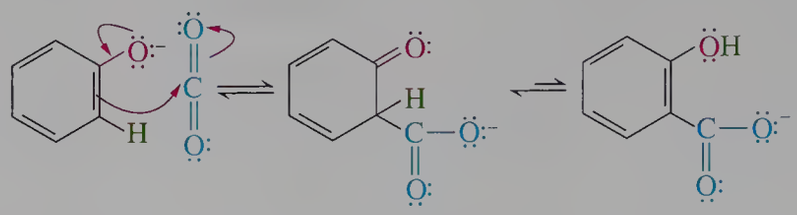
The phenolate ion can react with carbon dioxide to form carboxylic acids. This reaction is one of the steps in the synthesis of acetylsalicylic acid (aspirin).



The reaction, which is carried out under 100 atm pressure of carbon dioxide, is called the **Kolbe reaction**. It is named after the German chemist H. Kolbe, who developed the process.

The reaction is mechanistically similar to the reaction of Grignard reagents with carbon dioxide. The increased electron density at C-2 or C-4 in the phenolate ion allows either carbon atom to act as a nucleophile and attack the carbon atom of

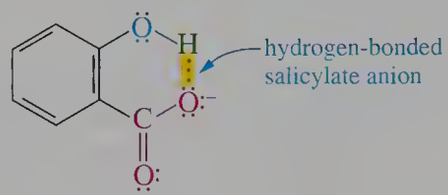
carbon dioxide. Reaction at the position ortho to the oxygen atom is shown. Tautomerization of the cyclohexadienone gives the phenol.



cyclohexadienone intermediate

salicylate anion

The para isomer can also form. However, the Kolbe reaction is reversible. Thermodynamic control favors the more stable ortho isomer. The stability of the ortho isomer may result from intramolecular hydrogen bonding.



Problem 27.10

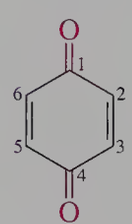
Draw the structure of the addition product of formaldehyde with phenol at the ortho position. Draw the structure of the Michael product of this compound with phenol at the ortho position.

Problem 27.11

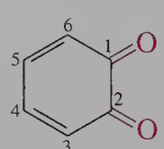
Draw the structure of the product obtained by the Kolbe reaction of *p*-methylphenol (*p*-cresol).

27.7 Quinones

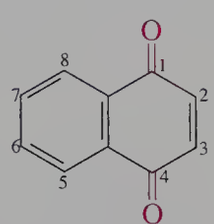
Quinones are cyclohexadienediones whose carbonyl groups can be either 1,2 or 1,4 to each other.



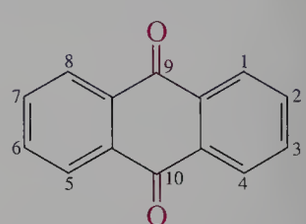
p-benzoquinone



o-benzoquinone

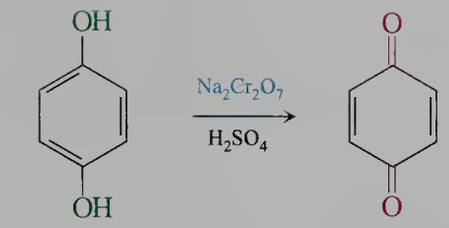


1,4-naphthaquinone



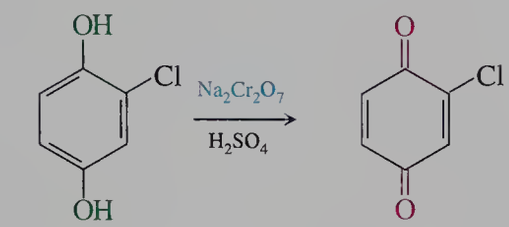
9,10-anthraquinone

Quinones can be prepared by the oxidation of phenols or anilines, although generally in poor yield. However, appropriately disubstituted phenols or anilines are easily oxidized to give better yields of quinones.



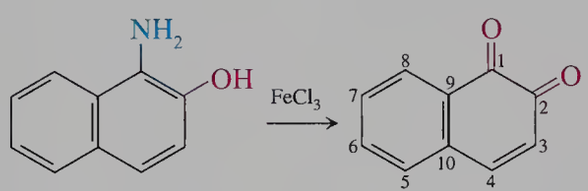
hydroquinone

p-benzoquinone
(quinone)



2-chloro-1,4-benzoquinone

The 1,4-quinones are more easily prepared and are substantially more stable than the 1,2-quinones. Milder oxidizing agents are required to prevent further oxidation of 1,2-quinones.



1-amino-2-naphthol

1,2-naphthoquinone

Quinones are easily reduced to regenerate the aromatic ring of a hydroquinone. The standard reduction potentials, $E°$, for quinones are listed in Table 27.3. We recall from general chemistry that as the standard reduction potential increases, the ease of reduction increases. Note that electron-attracting groups increase the reduction potential. This trend is reasonable because reduction occurs by transfer of electrons to the substrate.

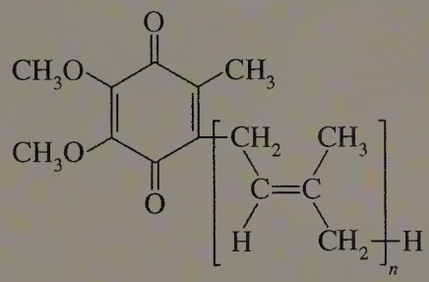
Table 27.3
Reduction Potentials of Quinones

Quinone	*Reduction potential, E° (volts)*
1,4-benzoquinone	0.699
2-methyl-1,4-benzoquinone	0.645
2-hydroxy-1,4-benzoquinone	0.590
2-bromo-1,4-benzoquinone	0.715
2-chloro-1,4-benzoquinone	0.713
1,4-naphthaquinone	0.47
1,2-naphthaquinone	0.56
9,10-anthraquinone	0.13
9,10-phenanthraquinone	0.44

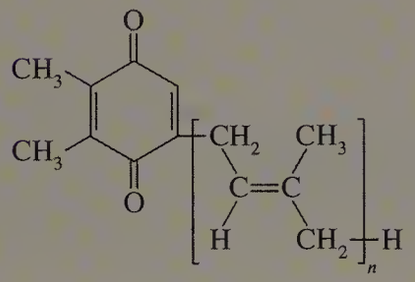
Quinones can be used as mild oxidizing agents. Because the standard potential for quinones varies with the substituent, it is possible to selectively oxidize substrates with specific quinones. Quinones with several electron-withdrawing groups are sufficiently strong oxidizing agents to dehydrogenate hydrocarbons in which a

Coenzyme Q—The Ubiquitous Quinone

Quinones of various types play important roles in cells. One of these quinones is coenzyme Q. It is synthesized by most organisms, including humans. Coenzyme Q is also called ubiquinone (Q), a pun on its apparently ubiquitous occurrence in nature. Ubiquinone is a 1,4-quinone. Its ring contains two methoxy groups, a methyl group, and a polyisoprene moiety. The polyisoprene group contains 6–10 isoprenyl units—6 in bacteria and 10 in mammals. Plants synthesize similar molecules that are called plastoquinones because they are found in chloroplasts. Plastoquinones usually contain 9 isoprene units.



ubiquinone



plastoquinone

Coenzyme Q participates in redox reactions in the respiratory electron transport chain. It undergoes facile one-electron transfer reactions with free radical intermediates (see the figure). Free radicals are often unstable, but the one generated by addition of an electron to ubiquinone is resonance stabilized and also stabilized by electron-releasing substituents on the ring. The reduced form is ubiquinol (QH_2).

Ubiquinone accepts electrons from NADH in a reaction in the respiratory electron transport chain catalyzed by the enzyme NADH ubiquinone reductase. This enzyme complex contains at least 16 polypeptide chains, and perhaps as many as 25. The net reaction is

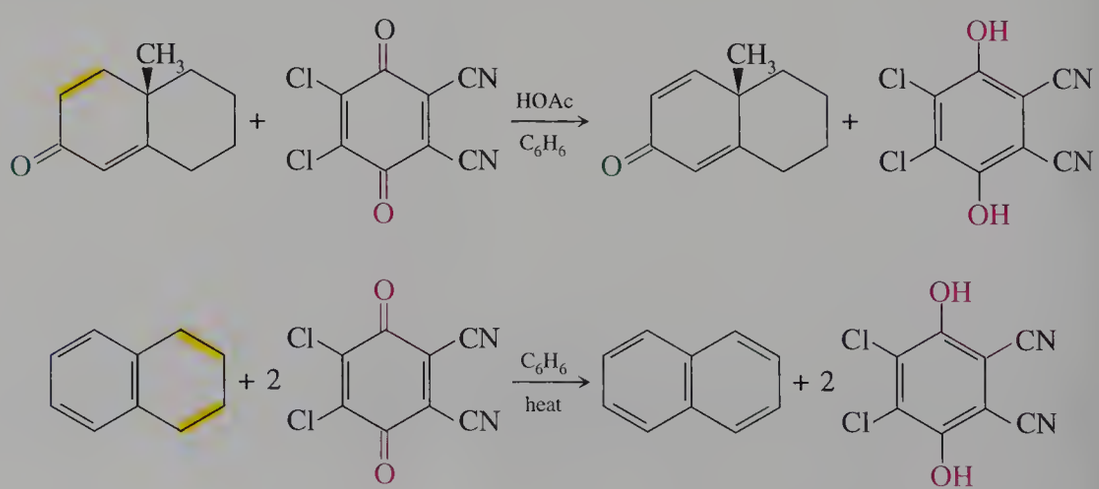
$$NADH + H^+ + Q \rightleftharpoons NAD^+ + QH_2$$

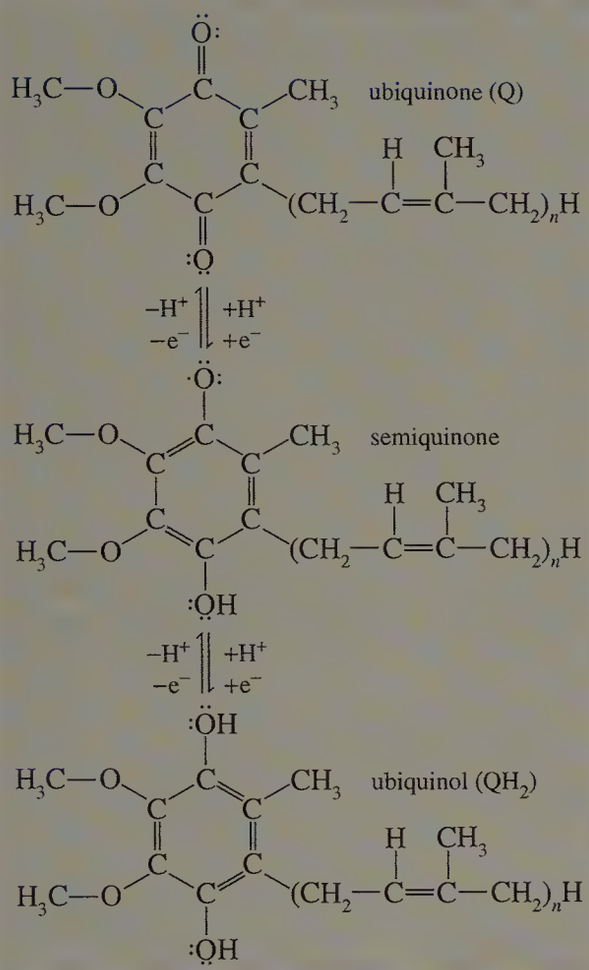
Many proteins and another coenzyme called flavin mononucleotide participate in this process, which involves five redox reactions. These redox reactions generate the various free radicals shown in the figure.

The reduced form of ubiquinone, called ubiquinol, subsequently transfers electrons one at a time to an Fe^{3+} ion in the heme group of a protein called cytochrome c. The net reaction is

$$QH_2 + \text{cytochrome c}(Fe^{3+}) \rightleftharpoons Q + \text{cytochrome c}(Fe^{2+}) + 2H^+$$

conjugated product can form. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can oxidize ketones to give α,β-unsaturated ketones. It can also oxidize some nonaromatic hydrocarbons to aromatic hydrocarbons.





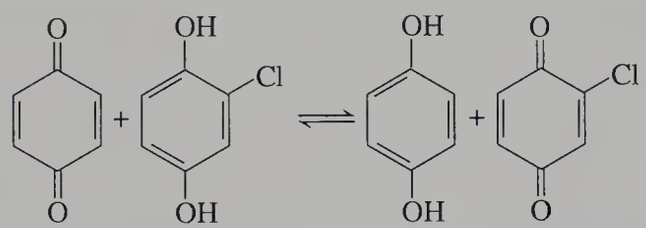
Ubiquinone is reduced in two successive one-electron transfer steps. The product of the first electron transfer, called a semiquinone, is a resonance-stabilized free radical.

The enzyme ubiquinone–cytochrome c reductase catalyzes this very complicated reaction. The enzyme is another gigantic protein complex with a molecular mass of about 500,000. Three different cytochromes and another protein containing a complex of iron and sulfur are components of ubiquinone–cytochrome c reductase.

The processes in which ubiquinone participates occur in the inner mitochondrial membrane of eukaryotic cells and in the plasma membrane of bacterial cells. Ubiquinone and ubiquinol are soluble in the membrane, and they act as shuttles to transport electrons and protons from one multiprotein complex to another. Similar processes occur in the photoelectron transport chain in plants with coenzymes called plastiquinones.

Problem 27.12

What is E° for the following reaction? Is the equilibrium constant greater than or less than 1?



27.8 Substitution Reactions of Aryldiazonium Salts

We recall that primary alkylamines form unstable diazonium ion salts (Section 25.6). However, the carbon atom of the C—N bond of aryldiazonium ions is sp^2 hybridized rather than sp^3 hybridized as it is in alkyldiazonium ions. Homolytic cleavage of the bond to give an aryl cation and nitrogen therefore occurs at a slower rate than for formation of an alkyl cation from an alkyldiazonium ion. Aryldiazonium ions can be prepared in solution and reacted with a variety of

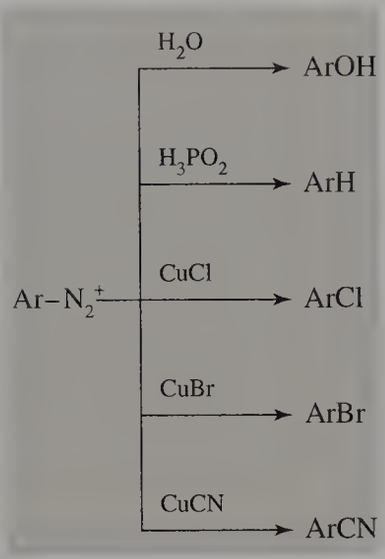
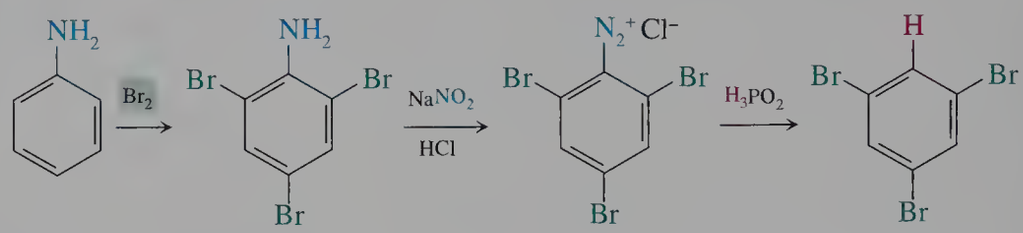


FIGURE 27.4 Summary of Syntheses Using Diazonium Ion Reactions

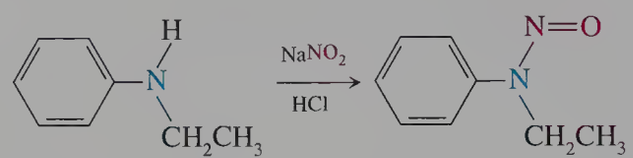
reagents that replace nitrogen in regiospecific reactions. Figure 27.4 summarizes these reactions, first presented in Section 14.8.

Aryldiazonium ions are important synthetic intermediates because they provide a means of modifying substituents already located at specific positions on the ring. The synthesis of an aryldiazonium ion on a multiply substituted aromatic ring allows us to make compounds that sequential electrophilic aromatic substitution could not produce. For example, bromination of aniline yields tribromoaniline. Diazotization of the product followed by treatment with hypophosphorous acid removes the amino group. The three bromine groups are located meta to one another. Direct bromination of benzene would not produce this compound because bromine is an ortho,para director.



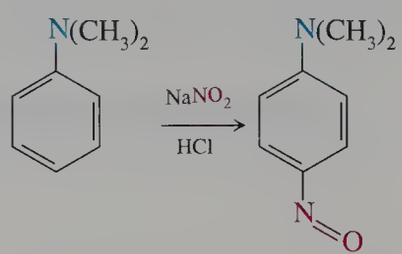
Nitrosation of Arylamines

N-Alkylarylamines are secondary amines that react by direct electrophilic attack of the nitrosonium ion on the electron pair of the amine to give *N*-nitrosoamines.



N-ethylaniline — *N*-ethyl-*N*-nitrosoaniline

The nitrosation of tertiary alkylamines gives no isolable product. However, a tertiary arylamine such as *N,N*-dialkylarylamine undergoes an alternative reaction. The nitrosonium ion is a weak electrophile, but is sufficiently reactive to nitrosate the activated aromatic ring.



27.9 Azo Compounds

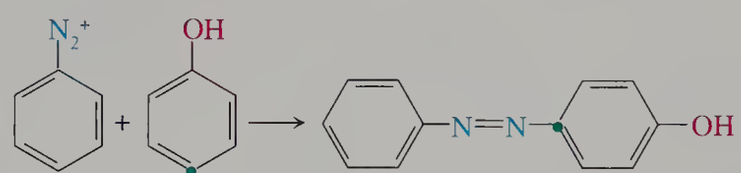
The diazonium ion portion of an aryldiazonium ion has two contributing resonance structures. The more important contributor has Lewis octets at both nitrogen atoms. The second form is electron deficient at the terminal nitrogen atom.

Noting the electron deficiency of the terminal nitrogen atom in the second resonance form, we understand why the aryldiazonium ion is electrophilic and reacts with

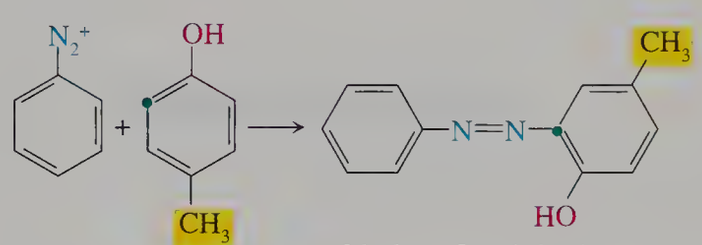
nucleophilic centers at the terminal nitrogen atom. For example, aryldiazonium ions can attack aromatic rings to give substitution reactions. However, the aryl diazonium ions are weak electrophiles and therefore react only with very activated aromatic compounds, such as phenols or dimethylanilines. Substitution produces an —N=N— functional group called the azo group. In the following equation, G represents a group that supplies electrons by resonance. The π electrons of the azo group form part of a conjugated system between the two aromatic rings.

$$Ar{-}N_2^+ + H{-}Ar{-}G \longrightarrow Ar{-}N{=}N{-}Ar{-}G + H^+$$

Substitution of the activated aromatic ring by the electrophilic aryldiazonium ion occurs principally at the para position. However, if the para position is blocked by a substituent, substitution occurs at the ortho position.



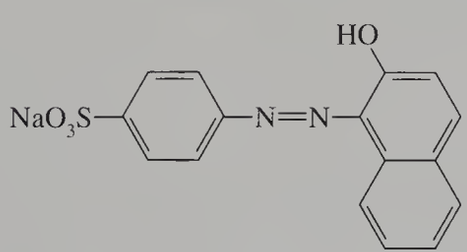
4-hydroxyazobenzene



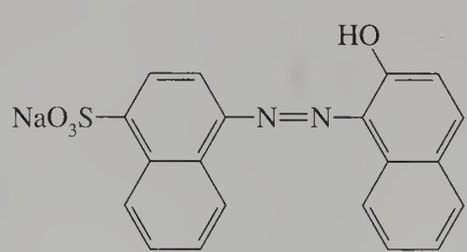
2-hydroxy-5-methylazobenzene

Extended conjugation occurs between aromatic rings linked by an azo group. These compounds are colored because the λ_{max} values of aromatic azo compounds are in the visible region. They are widely used as dyes for both food products and fabrics. Those used for fabric dyes usually contain one or more sulfonic acid groups both to increase water solubility and to provide binding sites between the dye and the surface of the fabric. (Because sulfonic acids are strong acids, they exist as sulfonate ions at pH 7.)

Variations in structure that affect the color of the azo compounds may involve both the aromatic rings and their substituents. Using naphthalene rings for both the diazonium ion and the activated ring produces compounds with different colors. For example, the product of azo coupling of the para sulfonic acid–substituted benzenediazonium ion with 2-naphthol is orange, whereas the product obtained using a similarly substituted naphthalenediazonium ion with 2-naphthol is red.

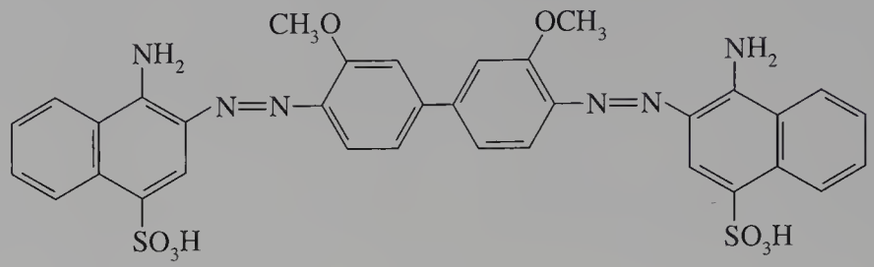


Orange II
λ_{max} = 484 nm

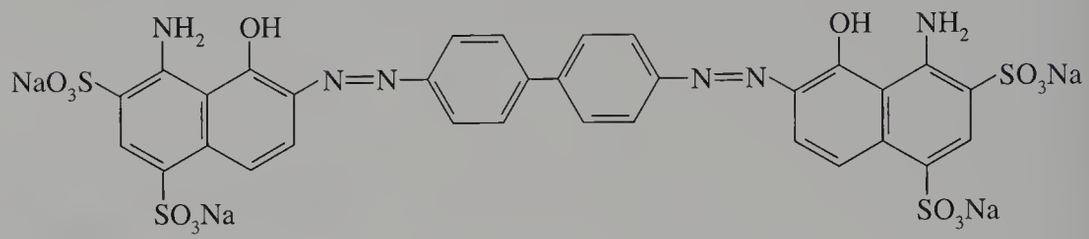


Fast Red A
λ_{max} = 505 nm

Substituents change the λ_{max} values of azo compounds and the corresponding colors. For example, adding hydroxy and sulfonic acid groups to Benzoazurin G changes the color, producing Sky Blue 6B.



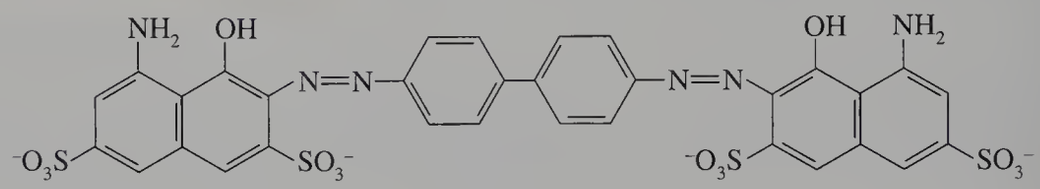
Benzoazurin G
λ_{max} = 569 nm



Sky Blue 6B
λ_{max} = 627 nm

Problem 27.13

Draw the structure of the amine needed to form the diazonium ion required to synthesize Direct Blue 2B.



Direct Blue 2B

EXERCISES

Properties of Aromatic Compounds

27.1 The boiling points of the 1,2-, 1,3-, and 1,4-benzenediols are 245, 276, and 285 °C, respectively. Explain why the boiling point of the ortho isomer is significantly lower than those of the other two isomers.

27.2 The boiling points of the three isomeric hydroxyanisoles are 205, 243, and 244 °C, respectively. What is the structure of the compound corresponding to the lowest boiling point?

27.3 The dipole moments of toluene and chlorobenzene are 0.4 and 1.7 D, respectively. Predict the dipole moment of *p*-chlorotoluene.

27.4 The dipole moments of toluene and phenol are 0.4 and 1.5 D, respectively. Predict the dipole moment of *p*-methylphenol.

27.5 The dipole moments of two of the isomeric dichlorobenzenes are 1.72 and 2.50 D. Assign a structure to each value.

27.6 The dipole moments of chlorobenzene and phenol are 1.7 and 1.5 D, respectively. Predict the dipole moment of *p*- chlorophenol.

27.7 Which compound has the longer C—N bond length, *p*-methoxyaniline or *p*-cyanoaniline?

27.8 Which compound has the larger activation energy for the nitrogen inversion, cyclohexylamine or aniline?

27.9 The dipole moment of pyrrolidine is 1.57 D, and the negative end of the dipole is directed toward nitrogen. The dipole moment of pyrrole is 1.80 D, but the dipole is opposite that of pyrrolidine. Explain why.

27.10 The dipole moments of aniline, *p*-(trifluoromethyl)aniline, and (trifluoromethyl)benzene are 1.3, 4.3, and 2.9 D, respectively. Explain how these data are used to deduce the direction of the dipole moment of aniline.

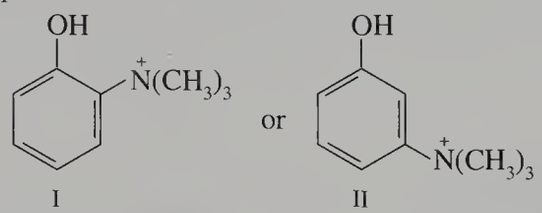
Acid–Base Properties

27.11 Explain why *p*-hydroxybenzaldehyde (pK_a = 7.62) is a substantially stronger acid than phenol.

27.12 Explain why 2,4-dinitrophenol (pK_a = 3.96) is a stronger acid than 3,5-dinitrophenol (pK_a = 6.73).

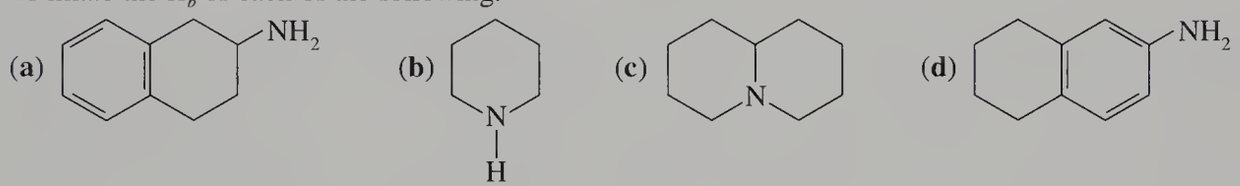
27.13 Based on resonance structures, explain why 1-naphthol (pK_a = 9.31) is a stronger acid than 2-naphthol (pK_a = 9.55). A review of Section 14.10 may be helpful.

27.14 Which of the following isomeric phenols is the more acidic?

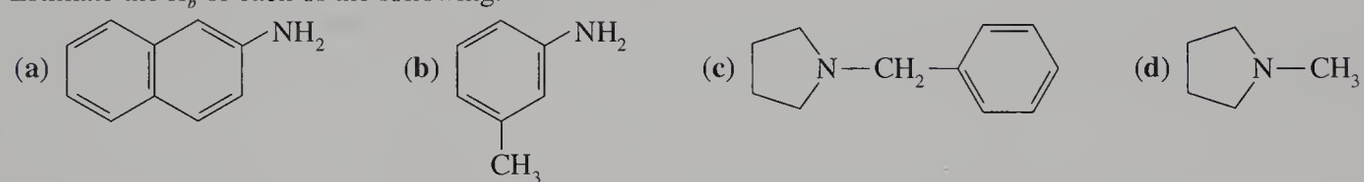


I II

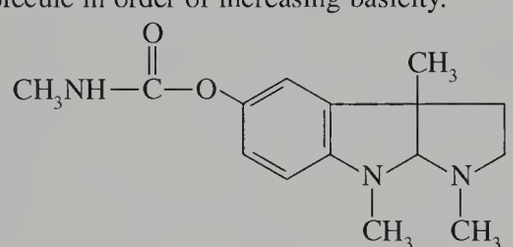
27.15 Estimate the K_b of each of the following.



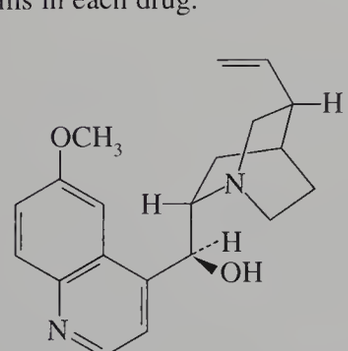
27.16 Estimate the K_b of each of the following.



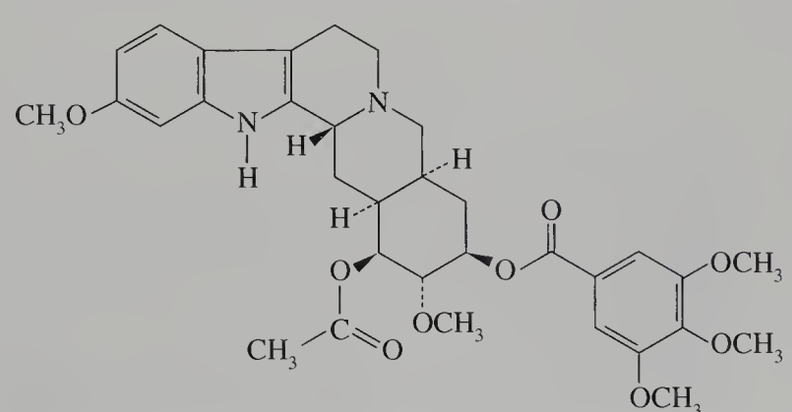
27.17 Physostigmine is used in 0.1–1.0% solutions to decrease the intraocular pressure in treatment of glaucoma. Rank the three nitrogen atoms in the molecule in order of increasing basicity.



27.18 Quinine is an antimalarial drug, and reserpine is an antihypertensive drug. Estimate the pK_b values of both nitrogen atoms in each drug.



quinine

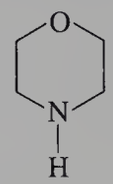


reserpine

27.19 Explain why the pK_a values of the anilinium ions of *m*-cyanoaniline and *p*-cyanoaniline are 2.75 and 1.74, respectively.

27.20 Explain why the pK_a values of the anilinium ions of *m*-methoxyaniline and *p*-methoxyaniline are 4.2 and 5.3, respectively.

27.21 Explain why morpholine (pK_b = 5.67) is a weaker base than piperidine (pK_b = 2.88).

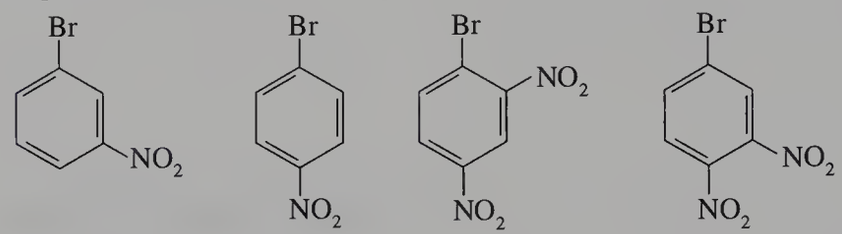


morpholine

27.22 The acidities of benzoic acid and of acetic acid differ by a factor of about 4, whereas the acidities of the anilinium ion and of the methylammonium ion differ by about a factor of 10^6. Why does the aromatic ring have so little effect on the acidity of carboxylic acids and a large effect on the acidity of ammonium ions?

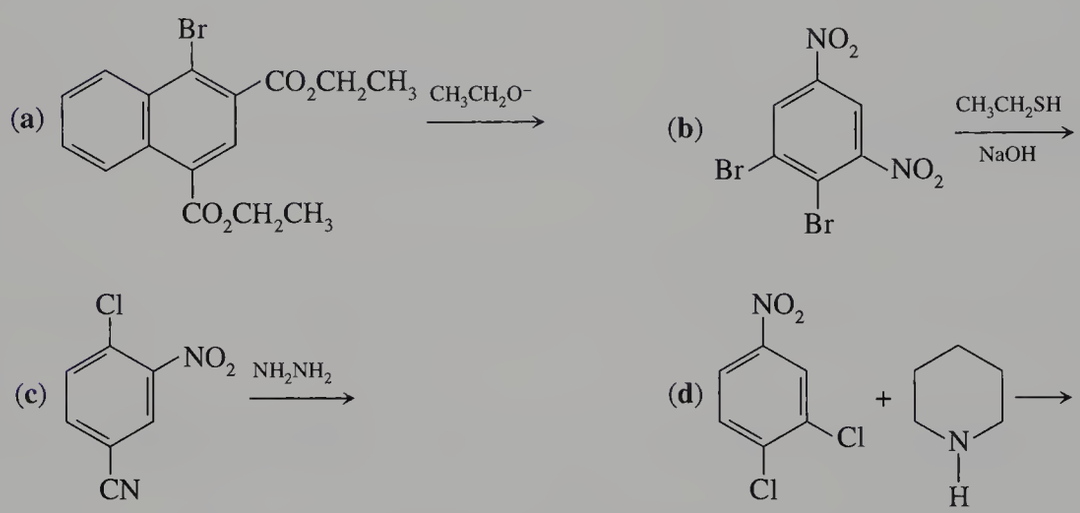
Nucleophilic Aromatic Substitution

27.23 Rank the following compounds in order of increasing reactivity toward sodium methoxide in methanol.



I II III IV

27.24 Draw the product of each of the following reactions.



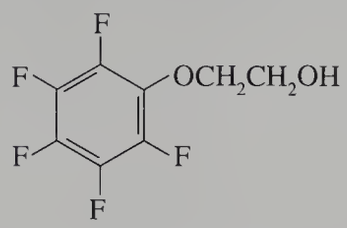
27.25 Explain why 4-chloropyridine reacts with methoxide to give 4-methoxypyridine under conditions where 3-chloropyridine is unreactive.

27.26 At one time 2,4-dinitrofluorobenzene was used to form derivatives of peptides at the N-terminal amino acid. Write a general structure of this type of derivative. Explain why the reaction readily occurs.

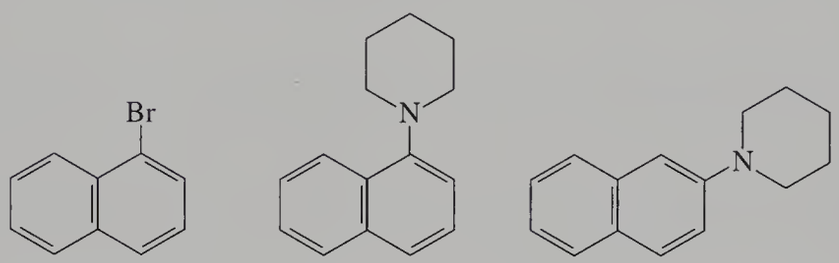
27.27 Explain why hexafluorobenzene readily reacts with sodium methoxide in methanol at 75 °C to yield 2,3,4,5,6-pentafluoroanisole.

27.28 2,3,4,5,6-Pentafluoronitrobenzene reacts with sodium methoxide in methanol at 25 °C to yield a mixture of two isomeric products with the molecular formula $C_7H_3F_4NO_3$. Draw their structures.

27.29 The following compound reacts in basic solution to give a product with the molecular formula $C_8H_4F_4O_2$. Suggest a structure for this product.



27.30 1-Bromonaphthalene reacts slowly with piperidine at 230 °C to give compound I. The addition of sodium amide accelerates the reaction, which now occurs at 100 °C to give compounds I and II. Explain the difference in the two reaction conditions and the product distribution.

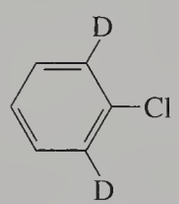


1-bromonaphthalene I II

27.31 The two benzyne intermediates derived from reaction of sodium amide and 3-chlorotoluene are formed in approximately equal amounts. Calculate the composition of the mixture of aniline isomers formed in this reaction.

27.32 The reaction of 3-chloro(trifluoromethyl)benzene with sodium amide is regioselective. Which of the two possible isomeric benzynes is formed? Suggest a reason why the reaction is regioselective.

27.33 Draw the structures of the products formed in the reaction of the following deuterated chlorobenzene with sodium amide in liquid ammonia.

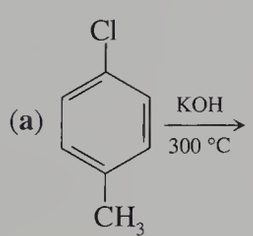


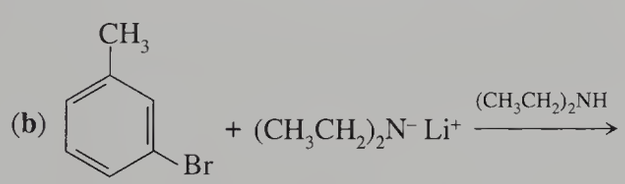
27.34 Reaction of 2-bromoanisole with sodium amide in liquid ammonia gives a high yield of 3-aminoanisole. Explain why the reaction of the benzyne intermediate is regioselective.

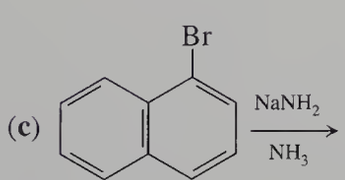
27.35 Reaction of *o*-bromofluorobenzene with magnesium in tetrahydrofuran gives an intermediate that decomposes to yield benzyne. Write the mechanism of this reaction.

27.36 Reaction of 2-aminobenzoic acid with nitrous acid yields an intermediate that decomposes to yield benzyne. Write the mechanism of this reaction.

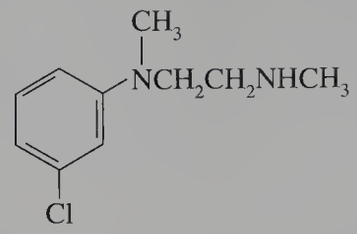
27.37 Draw the structure of the product(s) of each of the following reactions.







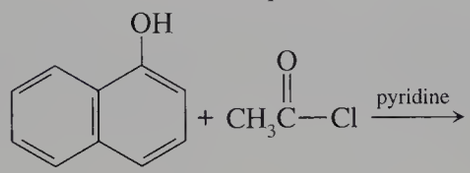
27.38 The following compound reacts with sodium amide in ether to give a product with the molecular formula $C_{10}H_{14}N_2$. Suggest a structure for this product.



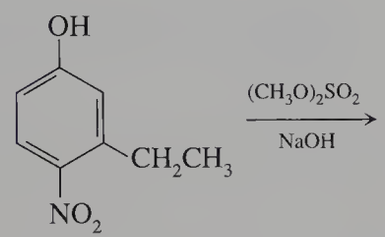
Reactions of Phenols

27.39 Draw the structure of the product for each of the following reactions.

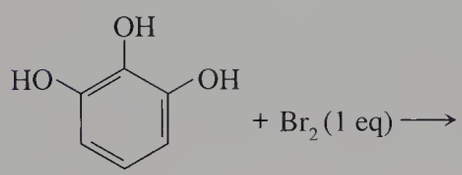
(a)



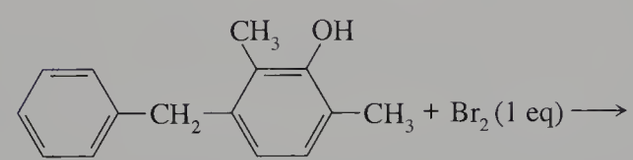
(b)



(c)

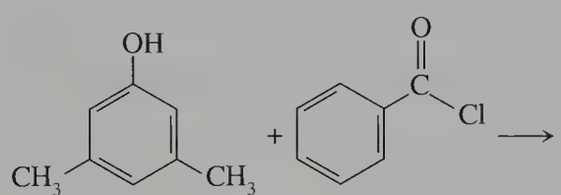


(d)

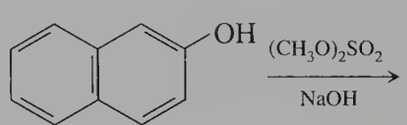


27.40 Draw the structure of the product for each of the following reactions.

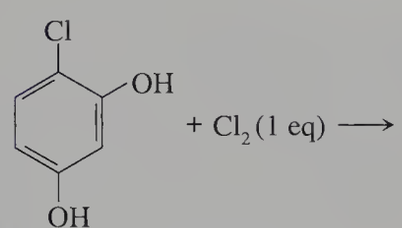
(a)



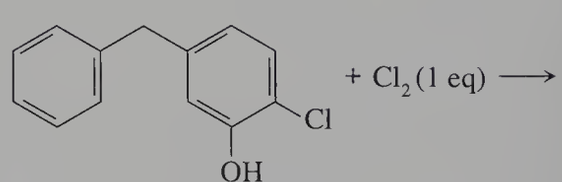
(b)



(c)



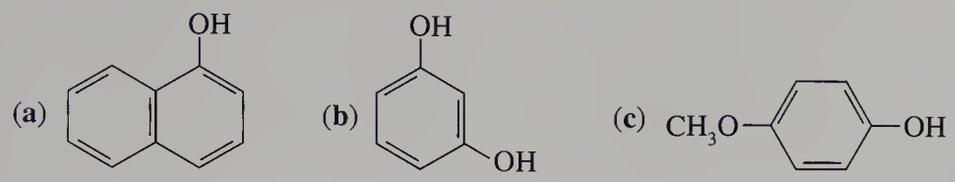
(d)



Reactions of Phenolate Ions

27.41 Could a polymer result from the reaction of phenolate ion with acetone?

27.42 Draw the structure of the product of reaction of CO_2 with the phenolate ion of each of the following compounds.

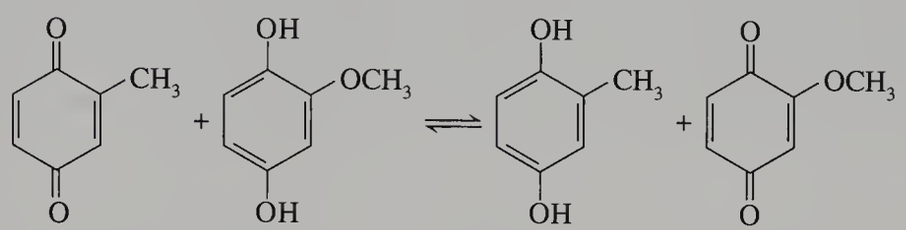


Quinones

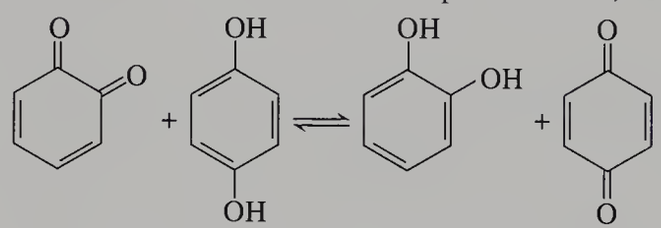
27.43 Based on the structures of ubiquinone and plastoquinone, which compound has the larger reduction potential?

27.44 Phenanthrene can be directly oxidized by vanadium(V) oxide to 9,10-phenanthraquinone. Based on the resonance forms of phenanthrene, explain why the central ring is oxidized rather than the other rings.

27.45 Predict whether the following reaction has an equilibrium constant greater or less than 1.



27.46 The $E°$ of the following reaction is 0.08 V. What is the reduction potential for 1,2-benzoquinone?



Chemical Properties of Amines

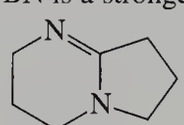
27.47 Select the better nucleophile from each of the following pairs of amines.

(**a**) aniline and cyclohexylamine

(**b**) *p*-nitroaniline and *p*-methoxyaniline

(**c**) aniline and *N,N*-dimethylaniline

27.48 The amidine group (—N—C=N—) is a stronger base than amines. Determine the site of protonation in DBN, a base used in organic reactions. Explain why DBN is a stronger base than an amine.

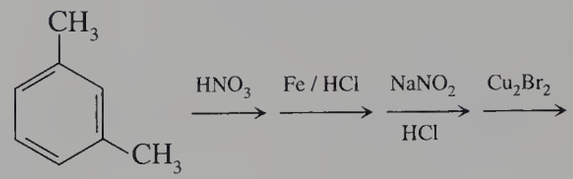


DBN

Synthesis Using Diazonium Compounds

27.49 Write a series of reactions required to prepare 2-bromo-4-methylphenol from toluene.

27.50 Starting from *m*-dimethylbenzene, write the products formed in each step of the following reaction sequence.



Azo Compounds

27.51 Explain why the *p*-nitrobenzenediazonium ion reacts faster than benzenediazonium ion with 2-naphthol.

27.52 Which member of each of the following pairs of aromatic compounds reacts faster with benzenediazonium chloride?

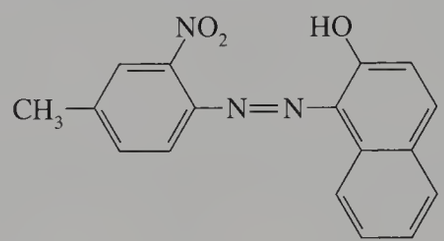
(**a**) aniline and *o*-bromoaniline

(**b**) *p*-methylphenol and *p*-methylphenoxide

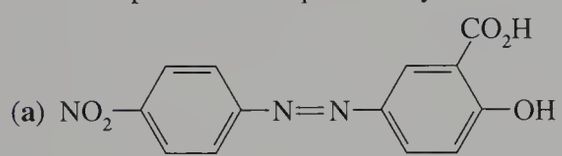
(**c**) anisole and *N,N*-dimethylaniline

27.53 When *o*-aminobenzoic acid (anthranilic acid) is treated with $NaNO_2$ and HCl followed by addition of *N,N*-dimethylaniline to the solution, a dye called methyl red is formed. Draw its structure.

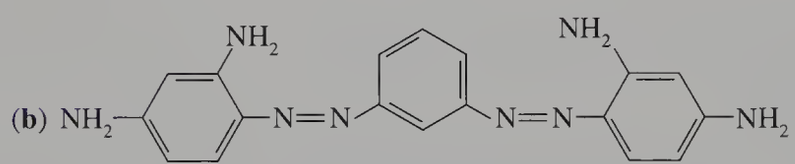
27.54 The following compound is a red dye used in some plastics. Write the structure of the amine needed to form the diazonium ion required to produce the compound. Outline a synthesis of this amine starting from toluene.



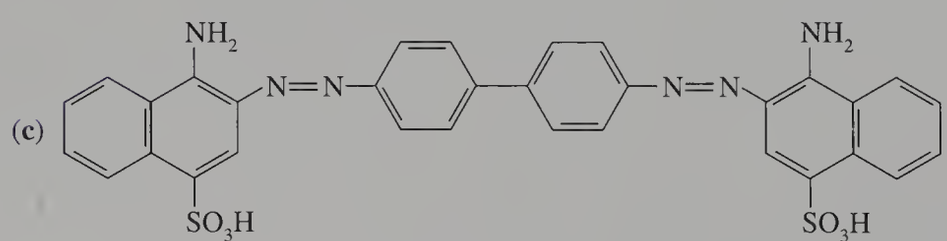
27.55 What compounds are required to synthesize each of the following dyes?



Alizarin Yellow R

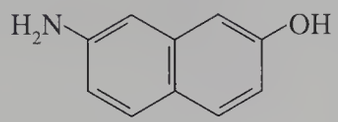


Bismarck Brown B

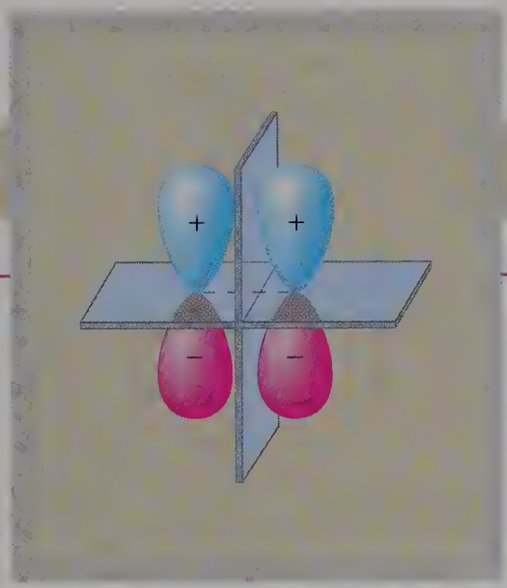


Congo Red

27.56 Reaction of 7-amino-2-naphthol with benzenediazonium ion at pH 9 results in substitution ortho to the hydroxyl group. At pH 5 the substitution occurs ortho to the amino group. Explain how the pH determines the ring in which substitution occurs. Remember that an amino group is a stronger ortho,para activator than the hydroxyl group.



7-amino-2-naphthol



28

Pericyclic Reactions

28.1 Concerted Reactions

Many chemical reactions occur by multistep mechanisms described in terms of electrophiles and nucleophiles. For these reactions, polarity determines the stability of the reactants and products, which is reflected in the equilibrium constant for the reaction. Because transition states and intermediates are charged species, the solvent also affects the rate of reaction.

Some organic reactions occur via concerted S_N2 and E2 mechanisms in which bond-making and bond-breaking occur simultaneously. These reactions are usually stereoselective. They often require catalysts, such as acid or base, and their transition states have charged sites so solvent polarity also affects these concerted reactions.

In this chapter we examine three classes of reactions collectively known as pericyclic reactions. These reactions are concerted, but have very different characteristics from the concerted reactions we have studied up to this point. In a historical sense, pericyclic reactions are newcomers because they have been investigated in detail only in the past two decades.

Pericyclic reactions (Greek *peri*, around) are concerted reactions in which changes in the positions of π and σ bonds occur via cyclic transition states. In simplest terms, pericyclic reactions occur by a cyclic shift of electrons to give a transition state that is transformed to product. No intermediate forms. These reactions require no catalysts, and solvent polarity has no effect on the stereochemistry of the products or the rate of the reaction.

Pericyclic reactions require an energy source, which can be either thermal or photochemical. Pericyclic reactions are called thermal if they only require heat energy for the conversion of one or more reactants into product. The temperature need not be high; some reactions even occur at room temperature. However, heat energy is still associated with these reactions. The common feature of all thermal pericyclic reactions is the transformation of ground state molecular orbitals of the reactant into the ground state molecular orbitals of the product. Photochemical pericyclic reactions occur when a reactant absorbs light energy to form an electronically excited state. Thus, the mechanisms of thermal and photochemical pericyclic reactions differ because they involve different molecular orbitals as well as different energy sources.

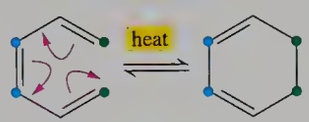
28.2 Classification of Pericyclic Reactions

Pericyclic reactions are divided into three classes: electrocyclic reactions, cycloadditions, and sigmatropic rearrangements. Within each class we will consider the number of electrons changing molecular orbitals in the transition state. Pericyclic reactions may involve either $4n$ or $4n + 2$ electrons, where n is an integer. This distinction is important because the symmetry of the molecular orbitals in thermal or photochemical reactions depends on the number of π electrons in the transition state. The stereochemistry of the products of pericyclic reactions depends on the symmetry of these molecular orbitals. We will see that the stereochemistry of a product of a pericyclic reaction derived from a $4n$ π electron system differs from that of a $4n + 2$ π electron system.

Electrocyclic Reactions

Electrocyclic reactions are intramolecular processes in which a polyene reacts to yield an isomeric cyclic product with one less double bond than the reactant. In this process, the two ends of the π system become linked by a single bond and the double bonds are relocated. The reverse of this reaction, in which a cyclic system opens to give an isomeric polyene, is also called an electrocyclic reaction.

The thermal cyclization of *cis*-1,3,5-hexatriene to yield 1,3-cyclohexadiene is an electrocyclic reaction. The C-1 and C-6 atoms of the original polyene are σ-bonded in the cyclic product.



$\Delta H^\circ_{rxn} = -60$ kJ mole^{-1}

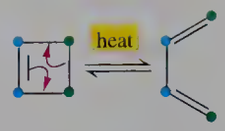
The reaction is exothermic, as we would expect from the change in the number and type of carbon–carbon bonds. The number of single bonds increases by two and the number of double bonds decreases by one. Using 350 kJ mole^{-1} as the bond dissociation energy of a C—C bond and 610 kJ mole^{-1} for the C=C bond, we would estimate ΔH°_{rxn} to be −90 kJ mole^{-1}.

form two single bonds	2(−350) kJ mole^{-1}
break one double bond	+610 kJ mole^{-1}
estimated ΔH°_{rxn}	−90 kJ mole^{-1}

The somewhat poor agreement between the experimental ΔH°_{rxn} and the estimated value results from considering only changes in the number and types of bonds. The reaction is less exothermic than predicted because the resonance energy of a triene versus a diene should also be considered. The resonance energy of butadiene is 15 kJ mole^{-1} (Section 12.2). Because the resonance energy of a triene is higher than a diene, the ΔH° of the reaction should be smaller than predicted by only bond energy changes.

We need consider only ΔH°_{rxn} to determine the direction of the reaction because $\Delta S^\circ_{rxn} \approx 0$ for this reaction. There is a small difference between the entropies of the reactant and the product due to restriction of molecular motion in the ring formed. However, we recall that usually only reactions in which the numbers of moles of reactant and product differ have a ΔS°_{rxn} sufficiently large to affect ΔG°_{rxn} and hence the equilibrium constant of a reaction.

The reverse of the cyclization of a polyene is also an electrocyclic reaction. For example, when cyclobutene is heated, it is converted to 1,3-butadiene.



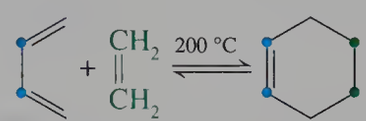
$\Delta H^\circ_{rxn} = -41$ kJ mole^{-1}

The changes that occur in this reaction are the reverse of those for the cyclization of 1,3,5-cyclohexatriene. So we might expect the reaction to be endothermic with $\Delta H^\circ_{rxn} = +60$ kJ mole^{-1}. However, the reaction is actually exothermic. The difference between this estimate and the experimental value is about 100 kJ mole^{-1}. We recall that the cyclobutane ring is strained, and its strain energy is 111 kJ mole^{-1} (Section 4.7). Therefore, the strain energy of the cyclobutene ring, somewhat larger than that of cyclobutane, drives the ring-opening reaction.

We will discuss both cyclization and ring-opening reactions in Section 28.4 and present the stereochemistry of these reactions as it relates to the number of π electrons. *cis*-1,3,5-Hexatriene has six π electrons. Its electrocyclic reactions will be examined as an example of a $4n + 2$ π electron system, where $n = 1$; 1,3-butadiene is a $4n$ π electron system, where $n = 1$.

Cycloaddition Reactions

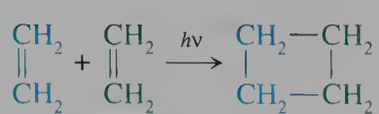
Two unsaturated molecules combine to form a ring in a **cycloaddition reaction**. The earliest studied example of this process is the **Diels–Alder** reaction that occurs between a conjugated diene and an alkene (or alkyne). The alkene is called a dienophile.



In the Diels–Alder reaction, the terminal carbon atoms of the diene bond to the carbon atoms of the alkene double bond. For geometric reasons, the diene must adopt either a cis configuration or an s-cis conformation.

The Diels–Alder reaction requires six π electrons: four in the diene and two in the alkene. It is termed a [4 + 2] cycloaddition. This reaction is an example of a $4n + 2$ system because the transition state contains six electrons.

The reaction of two alkene molecules to give a cyclobutane ring involves four π electrons and is an example of a $4n$ system. This [2 + 2] cycloaddition occurs photochemically, not thermally.

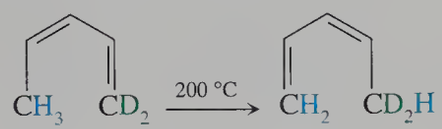


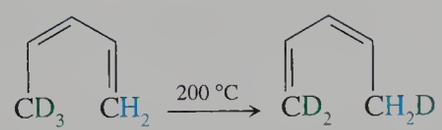
The ΔS°_{rxn} values for cycloaddition reactions are negative because two moles of reactant are converted into one mole of product. We recall that the approximate ΔS°_{rxn} value for a decrease of one mole of product in a reaction is −125 J mole^{-1} degree^{-1} (Section 3.9). This unfavorable entropy contribution for cycloaddition is opposed by a very favorable enthalpy term. In both the Diels–Alder reaction and the [2 + 2] cycloaddition reaction, two double bonds are "lost" as the product forms and four single bonds form. Both types of cycloaddition reactions should therefore be exothermic. However, the formation of cyclobutane is less exothermic because the ring is strained.

break two double bonds	2(+610) kJ mole^{-1}
form four single bonds	4(–350) kJ mole^{-1}
estimated ΔH°_{rxn}	–180 kJ mole^{-1}

Sigmatropic Rearrangements

Sigmatropic rearrangements are intramolecular reactions in which one atom or group of atoms linked by a σ bond formally migrates from one end of a π system to the other. In the process, the positions of single and double bonds simultaneously shift. Examples of one type of sigmatropic rearrangement are the isomerizations of the following deuterated 1,3-pentadienes.



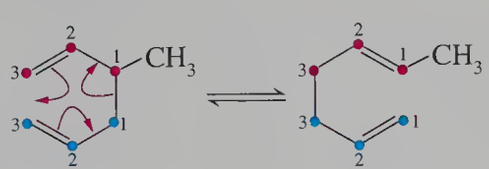


In these two rearrangements, a hydrogen (or deuterium) atom that is σ bonded at an sp^3-hybridized carbon atom moves from one end of a five-carbon-atom system to the other end. In the process, the locations of the alternating single and double bonds and the hybridization of the terminal atoms change. The rearrangement could not be detected without deuterium-labeled compounds because the reactant and product would be identical.

Sigmatropic rearrangements are identified by two numbers separated by a comma and enclosed within brackets. The two numbers refer to the number of atoms in the two groups connected by a σ bond. The numbers are also related to the orbitals in each piece of the original molecule that are involved in the rearrangement. The rearrangement of the 1,3-pentadiene occurs by a shift of a hydrogen atom across a five-carbon-atom system and is therefore termed a [1,5] sigmatropic rearrangement. The number 1 refers to the single orbital of the hydrogen atom, which is bonded to one end of the system that rearranges. The number 5 refers to the five carbon p orbitals of the reacting system. Four of the orbitals are in the π system. The remaining carbon orbital is involved in bonding to the migrating hydrogen atom.

Studies of more complex compounds that undergo [1,5] sigmatropic shifts have shown that the reaction is stereospecific. The group that leaves from the sp^3-hybridized site is transferred to the second site by a path along one side of the π system.

When groups of atoms migrate from one site to another, the σ-bonded atom that leaves one site is different than the one that forms a σ bond at the second site. In such reactions, both "ends" of a σ bond migrate. For example, in the rearrangement of 3-methyl-1,5-hexadiene, atom 3 of the three-atom migrating group eventually bonds to atom 3 of the second part of the molecule.



This is called a [3,3] sigmatropic rearrangement. Note that this numbering system is not related to nomenclature rules.

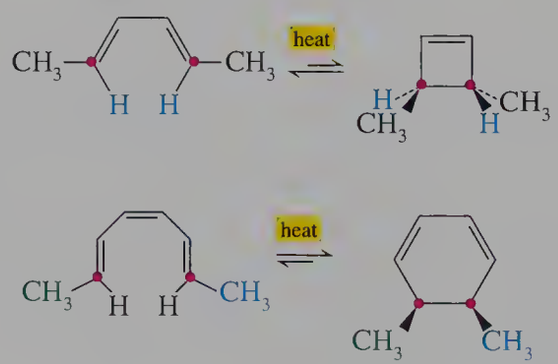
The ΔH°_{rxn} for the [1,5] sigmatropic rearrangement of the various deuterated 1,3-pentadienes are all approximately zero. The difference in the C—H and C—D bond energies is small, and the number and types of bonds in both reactant and product are the same. Also, because the molecules are structurally equivalent except for the position of deuterium labeling, the entropy of both product and reactant are the same and ΔS°_{rxn} is zero.

The ΔH°_{rxn} for the [3,3] sigmatropic rearrangement of 3-methyl-1,5-hexadiene is slightly negative. The number and types of bonds in both reactant and product are the same. However, the double bonds in the reactant are monosubstituted, whereas the product has a monosubstituted and a disubstituted double bond. The more stable disubstituted double bond increases the stability of the product. The ΔS°_{rxn} is approximately zero because the reactant and products are structurally similar, and have the same degree of flexibility.

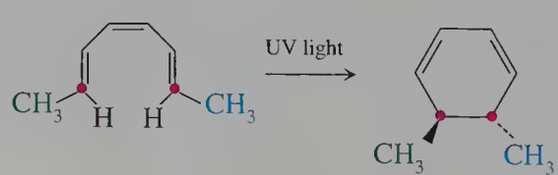
General Features of Pericyclic Reactions

Three factors will be considered for all classes of pericyclic reactions. First, we will determine the number of π electrons in the transition state. Second, we will consider whether the reaction occurs thermally or photochemically. Third, we will examine the stereochemical course of the reaction, which is related to both the number of electrons and the reaction conditions.

The following experimental results show the stereochemistry of some electrocyclic reactions. Each provides facts that must be accommodated by the mechanisms of pericyclic reactions.

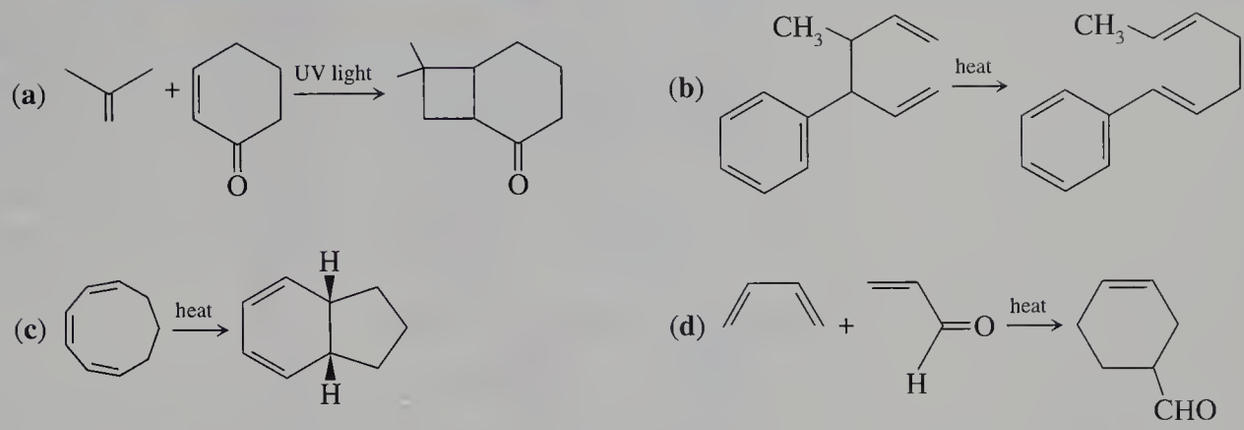


The effect of the number of π electrons upon the stereochemistry of a reaction is illustrated by the cyclization of a diene system compared to a triene system, as shown above. Although the methyl groups in both compounds have the *E* configuration, the stereochemistries of the products differ. Although both reactions are thermal, only the trans isomer results from the diene and only the cis isomer results from the triene. Thermal electrocyclic reactions of systems with $4n$ π electrons have the opposite stereochemistry to structurally related systems with $4n + 2$ π electrons. Furthermore, the stereochemistries of the thermal and photochemical pericyclic reactions are opposite. Photochemically initiated cyclization of the triene gives the trans isomer, whereas the cis isomer forms in the thermal cyclization.



Problem 28.1

Classify each of the following pericyclic reactions.



28.3 Stereospecificity and Molecular Orbitals

For a long time no general theory explained the three observed classes of pericyclic reactions. However, in 1965, R. B. Woodward and R. Hoffman showed that the stereospecificity of pericyclic reactions depends on the symmetry of the molecular orbitals of the reactants and the changes required to generate the molecular orbitals of the product. They called the principle they proposed to explain the stereochemistry of known pericyclic reactions **conservation of orbital symmetry**.

In our discussions of pericyclic reactions we will consider only simple polyene units and their molecular orbitals. Substituents bonded to the sp^2-hybridized carbon atoms may affect the energy of a molecular orbital slightly, but do not alter its symmetry. However, the locations of the substituents allow us to identify the changes in the molecular orbitals. The substituents move in a concerted way to generate a single stereoisomer as π molecular orbitals are transformed.

We can predict the outcome of pericyclic reactions by considering the symmetry of the molecular orbitals of the system. The Woodward–Hoffman method requires an analysis of the symmetry of all π molecular orbitals as they are transformed from those in the reactants to those in the products. We will use the similar but simpler **frontier orbital method** developed by K. Fukui of Kyoto University. Fukui's method considers only the orbital symmetry of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). These are the "frontier orbitals".

The importance of the HOMO and LUMO in explaining pericyclic reactions is somewhat related to the way in which we explain the chemistry of the elements. The HOMO of a polyene is akin to the outermost-shell electrons of an atom. The electrons of the HOMO have the highest energy, and they can be involved in chemical reactions with the lowest expenditure of energy. If more electrons are added to a π system, they go to the lowest unoccupied molecular orbital, the LUMO.

Symmetry-Allowed Reactions

The frontier molecular orbital approach considers only the symmetry of the HOMO and LUMO. A pericyclic reaction occurs only if the symmetry of the reactant molecular orbitals are the same as the symmetry of the product molecular orbitals. When this symmetry restriction is "obeyed", the lobes of molecular orbitals at atoms where bonding occurs have the correct algebraic sign. The signs of the wave

functions must be the same and allow constructive overlap for bonding overlap to occur in the transition state.

If the symmetries of the orbitals of the reactants and products match, a concerted reaction, called **symmetry allowed**, occurs. If the symmetries of the reactants and products do not match, the reaction is called **symmetry disallowed**. Symmetry-allowed reactions occur under reasonably mild conditions because the molecular orbitals can be smoothly transformed from reactant to product. Symmetry-disallowed reactions may actually occur, but they require much higher energies than symmetry-allowed reactions. Also, they are not concerted, usually generate intermediates in multistep reactions, and are not stereospecific.

Molecular Orbitals—A Review

We introduced the molecular orbital theory of polyenes in Chapter 12. Table 12.1 gives a list of guidelines for writing the molecular orbitals of polyenes. In this chapter we will restrict our interest to the symmetry of the molecular orbitals. The symmetric or antisymmetric character of a molecular orbital is described with respect to a vertical mirror plane through the center of the molecule and perpendicular to the plane of the molecule. If the signs of the lobes on the two sides of the mirror plane are the same, the molecular orbital is symmetric. If the signs are not the same, the orbital is antisymmetric. For example, π_1 and π_2 of ethylene are symmetric and antisymmetric, respectively (Figure 28.1).

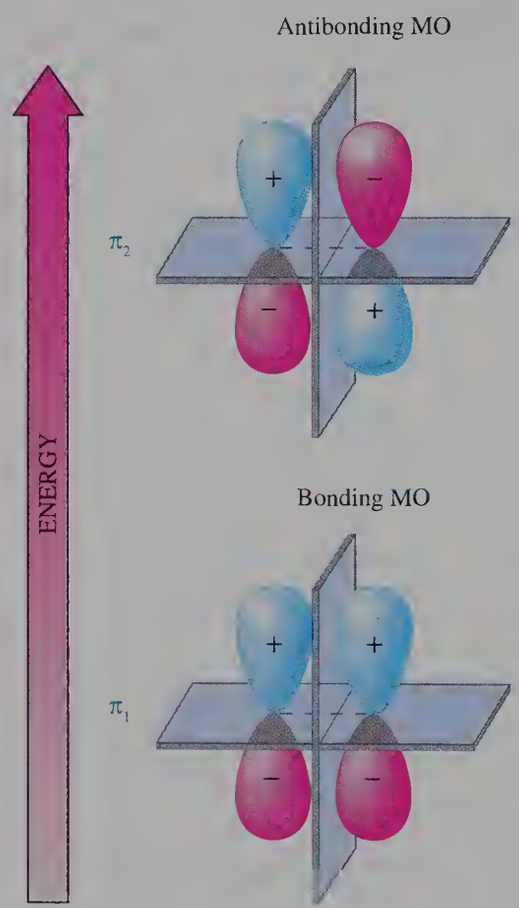


FIGURE 28.1 Molecular Orbitals of Ethylene
The symmetries of the two π molecular orbitals of ethylene with respect to a plane perpendicular to the molecule and bisecting the molecule differ. The bonding orbital is symmetric; the antibonding orbital is antisymmetric.

Figure 28.2 shows the bonding and antibonding molecular orbitals of 1,3-butadiene. Although the relative contributions of the 2*p* orbitals to molecular orbitals differ, the sizes of all 2*p* orbitals are shown the same because we are not concerned with the electron density at each atom. Only the symmetry of the mole-

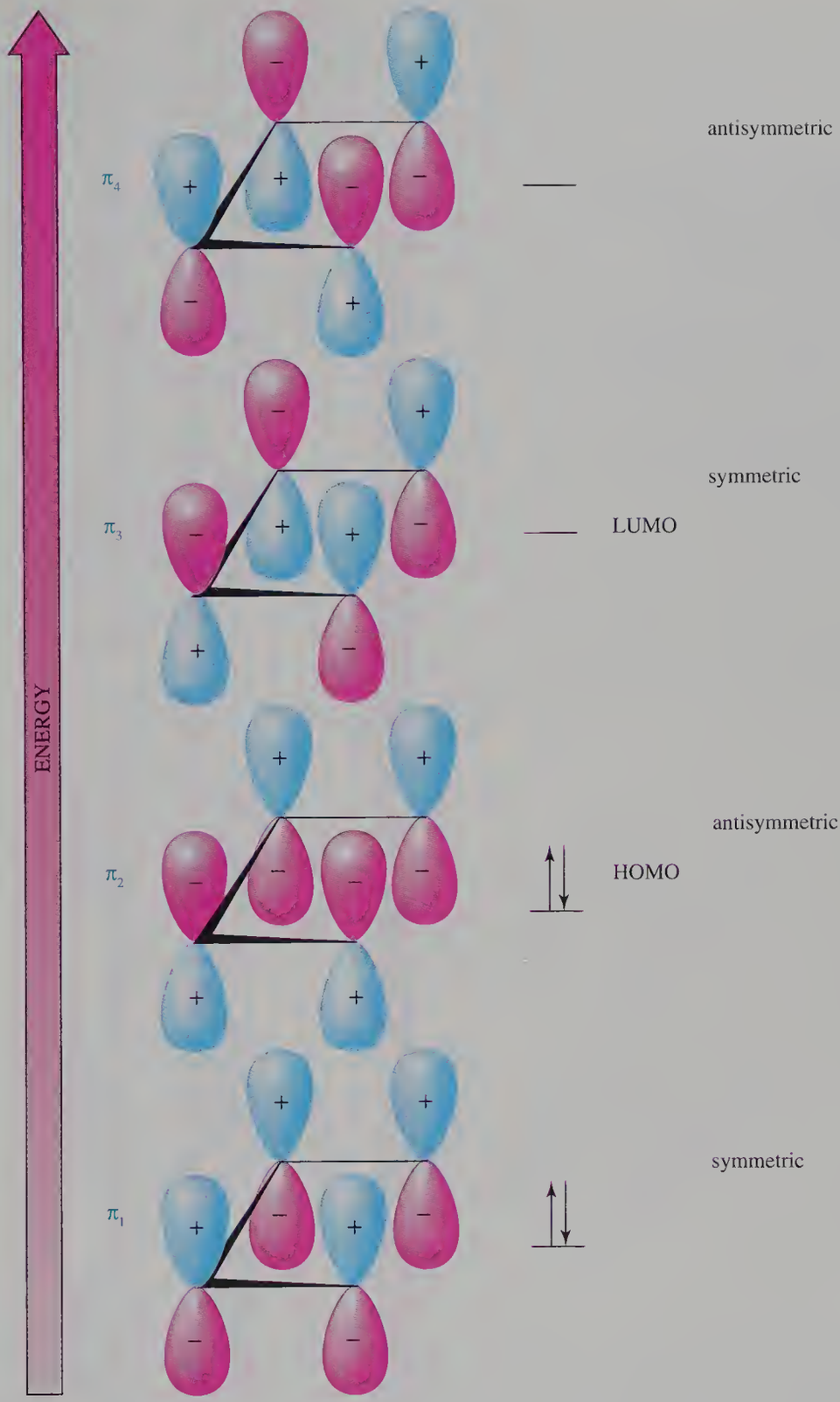


FIGURE 28.2 Symmetry of Molecular Orbitals of 1,3-Butadiene
The symmetry of the π molecular orbitals is evaluated with respect to the plane of the page because the molecule is viewed as perpendicular to the page. The highest occupied molecular orbital, π_2, is antisymmetric. The lowest unoccupied molecular orbital, π_3, is symmetric.

cular orbitals is required to understand the course of pericyclic reactions. The molecular orbitals are also shown in an s-cis conformation rather than in a linear arrangement used in Chapter 12 because the molecule must be in this conformation for electrocyclic reactions and cycloaddition reactions to occur.

Frontier molecular orbital theory considers only the signs of the wave functions at the terminal carbon atoms of the HOMO and LUMO. The HOMO of 1,3-butadiene is the π_2 molecular orbital. It is antisymmetric. As we noted earlier, this means that the signs of the wave functions of the contributing terminal $2p$ atomic orbitals are

reversed on opposite sides of the reference vertical plane. The LUMO of 1,3-butadiene is π_3; it is symmetric.

Figure 28.3 shows the bonding and antibonding molecular orbitals of 1,3,5-hexatriene. These molecular orbitals are also shown in an all s-cis conformation. The

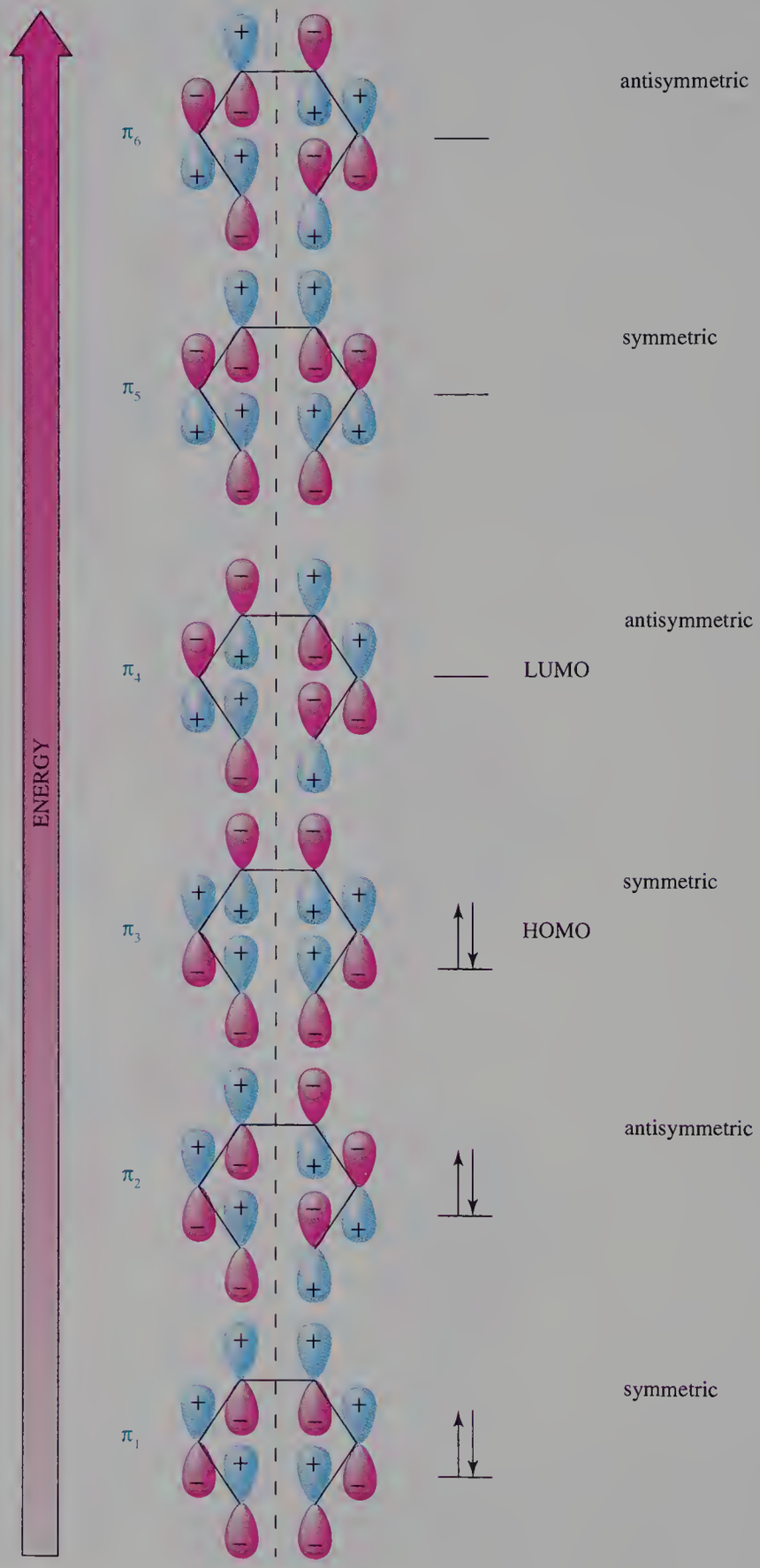


FIGURE 28.3 Symmetry of Molecular Orbitals of 1,3,5-Hexatriene
The symmetry of the π molecular orbitals is evaluated with respect to a plane perpendicular to the page. The highest occupied molecular orbital, π_3, is symmetric. The lowest unoccupied molecular orbital, π_4, is antisymmetric.

three lowest energy molecular orbitals contain the six π electrons of the conjugated triene. These orbitals all have lower energy than an isolated 2*p* orbital of carbon, and they are all bonding. The numbers of nodal planes of π_1, π_2, and π_3 are 0, 1, and 2, respectively. The remaining three molecular orbitals are antibonding, and the number of nodal planes increases for each orbital of successively higher energy.

To explain the pericyclic reaction of 1,3,5-hexatriene by frontier molecular orbital theory, we need only consider the symmetry of π_3 and π_4. The π_3 is the HOMO; it is symmetric. The π_4 is the LUMO; it is antisymmetric. Note that this order of symmetry is opposite that of 1,3-butadiene. The symmetry of the HOMO alternates with each additional double bond. The difference in the chemistry of polyenes noted earlier in this chapter for $4n$ and $4n + 2$ π systems results from this difference in symmetry for the highest energy occupied molecular orbital involved in the reaction.

28.4 Electrocyclic Reactions

In an electrocyclic reaction, a ring is closed and a single bond forms by bonding the carbon atoms at each end of a conjugated π system. The 2*p* orbitals of the terminal carbon atoms of the π system of the HOMO must rotate in a concerted motion to overlap to form a σ bond. The rotation must occur so that a favorable bonding overlap occurs between lobes of like sign. If the terminal 2*p* orbitals have the positively signed lobes on the opposite "sides" of the molecule, the two orbitals must rotate in the same direction to form a σ bond. This situation occurs if π_2 of 1,3-butadiene is the frontier molecular orbital (Figure 28.4a).

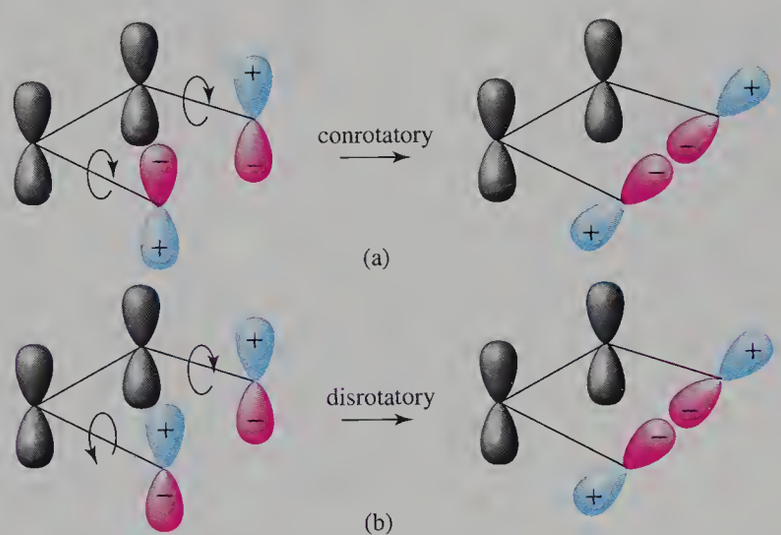


FIGURE 28.4
Conrotatory and Disrotatory Motion for a Diene
(a) A conrotatory motion is required for an electrocyclic reaction involving an antisymmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-4 to C-3 are both clockwise. (b) A disrotatory motion is required for an electrocyclic reaction involving a symmetric orbital. The direction of rotation viewed along the C-1 to C-2 bond is opposite that along the C-4 to C-3 bond.

Both rotations shown are clockwise. If both rotated counterclockwise, a bonding interaction would also result. Because the two rotations are in the same direction, they are said to be **conrotatory**. The actual direction of rotation may depend on steric factors that may differ for the two conrotatory pathways. However, the conrotatory motion is controlled by the symmetry of the molecular orbital.

Now let's consider the motion required for bond formation if the terminal 2*p* orbitals have the positively signed lobes on the same "side" of the molecule. The two orbitals must rotate in opposite directions. That is, one moves clockwise and the other counterclockwise. This situation occurs if π_3 of 1,3-butadiene is the frontier molecular orbital involved in a reaction (Figure 28.4b). This combination of motions of two orbitals is called **disrotatory**. As in the case of

conrotatory motion, there are two possible disrotatory motions. The difference between these two processes can only be seen when substituents are bonded to the polyene system.

Now let's compare the motions required for the HOMO and LUMO of 1,3,5-hexatriene with the corresponding molecular orbitals of 1,3-butadiene. The HOMO of 1,3,5-hexatriene is symmetric, and therefore a disrotatory motion is required to form a σ bond (Figure 28.5a). This result is the opposite of that for 1,3-butadiene. The LUMO of 1,3,5-hexatriene is antisymmetric. Therefore, a conrotatory motion is required to form a σ bond (Figure 28.5b). This result is again the opposite of that for 1,3-butadiene.

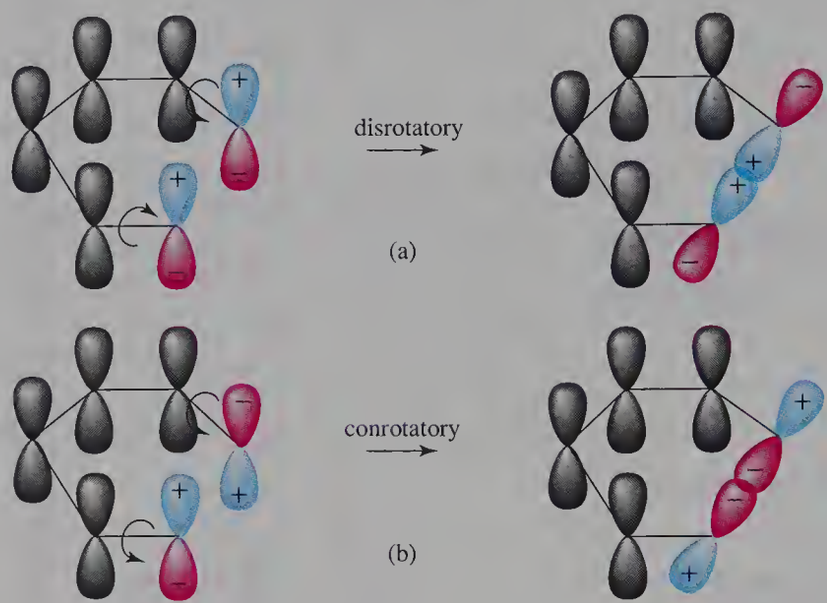


FIGURE 28.5
Conrotatory and Disrotatory Motion for a Triene
(a) A disrotatory motion is required for an electrocyclic reaction involving a symmetric orbital. The direction of rotation viewed along the C-1 to C-2 bond is opposite that along the C-5 to C-6 bond.
(b) A conrotatory motion is required for an electrocyclic reaction involving an antisymmetric orbital. The directions of rotation viewed along the C-1 to C-2 bond and along the C-6 to C-5 bond are both counterclockwise.

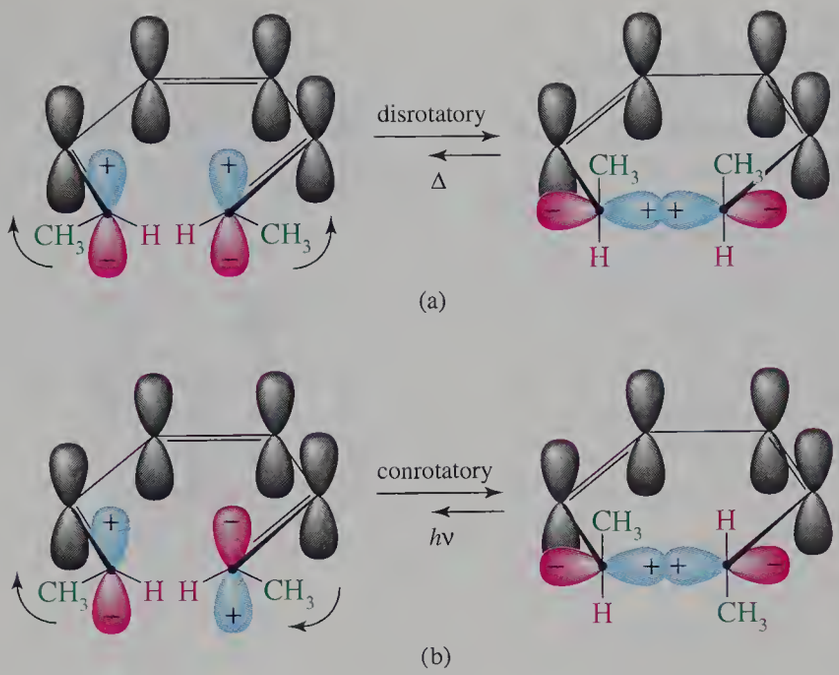
Analysis of 1,3,5-hexatriene (a $4n + 2$ π system) and of 1,3-butadiene (a $4n$ π system) allows us to conclude that the difference in the stereochemistry of the product as a result of conrotatory or disrotatory motion depends on the number of electrons in the π system. The motion of the orbitals involved in symmetry-allowed reactions of $4n$ systems is the opposite of that of $4n + 2$ π systems.

Thermal Cyclization of $4n + 2$ π Systems

The type of motion the orbital of the terminal carbon undergoes in an electrocyclic reaction can be detected only if substituents are bonded to these atoms. Substituents move as orbitals move. Let's examine the result of the motion required for the thermal cyclization of (2*E*,4*Z*,6*E*)-octatriene. We consider π_3 because it is the HOMO. It contains the highest energy electrons, so it is the frontier molecular orbital. As outlined above, disrotatory motion is required for σ bond formation at the ends of a conjugated triene. Disrotatory motion of the terminal 2*p* orbitals causes simultaneous disrotatory motion of the C-1 and C-8 methyl groups, and yields *cis*-5,6-dimethyl-1,3-cyclohexadiene (Figure 28.6a).

In this process, the hybridizations of the original C-2 and C-7 carbon atoms change, and the positions of the single and double bonds are interchanged.

FIGURE 28.6
Electrocyclic Reactions of Trienes
(a) The frontier molecular orbital for the thermal reaction is π_3, which is symmetric. A disrotatory motion is required for a symmetry-allowed reaction. (b) The frontier molecular orbital for the photochemical reaction is π_4, which is antisymmetric. A conrototary motion is required for a symmetry-allowed reaction.



Photochemical Cyclization of 4*n* + 2 π Systems

The product of the photochemical cyclization of a polyene has a different stereochemistry from the product of the thermal cyclization process. This difference results from the motion of the terminal 2*p* orbitals of a different frontier molecular orbital. Ultraviolet radiation promotes an electron from the HOMO to the LUMO of the molecule. The LUMO of a 1,3,5-hexatriene is π_4; it is antisymmetric. Because the signs of the terminal 2*p* orbitals on the same side of the molecule are opposite, the required motion of σ bond formation is conrotatory. Let's examine the result of this motion for (2*E*,4*Z*,6*E*)-octatriene. Conrotatory motion of the orbitals causes simultaneous conrotatory motion of the C-1 and C-8 methyl groups and yields *trans*-5,6-dimethyl-1,3-cyclohexadiene (Figure 28.6b).

Thermal Cyclization of 4*n* π Systems

We will examine the thermal cyclization of 1,3-butadiene as an example of a 4*n* π system. We account for this cyclization using the HOMO of this compound, π_2. This molecular orbital is antisymmetric. Because the signs of the contributing terminal 2*p* carbon orbitals on one side of the molecule are opposite, formation of a bond between atoms 1 and 4 of the π system requires a conrotatory motion. Let's examine the result of this motion for (2*E*,4*E*)-hexadiene. Conrotatory motion of the orbitals causes simultaneous conrotatory motion of the C-1 and C-6 methyl groups to yield *trans*-3,4-dimethylcyclobutene (Figure 28.7a).

The cyclization of (2*E*,4*E*)-hexadiene has a very small equilibrium constant because *trans*-3,4-dimethylcyclobutene is the thermodynamically unstable isomer. Therefore, the reverse ring-opening reaction of a cyclobutene to a 1,3-butadiene is favored and is the observed reaction. The symmetry rules must apply in both directions based on the principle of microscopic reversibility (Section 7.5). Thus, the ring must also open in a conrotatory manner. It is important to separate the concept

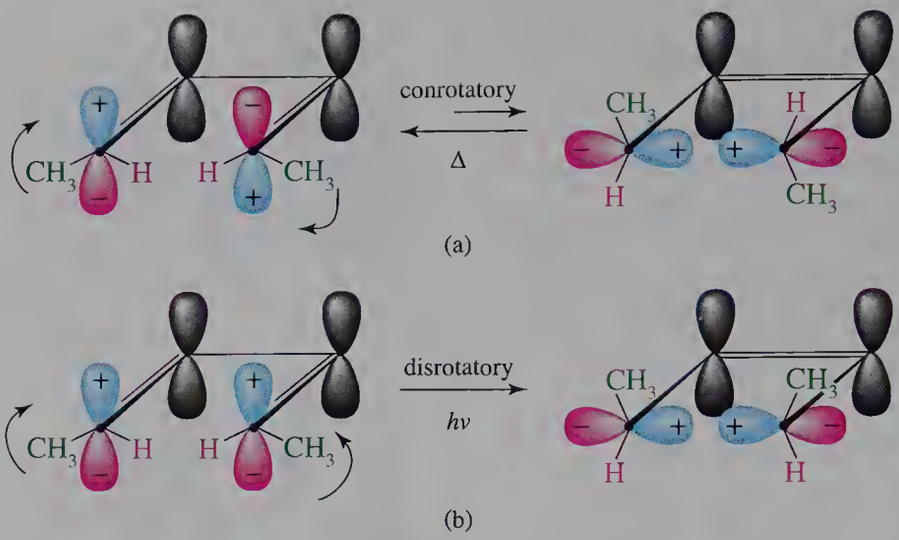


FIGURE 28.7
Electrocyclic Reactions of Dienes
(a) The frontier molecular orbital for the thermal reaction is π_2, which is antisymmetric. A conrotatory motion is required for a symmetry-allowed reaction. (b) The frontier molecular orbital for the photochemical reaction is π_3, which is symmetric. A disrotatory motion is required for a symmetry-allowed reaction.

of the equilibrium constant from that of symmetry-allowed reactions. The frontier molecular orbitals control the motions of the atoms in a reaction. The position of an equilibrium is controlled by ΔG°_{rxn}. Both a conjugated diene and a triene can undergo thermal electrocyclic reactions. In both cases, the cyclic compounds have more σ bonds and fewer π bonds. However, ΔH°_{rxn} is favorable only for the triene. The strain of the four-membered ring of the diene effectively reverses the relative stability of the reactants and products in the cyclization of the diene.

Photochemical Cyclization of 4*n* π Systems

As noted above, the product of the photochemical cyclization of polyenes with $4n + 2$ π electrons has a different stereochemistry from that of the product of the thermal cyclization process. The same reversal of stereochemistry is observed for $4n$ π electron systems. Ultraviolet radiation of a 1,3-butadiene system results in promotion of an electron from π_2, the HOMO, to π_3, the LUMO. In 1,3-butadiene, π_3 is symmetric. Because the signs of the terminal $2p$ orbitals on the same side of molecule are the same, the required motion to form a σ bond is disrotatory. Let's examine the result of this motion for (2*E*,4*E*)-hexadiene. Disrotatory motion of orbitals causes simultaneous disrotatory motion of the C-1 and C-6 methyl groups and yields *cis*-3,4-dimethylbutene (Figure 28.7b).

Note that this reaction converts the thermodynamically stable isomer into the less stable cyclic cyclobutene product, a common result for photochemical reactions. However, no thermodynamic principles are violated. The reverse thermal reaction does not occur because at the low temperature used for the photochemical reaction, such thermal processes are very slow. Only the diene absorbs the ultraviolet radiation because λ_{max} of the cyclobutene is out of the range of the light source used. Thus, the energy of the light used to promote an electron from a HOMO to a LUMO drives the reaction "uphill" to yield the thermodynamically less stable isomer. The cyclobutene cannot absorb light. After it forms, cyclobutene is "trapped" and cannot revert to the diene. In other words, equilibrium cannot be achieved under the photochemical reaction conditions.

Summary

Thermal reactions of $4n$ and $4n + 2$ π systems occur via the HOMO, the HOMO for $4n$ π systems being antisymmetric and the HOMO for $4n + 2$ π systems symmetric. Photochemical reactions of both $4n$ and $4n + 2$ π systems occur via the LUMO. In $4n$ π systems, the LUMO is symmetric. In $4n + 2$ π systems it is antisymmetric. From these generalizations, we can predict the outcome of any symmetry-allowed electrocyclic reaction. Table 28.1 lists the selection rules that correlate the number of π electrons, the mode of activation of the reaction, and the allowed stereochemistry.

Table 28.1
Selection Rules for Electrocyclic Reactions

Number of electrons	*Type of reaction*	*Stereochemistry*
$4n$	thermal	conrotatory
$4n$	photochemical	disrotatory
$4n + 2$	thermal	disrotatory
$4n + 2$	photochemical	conrotatory

Problem 28.2

Assume that a thermal cyclization occurs in a tetraene to give a cyclic triene. What is the frontier molecular orbital and what is its symmetry? What type of orbital motion leads to cyclization?

Sample Solution

The highest occupied molecular orbital of a tetraene is π_4 because the eight electrons are distributed starting at π_1 and two electrons are added to each molecular orbital until π_4 is filled. The symmetry of molecular orbitals in an array of molecular orbitals alternates between adjacent orbitals. The π_1 molecular orbital of any linear polyene is symmetric. Thus π_4 is antisymmetric.

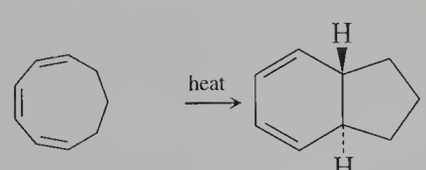
The terminal $2p$ orbitals of an antisymmetric molecular orbital have the positively signed lobes on the opposite sides of the molecule. Thus, the orbitals must rotate in the same direction to form a σ bond. The rotation is conrotatory.

Problem 28.3

Draw the product of the photochemical cyclization of 1,3-cycloheptadiene.

Problem 28.4

Is the following thermal cyclization reaction of 1,3,5-cyclononatriene symmetry allowed or forbidden?



1,3,5-cyclononatriene

28.5 Cycloaddition Reactions

In a cycloaddition reaction, the 2*p* orbitals of the terminal atoms of one π system overlap with the 2*p* orbitals of the terminal atoms of a second π system. Such overlap can occur only if the orbitals have the proper symmetry. The signs of each individual set of 2*p* orbitals that overlap to form a σ bond must be the same.

Cycloaddition reactions are classified with respect to the two planes of the reacting molecules and the stereochemistry of their interaction. Two π systems can interact in two ways. In **suprafacial** cycloadditions, an overlap occurs between the terminal atoms of one π system and the terminal atoms of the other π system on the same face. Such an arrangement is shown for a [4 + 2] cycloaddition reaction in Figure 28.8.

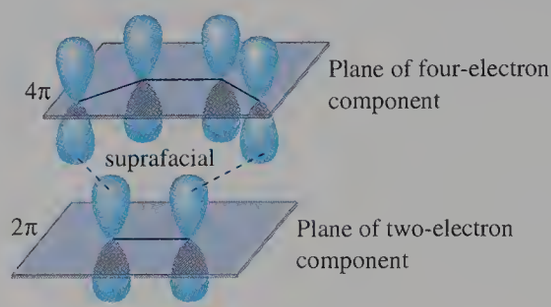


FIGURE 28.8
Suprafacial Cycloaddition of a (4 + 2) System
A bonding interaction is required between the terminal orbitals of both π systems. If the bonding occurs across the same face, the addition is suprafacial.

If one of the interacting molecular orbitals for a cycloaddition reaction is symmetric, then the other must also be symmetric for a suprafacial process. If one of the interacting molecular orbitals is antisymmetric, then the other must also be antisymmetric.

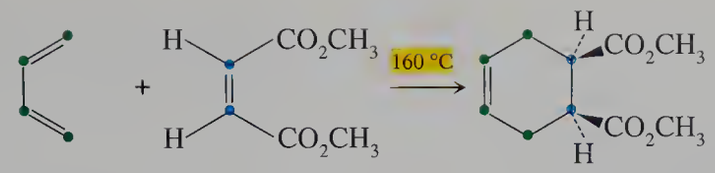
The other possible mode of cycloaddition is **antarafacial**. This cycloaddition results in bridging between opposite faces of the two π systems. This type of addition is symmetry allowed if one molecular orbital is symmetric and the other is antisymmetric. However, this type of cycloaddition has geometric constraints. A bridge that contains many atoms is required to permit simultaneous bonding to the opposite sides of a π system. So, antarafacial additions are rare.

The two modes of addition and the associated stereochemistry resemble other addition reactions we studied earlier. The suprafacial addition is a concerted syn addition to one of the π systems. The antarafacial addition corresponds to a concerted anti addition. Although anti addition reactions are common in the chemistry of alkenes, the two groups that add are not bonded to each other in the transition state. In cycloaddition reactions, both atoms of the molecule that bond to the terminal atoms of the second molecule are also connected to each other. Thus, only if the number of atoms in each of the two molecules is quite large can one molecule add to the other in an antarafacial manner.

Stereochemistry of Cycloaddition Reactions

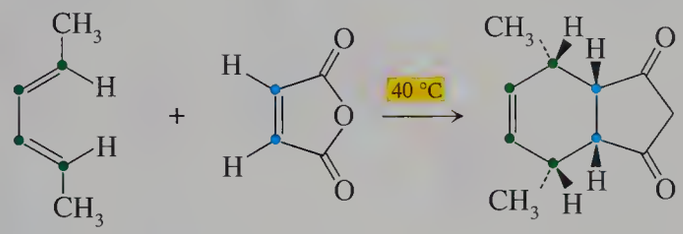
The Diels–Alder reaction has been studied for many years. The simplest Diels–Alder reaction converts 1,3-butadiene and ethylene into cyclohexene. However, the reaction occurs readily only at temperatures above 200 °C, and it has a low yield. Substituted dienes and dienophiles react at much lower temperatures with better yields. The best combination of reactants is a diene substituted with electron-donating groups and a dienophile substituted with electron-withdrawing groups.

Diels–Alder reactions occur with retention of stereochemistry in each component. For example, when dimethyl maleate reacts with 1,3-butadiene, the cis arrangement of the carbomethoxy groups of the reactant remains in the product.



1,3-butadiene dimethyl maleate

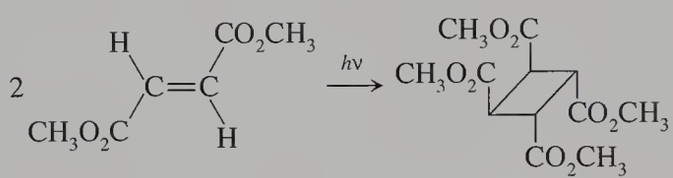
Retention of stereochemistry also occurs for the diene. For example, (2*E*,4*E*)-hexadiene reacts with maleic anhydride to give a product with cis methyl groups. Many examples of this type lead to the conclusion that the Diels–Alder and other [4 + 2] cycloaddition reactions occur suprafacially on each component.



(2*E*,4*E*)-hexadiene maleic anhydride

Thermal [2 + 2] cycloadditions, which are rare, do not occur by a concerted mechanism. These reactions occur by a stepwise radical mechanism. As a consequence, the reactions are not stereospecific. Because these reactions are not concerted, the rules of orbital symmetry do not apply.

Photochemical [2 + 2] cycloadditions do occur. The process is useful as a method to produce cyclobutanes. From stereochemical studies, we conclude that the reaction occurs suprafacially.



Molecular Orbitals in Cycloadditions

To explain the stereochemistry of cycloaddition reactions using molecular orbitals, we must first determine which molecular orbitals in each reaction are involved in the transition state. The reaction can be thought of as a Lewis acid–Lewis base process in which one reactant donates an electron pair to the second reactant. We will arbitrarily assign the role of electron pair donor to one of the two reactants. This reactant provides electrons from the HOMO. The second reactant is the electron pair acceptor. It uses its LUMO in the reaction. The assignment of roles of electron donor and electron acceptor is arbitrary because the same stereochemical result is predicted if the roles are reversed. We recall that the symmetry of adjacent molecular orbitals in an array of molecular orbitals alternates. Thus, the reversal of HOMO and LUMO in one reactant results in a change of symmetry. However, the reversal of the LUMO and HOMO of the second reactant also leads to a change of symmetry, so there is no net change.

For the Diels–Alder reaction, we will select the HOMO of the diene and the LUMO of the alkene. Therefore π_2 in the diene supplies the electrons. To accommodate the electron pair, the alkene uses π_2. Both orbitals are antisymmetric, and the bonding of the terminal lobes occurs if the two molecules are arranged with

suprafacial geometry (Figure 28.9). Note that we have to consider the signs of the wave functions only at the terminal lobes.

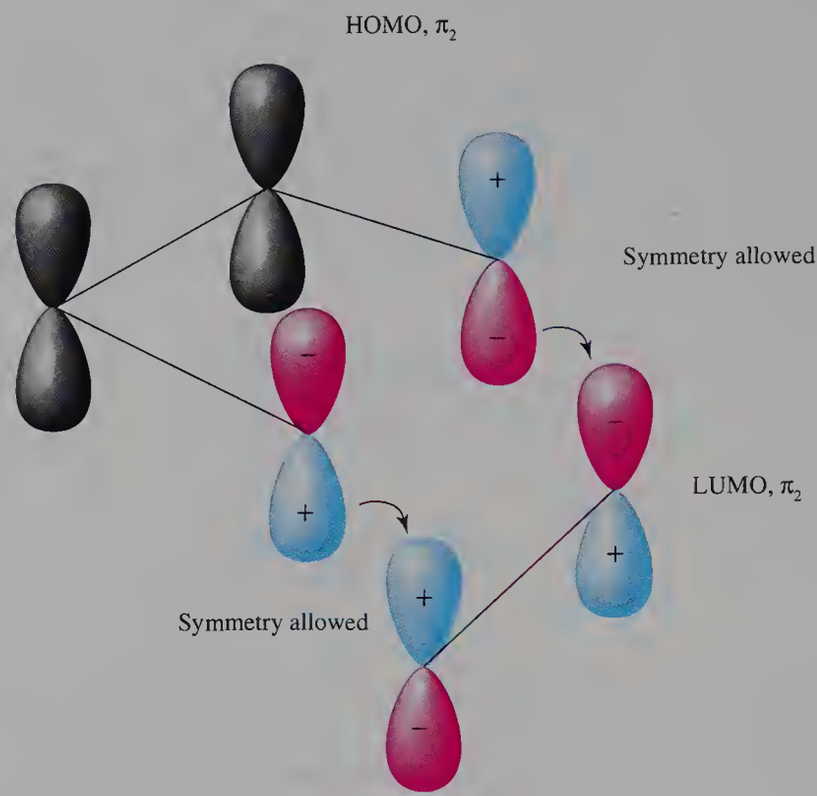


FIGURE 28.9 Molecular Orbitals for the Diels–Alder Reaction
The HOMO of the diene, which is antisymmetric, can interact with the LUMO of the dienophile, which is also antisymmetric. The process is suprafacial.

Now let's consider the possibility of a thermal [2 + 2] cycloaddition of two alkenes. The HOMO of one alkene is symmetric, and the LUMO of the other alkene is antisymmetric (Figure 28.10). Constructive overlap of one set of 2*p* orbitals is shown in a suprafacial arrangement. The overlap of the second set of 2*p* orbitals would be destructive. To achieve a constructive overlap of these 2*p* orbitals, an antarafacial arrangement would be required. However, geometric constraints prevent an antarafacial addition.

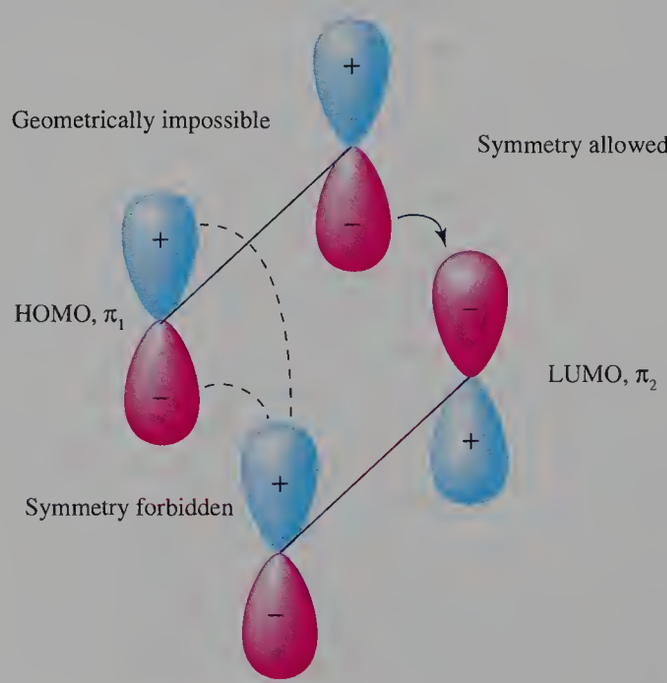


FIGURE 28.10 Symmetry-Disallowed Thermal (2 + 2) Addition Reaction
The HOMO of one alkene cannot interact with the LUMO of another alkene in a thermal reaction. Bonding is possible only at one set of carbon atoms for a suprafacial addition. An antarafacial addition of the positively signed lobes of the carbon atoms on the left of each alkene is geometrically impossible.

Two alkenes do react in a photochemical [2 + 2] cycloaddition. In this process, an electron is promoted to π_2 of one alkene. This alkene functions as the "donor". The second alkene, which functions as the "acceptor", must use π_2 (Figure 28.11). Because both molecular orbitals are antisymmetric, the overlap of two 2*p* orbitals with a positive value of the wave function can occur simultaneously with overlap of the other two 2*p* orbitals with negative values of the wave function.

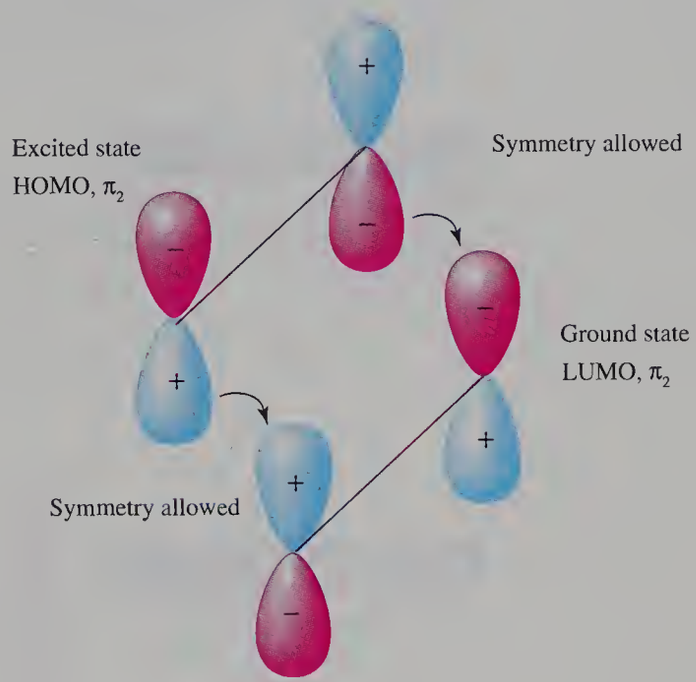


FIGURE 28.11
Symmetry-Allowed Photochemical (2 + 2) Addition Reaction
The LUMO of a ground state alkene can interact with the HOMO of an excited state alkene in a photochemical reaction. Bonding can occur at both sets of carbon atoms for a suprafacial addition.

The generalizations about the stereochemistry of cycloaddition reactions based on orbital symmetry rules are listed in Table 28.2. Again we note that geometric constraints prevent antarafacial reactions even though the reacting molecular orbitals have the proper symmetry relationship. Inadequate chain length as well as severe twisting of the molecules may make the transition state energy so high that no reaction occurs.

Table 28.2
Selection Rules for Cycloaddition Reactions

Number of electrons	*Type of reaction*	*Stereochemistry*
$4n$	thermal	antarafacial
$4n$	photochemical	suprafacial
$4n + 2$	thermal	suprafacial
$4n + 2$	photochemical	antarafacial

Problem 28.5

What type of reaction would be required for two molecules of 1,3-butadiene to undergo a thermal [4 + 4] cycloaddition to yield 1,5-cyclooctadiene?

Sample Solution

The HOMO of the diene that "donates" electrons in a cycloaddition reaction is π_2, which is antisymmetric. The LUMO of the diene that "accepts" electrons in a cycloaddition reaction is π_3, which is symmetric. In a suprafacial arrangement, the overlap of one set

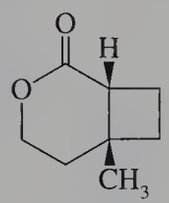
of orbitals at terminal atoms can be constructive. However, overlap of the second set of orbitals would be destructive and the suprafacial addition is forbidden. Only the alternate antarafacial addition could provide constructive overlap of orbitals at both ends of the two π systems.

Problem 28.6

Two molecules of 1,3-butadiene readily react in a thermal [4 + 2] cycloaddition reaction. Draw the structure of the product.

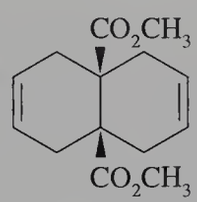
Problem 28.7

What type of reaction and reactants are required to synthesize the following compound using a cycloaddition reaction?



Problem 28.8

The following compound can be prepared by a thermal [4 + 2] cycloaddition reaction. Draw the structure of the two reactants required for the reaction.



28.6 Sigmatropic Rearrangements

Migration of a group from one site of a π system to another can occur in two ways. Migration across the same face is a suprafacial rearrangement; migration from one face to the other face is an antarafacial rearrangement. Therefore, sigmatropic rearrangements are controlled by the same orbital symmetry considerations as cycloaddition reactions. Table 28.3 lists the rules for thermal and photochemical sigmatropic rearrangements.

Table 28.3
Selection Rules for Sigmatropic Rearrangements

Number of electrons	*Type of reaction*	*Stereochemistry*
$4n$	thermal	antarafacial
$4n$	photochemical	suprafacial
$4n + 2$	thermal	suprafacial
$4n + 2$	photochemical	antarafacial

Molecular Orbitals

To analyze sigmatropic rearrangements, it is convenient to consider a homolytic cleavage of the migrating group's σ bond. Two radical fragments result from homolytic cleavage, and we can then examine the symmetry of their individual molecular orbitals. The reaction does not occur by this mechanism, but the stereochemical consequences are the same if the "radicals" are not allowed to move out of contact with each other. Because we will consider the allyl system to explain [3,3] sigmatropic rearrangements and the pentadienyl system to explain [1,5] sigmatropic rearrangements, we will first examine the molecular orbitals for these two systems.

The molecular orbitals for allyl radicals and their orbital symmetry were presented in Chapter 12. Figure 28.12 shows the three π orbitals of the allyl system. The lowest energy MO is bonding over all three atoms and is symmetric. The MO labeled π_3 is entirely antibonding, has two nodes, and is symmetric. The MO labeled π_2 is nonbonding. Because there are three atoms, the single nodal plane of this MO must contain the center carbon atom. This MO, which is antisymmetric, is the one involved in [3,3] sigmatropic rearrangements.

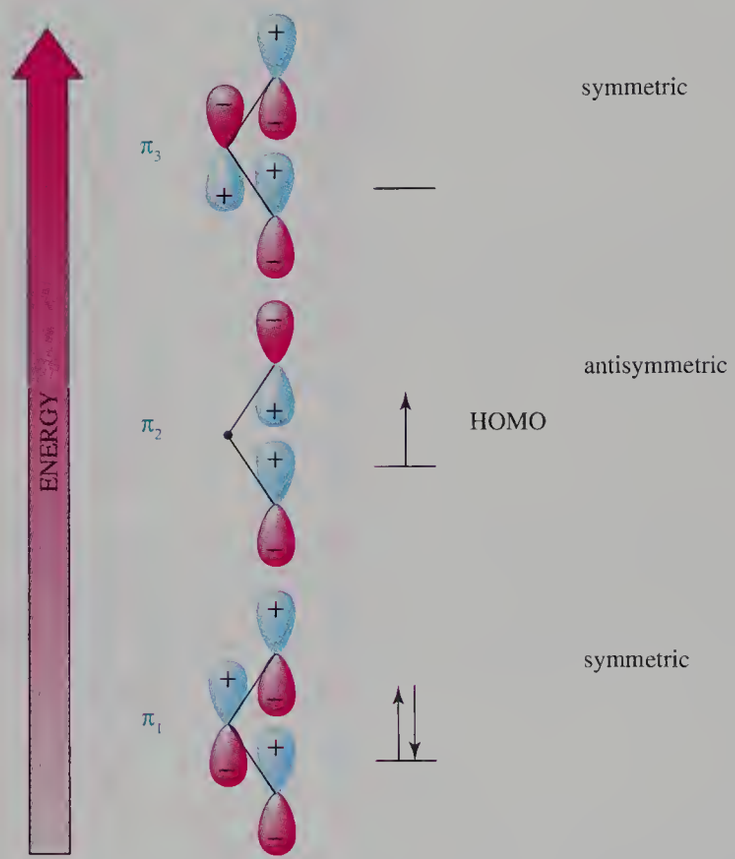


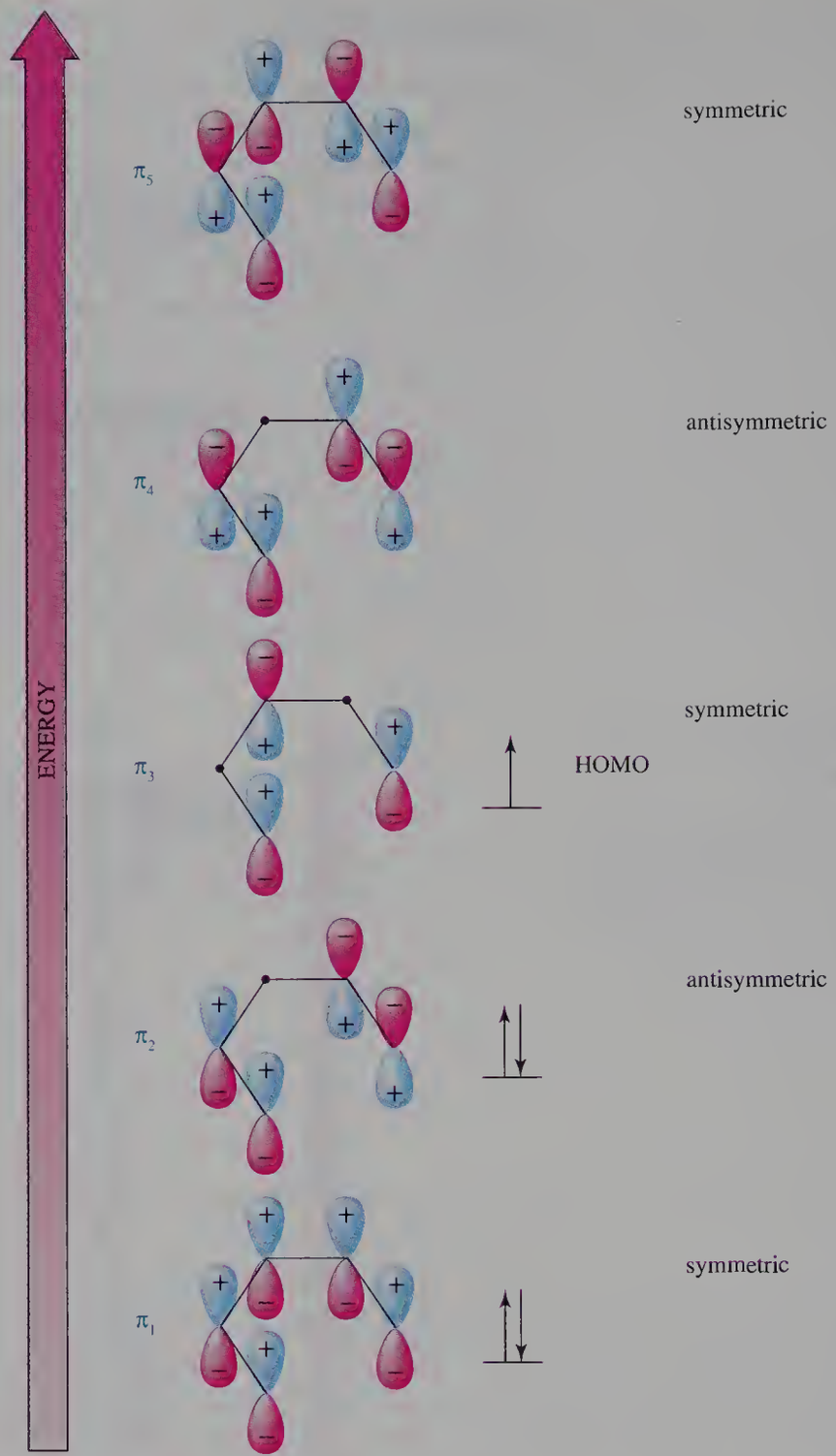
FIGURE 28.12
Molecular Orbitals of an Allyl Radical
The HOMO of the allyl radical is π_2. If we view the allyl radical as perpendicular to the plane of the page and bisected at C-2 by the page, we see that the HOMO is antisymmetric.

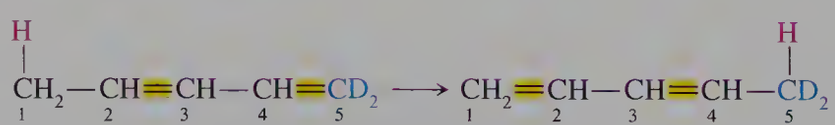
Figure 28.13 shows the five π orbitals of the pentadienyl system. The lowest energy MO is bonding over all five atoms and is symmetric. The symmetry of each succeeding MO of higher energy alternates. The MO required to explain [1,5] sigmatropic rearrangements is π_3. It is symmetric.

[1,5] Sigmatropic Rearrangements

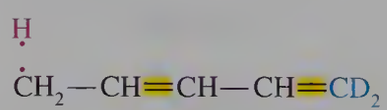
Let's consider the most common type of [1,5] sigmatropic rearrangement: the migration of a hydrogen atom over a pentadienyl system.

FIGURE 28.13
Molecular Orbitals of a Pentadienyl Radical
There are five π molecular orbitals for a pentadienyl radical. The HOMO is π_3 and is symmetric with respect to a plane that is perpendicular to the plane of the radical and bisecting C-3.





If we picture a homolytic cleavage of a C—H bond, the result is a hydrogen atom and a pentadienyl radical.



The pentadienyl radical has 5 π electrons that must be accommodated in the lowest energy molecular orbitals. Two electrons are located in the π_1 and π_2 molecular orbitals. The fifth electron is located in π_3, which is thus the HOMO. This molecular orbital is involved in the transfer of the migrating hydrogen atom. Because π_3 is symmetric, the terminal 2p orbitals have the same signs of the wave function on one side of the plane. As a result, the hydrogen atom moves suprafacially between the C-1 and C-5 atoms (Figure 28.14).

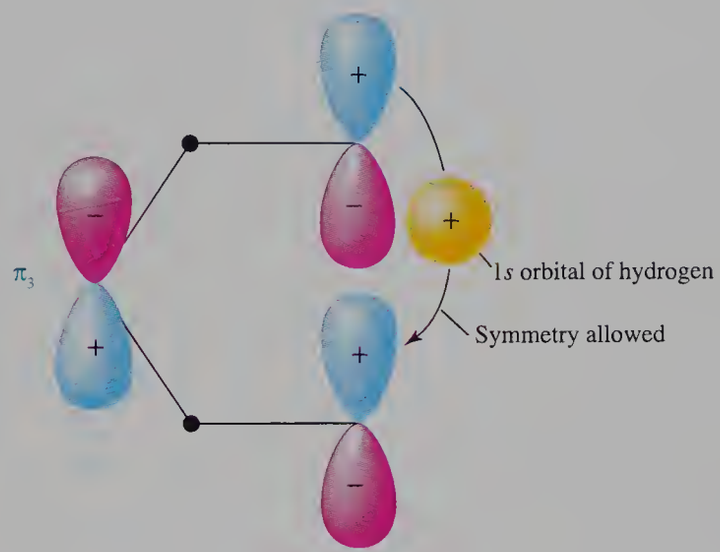
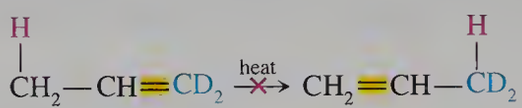
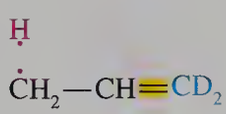


FIGURE 28.14
Molecular Orbitals and a [1,5] Sigmatropic Rearrangement
The HOMO of a pentadienyl radical, which is π_3, is symmetric. A [1,5] sigmatropic rearrangement can occur suprafacially.

Sigmatropic rearrangements of a [1,3] type do not occur thermally. Let's examine the molecular orbitals that would have to be involved in such a process to show why the model predicts that the reaction should not occur.



To visualize the reaction, we consider the homolytic cleavage of the C—H bond of the allyl system. Although the reaction does not occur this way, the orbitals involved in the concerted reactions have the same symmetry as those in the separate radical fragments. Thus, we consider the allyl radical and a hydrogen atom.



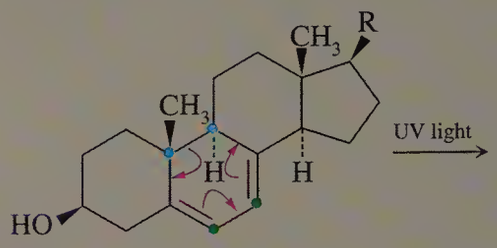
Two π electrons occupy π_1 and one occupies the π_2 molecular orbital. Thus, the HOMO is π_2, which is antisymmetric. Migration of a hydrogen atom suprafacially is geometrically possible, but not allowed by orbital symmetry. The hydrogen atom cannot leave C-1 and bond to C-3 because the symmetries of the orbitals are different (Figure 28.15).

Now consider the antarafacial migration of a hydrogen atom from C-1 to C-3. The signs of the wave functions corresponding to the two 2*p* orbitals are the same. The process is therefore allowed by the rules of orbital symmetry. However, such a concerted process is geometrically impossible because a single atom cannot form a bridge from one side of the three-carbon allyl system to the other.

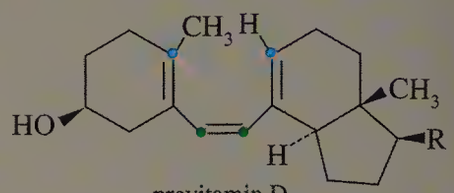
Vitamin D is a necessary part of the human diet for bone growth. Inadequate amounts of this vitamin cause inadequate calcification of bones. This condition in children is called *rickets*. The disease in adults is called *osteomalacia*. In spite of a vitamin D deficiency in the diet, it is known that an individual may generate vitamin D if there is sufficient exposure of one's skin to the sun. But in northern climates where the days are short in the winter and one's skin is covered, it is not possible to produce enough vitamin D to make up for dietary deficiencies.

Several structurally related compounds are called vitamin D. The differences are denoted by subscripts as in vitamin D_2 or D_3. All of these vitamins come from steroid precursors and differ in the identity of the alkyl group bonded to the five-membered ring.

Vitamin D_2 is produced by two pericyclic reactions, one of which is photochemically initiated and the second thermally initiated. The first step is a photochemical electrocyclic reaction in which a cyclohexadiene of the B ring is isomerized to a triene. The reaction involves six π electrons and is the reverse of the photochemical cyclization reaction discussed in Section 28.4. Thus, by the principle of microscopic reversibility, this photochemically allowed ring opening involving a $4n + 2$ π system must occur by a conrotatory process.



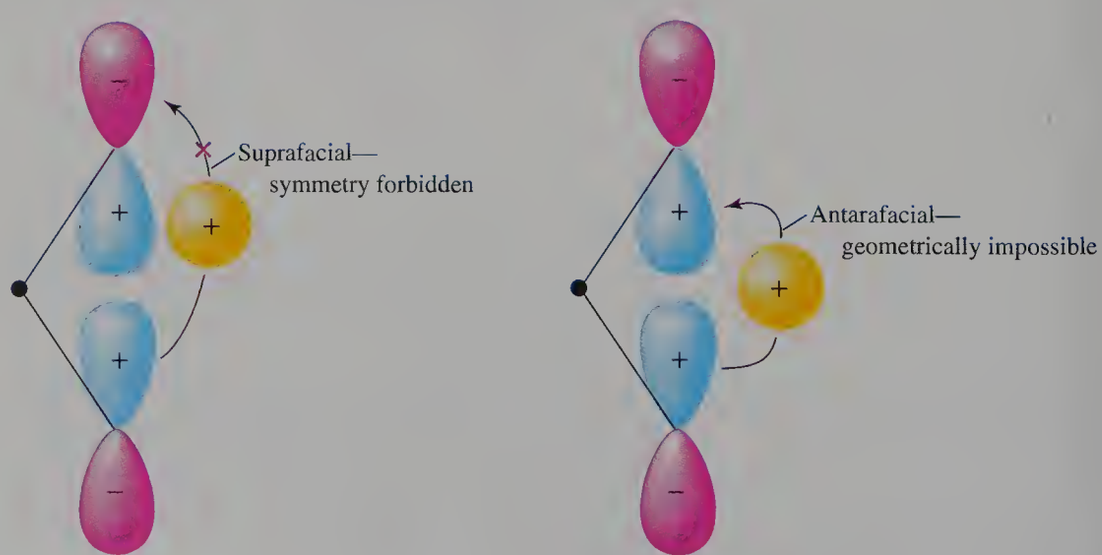
7-dehydrocholesterol

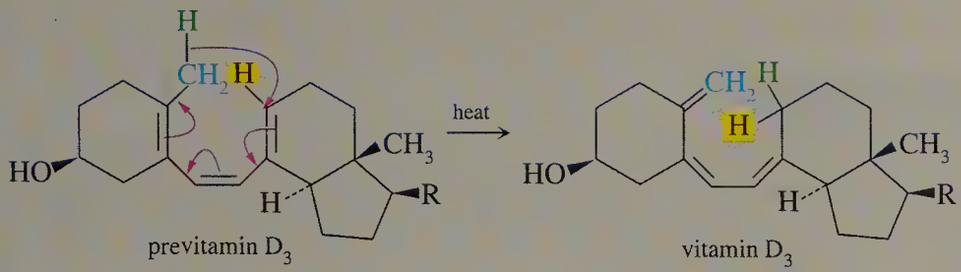


previtamin D_3

The second step, which yields vitamin D_3, is a thermal [1,7] sigmatropic shift of hydrogen. Based on the symmetry of the HOMO of a heptatrienyl system, the transfer of the hydrogen must occur antarafacially. Both the number of single bonds and the number of atoms provide sufficient flexibility for this reaction to occur.

FIGURE 28.15
Molecular Orbitals of a [1,3] Sigmatropic Rearrangement
The HOMO of an allyl radical is antisymmetric. A [1,3] sigmatropic rearrangement cannot occur suprafacially. An antarafacial rearrangement is symmetry allowed, but cannot occur because of geometric restrictions.

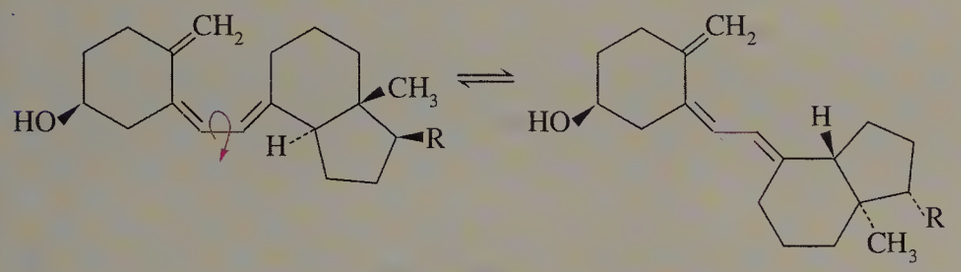




previtamin D_3 vitamin D_3

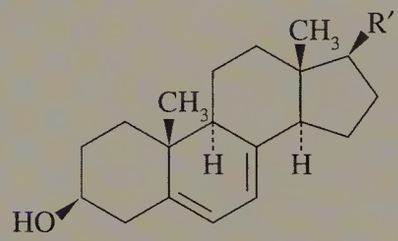
The thermal [1,7] sigmatropic shift is slow at body temperature, and it takes several days to "use up" the previtamin D_3 originally produced by exposure to sunlight.

Vitamin D_3 actually exists in an s-trans conformation that results from rotation around the σ bond located between the two rings.



s-cis s-trans

Another form, called vitamin D_2, is commonly added to milk. It is derived from ergosterol, which differs from 7-dehydrocholesterol by an additional methyl group and a double bond in the side chain bonded to the D ring.

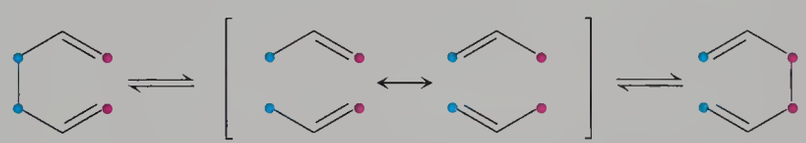


ergosterol

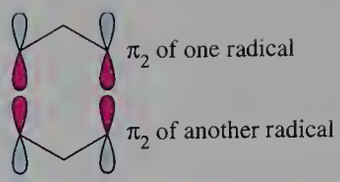
Ergosterol is irradiated to give a previtamin D_2 by a photochemically allowed conrotatory ring-opening reaction. A subsequent thermal [1,7] sigmatropic shift occurs to give vitamin D_2. Because of labeling laws, milk that contains vitamin D_2 is indicated by the term *irradiated ergosterol*.

[3,3] Sigmatropic Rearrangements

A [3,3] sigmatropic rearrangement such as the Cope rearrangement of 1,5-hexadiene can be thought of as a process in which two three-carbon radical fragments form and then bond again in a different position. Again, as noted previously, the reaction does not proceed by free radical intermediates. However, the same orbitals are involved in the concerted process. So we can explain the experimental results using this model. The resonance forms of the two allyl radicals used as models for the reactions are shown as a transition state in the following equation.

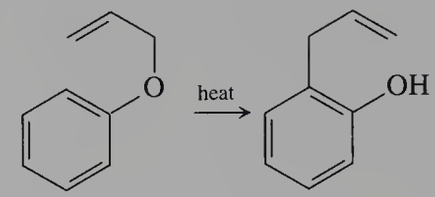


An allyl radical contains three π electrons, two in π_1 and one in the π_2 molecular orbital. Therefore, the frontier molecular orbital is π_2, which is antisymmetric. The bond that is broken must generate 2*p* atomic orbitals with lobes of the same sign directed toward each other. The bond to be formed must occur between 2*p* atomic orbitals with lobes of the same sign directed toward each other. This can be accomplished using the HOMO of one radical to form a σ bond with the HOMO of the other radical.



Problem 28.9

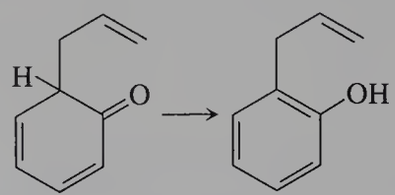
The Claisen rearrangement of allyl aryl ethers to give *o*-allylphenols is an example of a [3,3] sigmatropic shift. The initial product is an isomer of the *o*-allylphenol, which undergoes a familiar isomerization reaction. Draw the structure of the initial product. What is the subsequent isomerization reaction?



allyl phenyl ether *o*-allylphenol

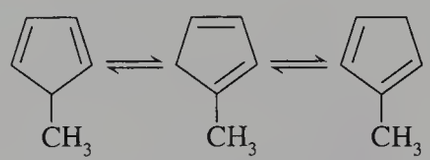
Sample Solution

A [3,3] sigmatropic rearrangement gives a ketone that lacks the resonance stabilization of an aromatic ring. However, tautomerization gives the enol form, which is a phenol and contains an aromatic ring.



Problem 28.10

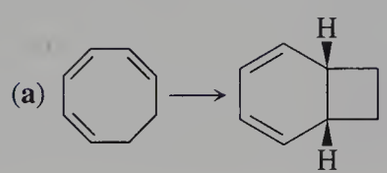
5-Methyl-1,3-cyclopentadiene rapidly rearranges to give a mixture of that compound and its 1-methyl and 3-methyl isomers. Explain how this isomerization occurs.

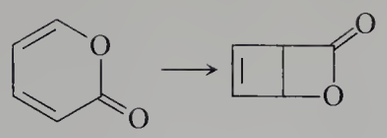


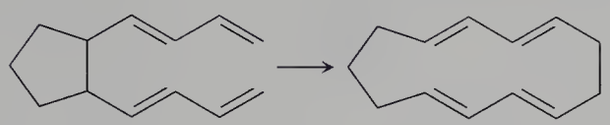
EXERCISES

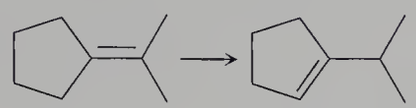
Classification of Pericyclic Reactions

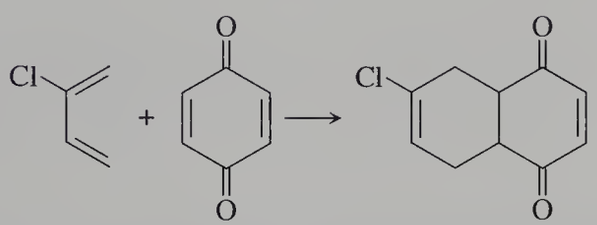
28.1 Classify each of the following reactions as electrocyclic, cycloaddition, or sigmatropic.



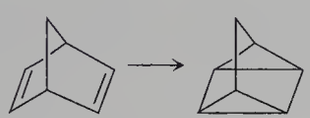
(b) 

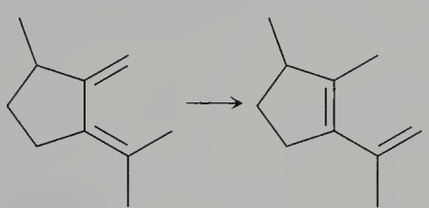
(c) 

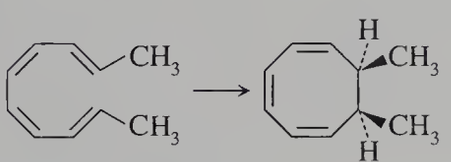
(d) 

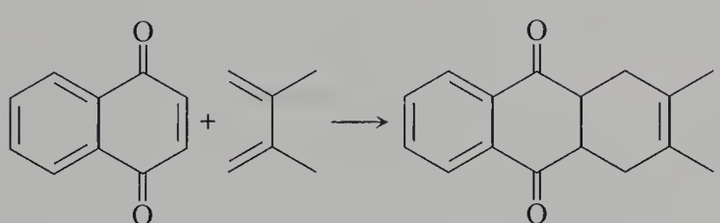
(e) 

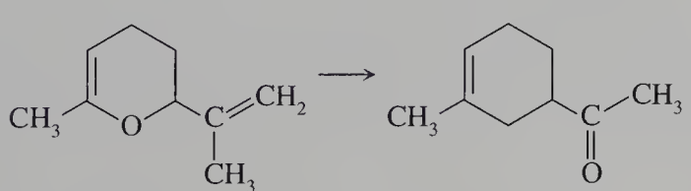
28.2 Classify each of the following reactions as electrocyclic, cycloaddition, or sigmatropic.

(a) 

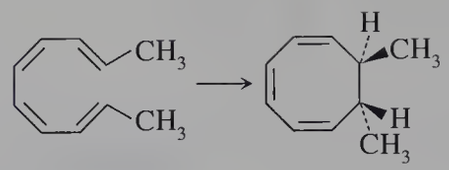
(b) 

(c) 

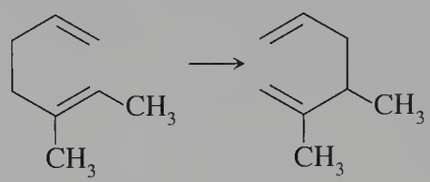
(d) 

(e) 

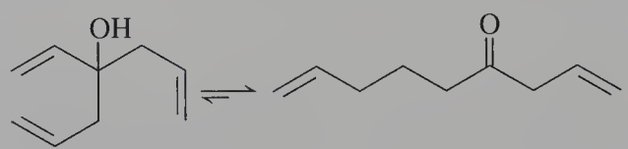
28.3 Estimate the ΔH°_{rxn} for the following electrocyclic reaction.



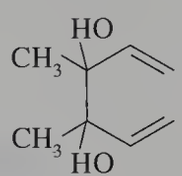
28.4 Estimate the ΔH° for the following sigmatropic rearrangement.



28.5 The following reaction occurs by a [3,3] sigmatropic shift and a subsequent rearrangement reaction. Explain why the equilibrium constant is large.

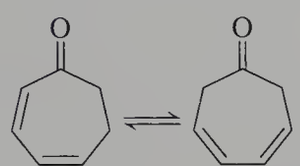


28.6 The following compound undergoes a [3,3] sigmatropic shift and a subsequent rearrangement reaction to give a diketone. Draw the structure of the final product. Is the equilibrium constant expected to be greater or less than one?

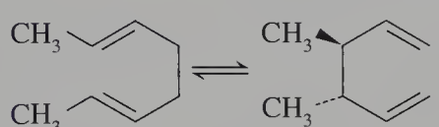


28.7 Which side is favored in each of the following equilibria?

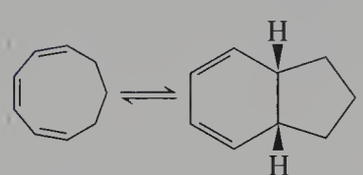
(a)



(b)

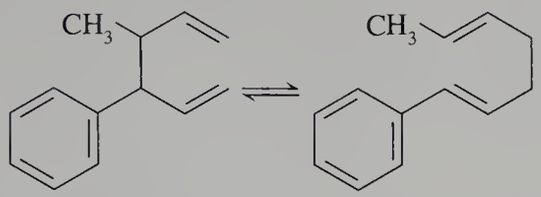


(c)

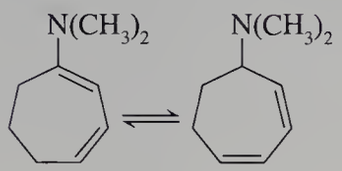


28.8 Which side is favored in each of the following equilibria?

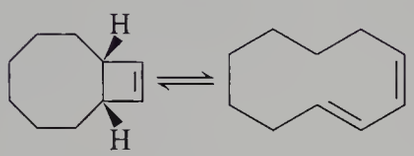
(a)



(b)



(c)

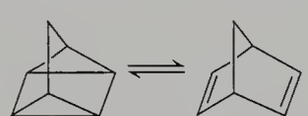


28.9 The ΔH°_{rxn} for the Diels–Alder reaction of 1,3-butadiene and ethylene is −168 kJ mole^{-1}. Compare this value with the estimated value determined in Section 28.2 and propose a reason for the difference between the two quantities.

28.10 Using average bond energies and the strain energy of a cyclobutane ring, calculate the ΔH° for the conversion of cyclobutane into two moles of ethylene.

28.11 The ΔS°_{rxn} for the Diels–Alder reaction of 1,3-butadiene and ethylene is −188 J mole^{-1} deg^{-1}. Using ΔH°_{rxn} = −168 kJ mole^{-1}, calculate the temperature at which the equilibrium constant is 1.

28.12 The thermal conversion of cyclobutane into two moles of ethylene is a thermodynamically favorable reaction. Consider the isomerization of the following compound, which contains a cyclobutane ring. What factors must be considered to determine if the reaction is more or less favorable than the ring cleavage of cyclobutane?



Molecular Orbitals

28.13 What π molecular orbital would account for the thermal [1,7] sigmatropic shift in previtamin A? What is the symmetry of the molecular orbital?

28.14 What molecular orbital would account for the photochemical electrocyclization of an octatetraene to give a cyclooctatriene? What is the symmetry of the molecular orbital?

Symmetry-Allowed Reactions

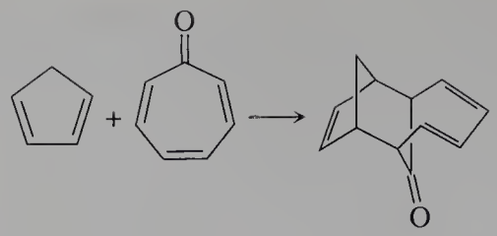
28.15 Describe the stereochemistry associated with each of the following symmetry-allowed reactions.

(a) a thermal [4 + 6] cycloaddition
(b) a photochemical [2 + 6] cycloaddition
(c) a thermal [1,7] sigmatropic rearrangement
(d) a photochemical [1,3] sigmatropic rearrangement

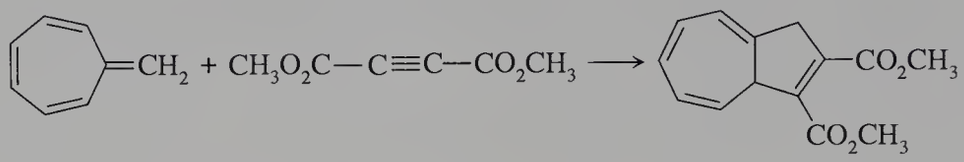
28.16 Describe the motion that occurs in each of the following symmetry-allowed reactions.

(a) thermal ring closure of a triene to a cyclohexadiene
(b) photochemical ring closure of a diene to a cyclobutene
(c) thermal ring opening of a cyclic triene to a tetraene
(d) photochemical ring opening of a cyclic diene to a triene

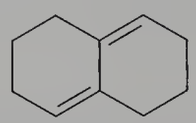
28.17 Classify the following thermal cycloaddition reaction. Is the reaction symmetry allowed? What π molecular orbitals are required to explain your answer? What are their respective symmetries?



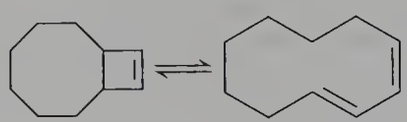
28.18 Show why the following thermal reaction is regarded as a [2 + 8] cycloaddition. What π molecular orbitals are required to determine if the reaction is symmetry allowed? What are their respective symmetries?

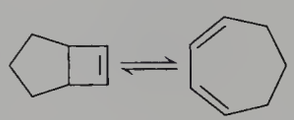


28.19 The following diene does not undergo a Diels–Alder reaction with maleic anhydride. Explain why this symmetry-allowed reaction does not occur.

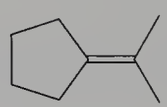


28.20 The ring-opening reaction of a cyclobutene ring fused to an eight-membered ring occurs at temperatures below 200 °C. Even though a structurally related compound with a cyclobutene ring fused to a five-membered ring is more strained, this ring-opening reaction requires temperatures near 300 °C. Explain why.

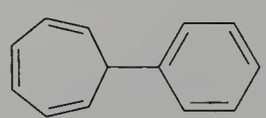




28.21 Photochemical [1,3] sigmatropic shifts do occur in some allylic systems. Draw the structures of the products resulting from the following alkene. Which product should predominate?

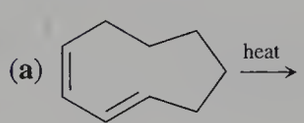


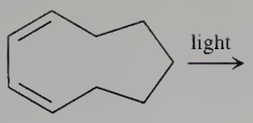
28.22 Explain why the following compound cannot undergo a [1,7] sigmatropic rearrangement, whereas previtamin D can. A photochemical [1,7] sigmatropic rearrangement occurs. Draw the structure of the first product formed.

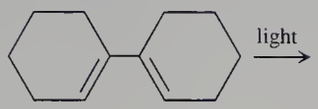


Electrocyclic Reactions

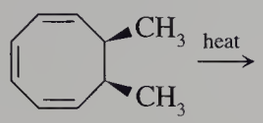
28.23 Draw the structure of the product of each of the following reactions, and indicate the stereochemistry.

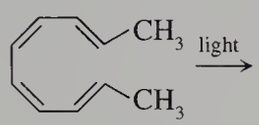


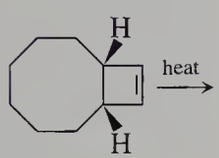
(b) 

(c) 

28.24 Draw the structure of the product of each of the following reactions, and indicate the stereochemistry.

(a) 

(b) 

(c) 

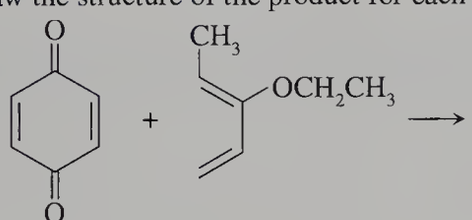
28.25 Explain why the thermal ring opening of *trans*-3,4-dimethylcyclobutene could yield two isomeric 2,4-hexadienes. Explain why only one isomer forms.

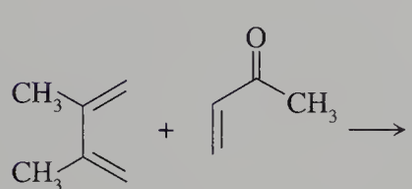
28.26 Which of the following compounds cannot undergo a thermal electrocyclic ring closure?

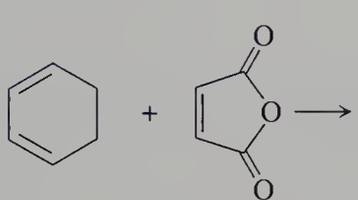
(a) (2*E*,4*Z*,6*E*)-2,4,6-octatriene
(b) (2*E*,4*E*,6*E*)-2,4,6-octatriene
(c) (2*E*,4*Z*,6*Z*)-2,4,6-octatriene

Cycloaddition Reactions

28.27 Draw the structure of the product for each of the following reactions.

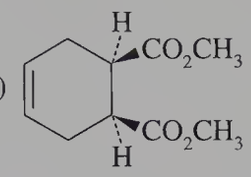
(a) 

(b) 

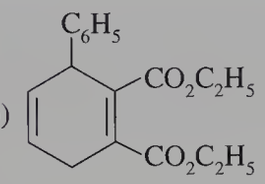
(c) 

28.28 What reactants are required to produce each of the following compounds via a Diels–Alder reaction?

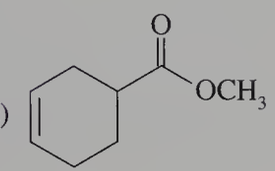
(a)



(b)



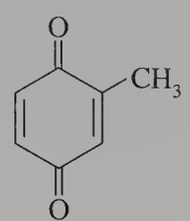
(c)



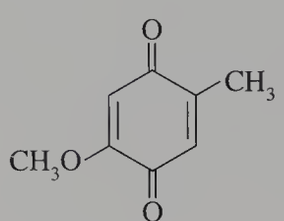
28.29 Explain why 1,3-cyclopentadiene reacts faster than 1,3-butadiene with maleic anhydride.

28.30 Explain why (2*Z*,4*Z*)-hexadiene does not react with maleic anhydride even though the diene has two methyl groups that increase the electron density of the diene.

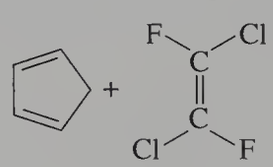
28.31 One equivalent of 1,3-butadiene reacts with the following quinone to give a single product. Draw the structure and explain why it forms.



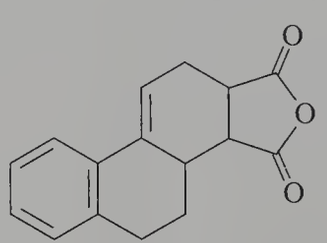
28.32 One equivalent of (*E*)-1,3-pentadiene reacts with the following quinone to give a mixture of two products. Draw their structures and explain why they form.



28.33 Draw the structure of the Diels–Alder product of the following combination of reactants.



28.34 What reactants are required to synthesize the following compound by a Diels–Alder reaction?



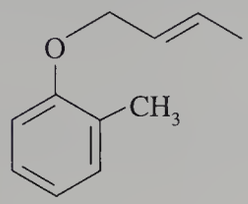
Sigmatropic Rearrangements

28.35 Explain why *cis*-1,2-divinylcyclobutane undergoes a [3,3] sigmatropic rearrangement faster than does 1,5-hexadiene.

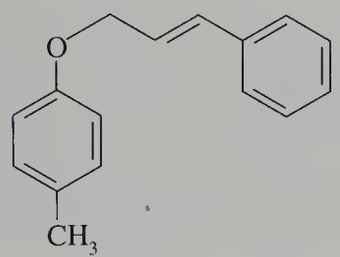
28.36 What type of reaction occurs in the conversion of allyl vinyl ether into 4-pentenal? Why does the reaction have a large equilibrium constant?

28.37 Draw the structure of the product of the Claisen rearrangement of each of the following compounds.

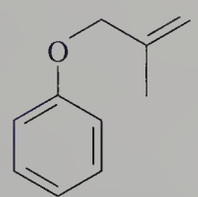
(a)



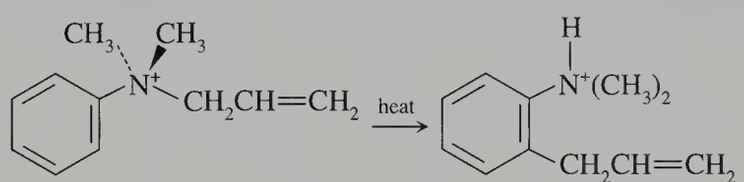
(b)



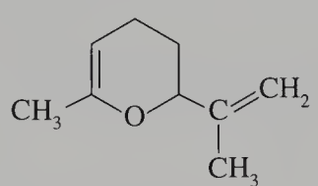
(c)



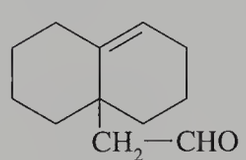
28.38 Write a mechanism to account for the following rearrangement reaction.



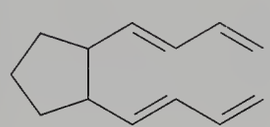
28.39 The following compound undergoes a Claisen-type rearrangement to yield a ketone. Draw the structure of the product.



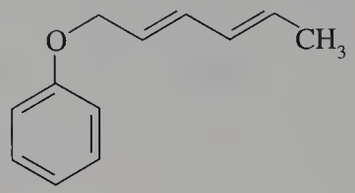
28.40 What reactant is required to yield the following aldehyde by a Claisen-type rearrangement?



28.41 Draw the product of a thermal [5,5] sigmatropic rearrangement of the following compound. Does the reaction occur by a suprafacial or antarafacial process?

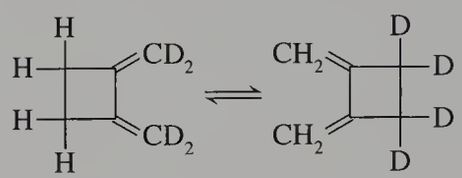


28.42 Assume that following ether undergoes a thermal [5,5] sigmatropic rearrangement. Draw the structure of the product.

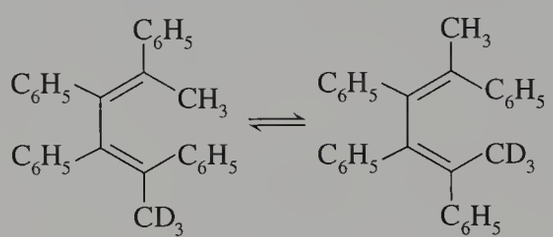


Multiple Pericyclic Reactions

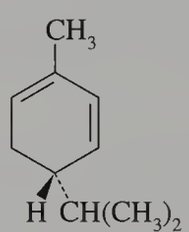
28.43 The following thermal isomerization reaction occurs by two similar sequential pericyclic reactions. Identify them and draw the structure of the intermediate compound.



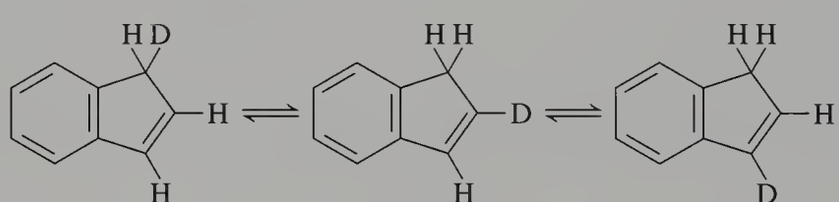
28.44 The following thermal isomerization occurs by two similar sequential pericyclic reactions. Identify them and draw the structure of the intermediate compound.



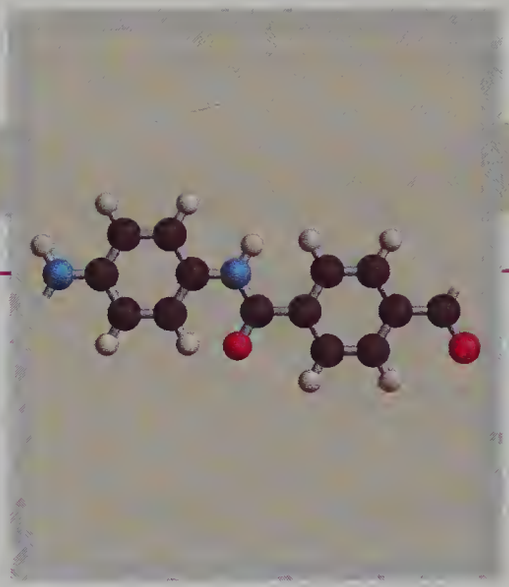
28.45 The following compound can lose its optical activity when heated. Two similar sequential pericyclic reactions are required to account for this result. Identify them and draw the structure of the intermediate compound.



28.46 The following isomerization reactions occur by related sequential pericyclic processes. Draw the structure of the intermediate compound involved in each reaction.



29



Synthetic Polymers

29.1 Natural and Synthetic Macromolecules

In most of our study of organic chemistry, we have focused on the chemical reactions, structure, and physical properties of "small" molecules. We examined very large molecules, or **macromolecules**, in only two chapters. Repeated condensation reactions of small molecules called monomers form polysaccharides and proteins (polyamides), two classes of macromolecules found in living organisms.

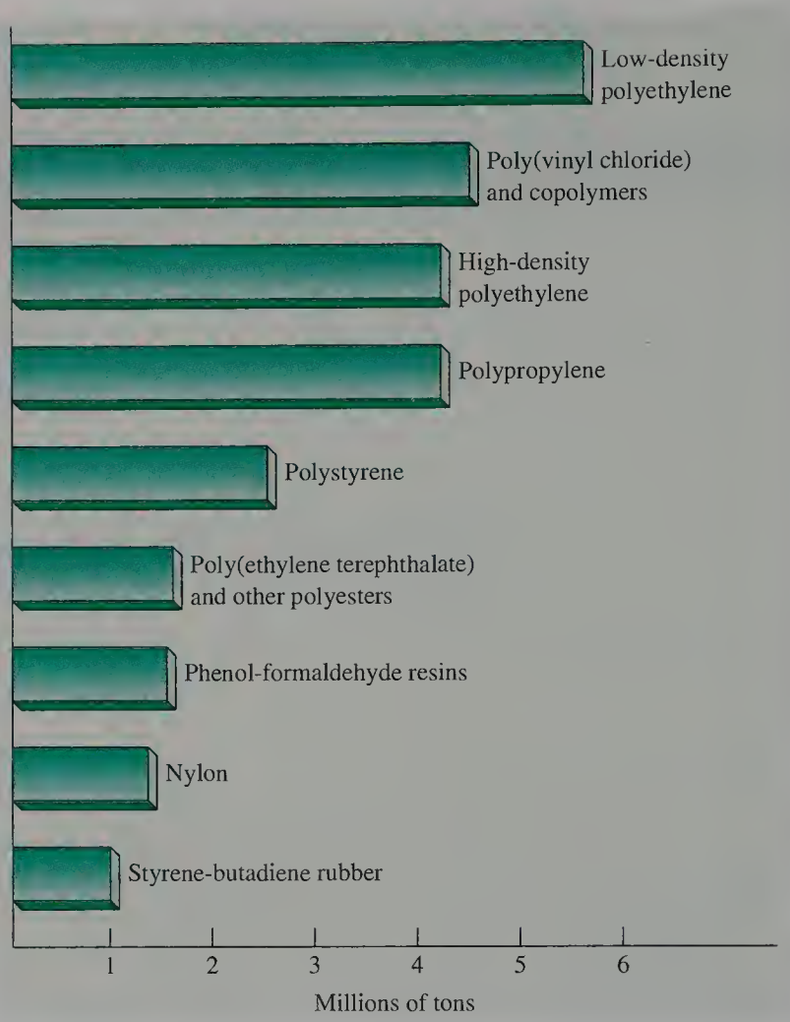
Some naturally occurring macromolecules are important commercial products. For example, wood and cotton are carbohydrates; wool and silk are proteins. But synthetic polymers far outstrip natural polymers in commercial importance. The chemical industry has developed many synthetic macromolecules with diverse properties and a wide variety of uses. These synthetic macromolecules are indispensable in a modern society. They include the rubber of tires, PVC of pipes and floor tile, and synthetic fibers such as nylon. The annual production of raw polymers by U.S. chemical industry totals more than 30 million tons (Figure 29.1). These polymers are subsequently converted into products accounting for about 5% of the total value of all goods and services of the U.S. economy. Approximately 50% of these products are used in packaging and construction.

29.2 Physical Properties of Polymers

Synthetic polymers have a wide range of properties. For example, certain transparent polymers can be molded into precise shapes in the manufacture of corrective lenses. The polymer rubber used in tires is flexible enough to be distorted from one shape to another but also capable of returning to its original shape. It also is durable and sufficiently stable to withstand exposure to extremes of weather conditions. Synthetic fibers used for clothing feel good against the body and are able to hold a dye.

The physical properties of synthetic macromolecules result from the number and kind of monomer units, as well as resulting intermolecular interactions and intramolecular interactions such as London forces and dipole–dipole forces. We recall that the properties of proteins and other natural macromolecules result from

FIGURE 29.1 Annual Production of Polymers



intermolecular interactions. For example, the strength of structural proteins such as collagen and cellulose is due to the many intermolecular hydrogen bonds. Hydrogen bonding can also be an important feature to consider in designing synthetic macromolecules.

Primary Structure and Properties

By synthesizing appropriate monomers and learning how to polymerize them, organic chemists can prepare macromolecules to meet required specifications. The number of monomer units—a few hundred to several thousand—in a polymer affects its physical properties. However, no synthetic polymerization process can be stopped precisely after a specific number of monomers have been incorporated into the polymer. All polymerization reactions give mixtures of polymer molecules with a range of molecular weights. Therefore, we refer to the average molecular weight of a polymer. The average molecular weight of synthetic polymers is in the 10^5 to 10^6 range.

Nylon, for example, must have a molecular weight of at least 10,000 to function well as a fiber. Below that molecular weight, the polymer is a brittle solid with no commercial value. The unique properties of polymers are also related to interactions between polymer chains. Therefore, a minimum size is required to give a material with useful properties. However, as the molecular weight increases, the properties of a polymer often change. For example, if the molecular weight of nylon is greater than 100,000, it does not form a fiber. However, it can be used in products that require high mechanical strength.

The types of monomers incorporated in a polymer strongly influence the flexibility and shape of the polymer. For example, polymers whose monomers contain aromatic rings are less flexible than those whose monomers are acyclic. In some polymers, the chains are cross-linked by covalent bonds. Cross-linking creates larger macromolecules with more rigid structures. Cross-links are also important in naturally occurring polymers. For example, the proteins in wool fibers are cross-linked by many disulfide bonds.

London Forces and Physical Properties

As in the case of proteins, the intermolecular and intramolecular interactions of polymer chains are extremely important in determining physical properties. London forces are largely responsible for the folded or coiled conformations of a polymer. Intermolecular London forces between individual chains help to hold them together. Both intramolecular and intermolecular London forces increase with the polarizability of functional groups in the polymer.

Only London forces affect the properties of polyethylene. This molecule, which can be produced as a linear polymer, resembles a giant alkane (Figure 29.2). We know that as the size of an alkane increases, the number of sites for intermolecular attractions increases. For example, the boiling points of alkanes increase as the number of hydrogen–hydrogen interactions between individual molecules increases. The attractive forces between pairs of hydrogen atoms on adjacent chains of a polymer may be only 0.5 kJ mole^{-1}. However, thousands of those interactions exist in a polymer, producing a total interaction energy as large as that of covalent bonds.

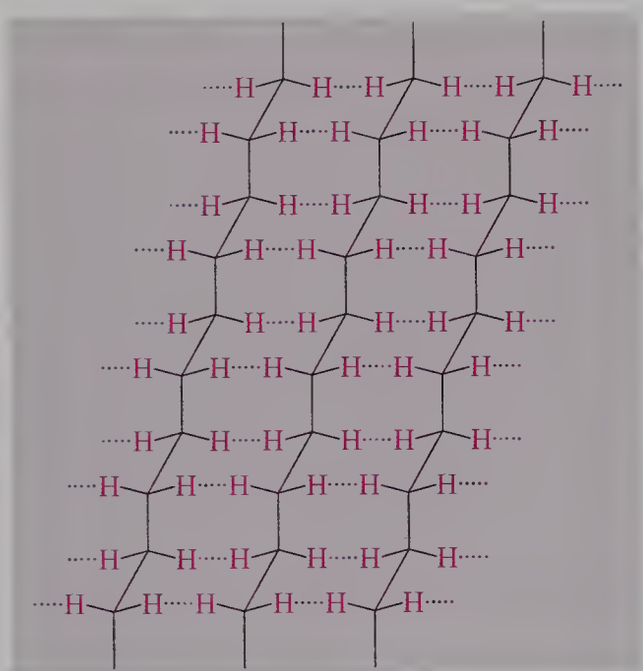


FIGURE 29.2 London Forces in Polyethylene
The dotted lines represent London attractive interactions between hydrogen atoms. Additional chains (not shown) may be above and below the represented plane.

The linear polymer of ethylene is called high density polyethylene (HDPE). It has a high density and is high melting (135 °C) because parts of the molecules "line up" in a tightly packed, orderly array. HDPE is used to make materials as simple as bottle caps for milk containers and as complex as cabinets for televisions and computers.

Ethylene can also be polymerized with branches off the main chain (Figure 29.3). The resulting polymer is called low density polyethylene (LDPE). LDPE is

less dense than HDPE because the branches prevent the main chains from packing closely. The more open structure not only is less dense but also has smaller London forces. Because the intermolecular forces between chains are smaller, LDPE has a lower melting point (120 °C) and is a more flexible material. It is used to make plastic bags and flexible bottles for consumer products such as soft drinks and bleach. Containers made of LDPE are also used for windshield wiper fluid, antifreeze, and engine oil.

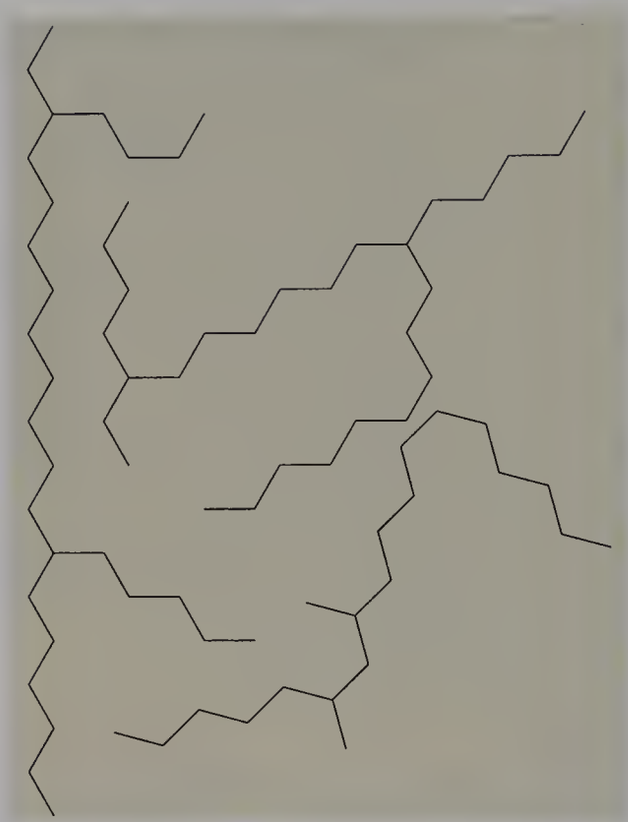
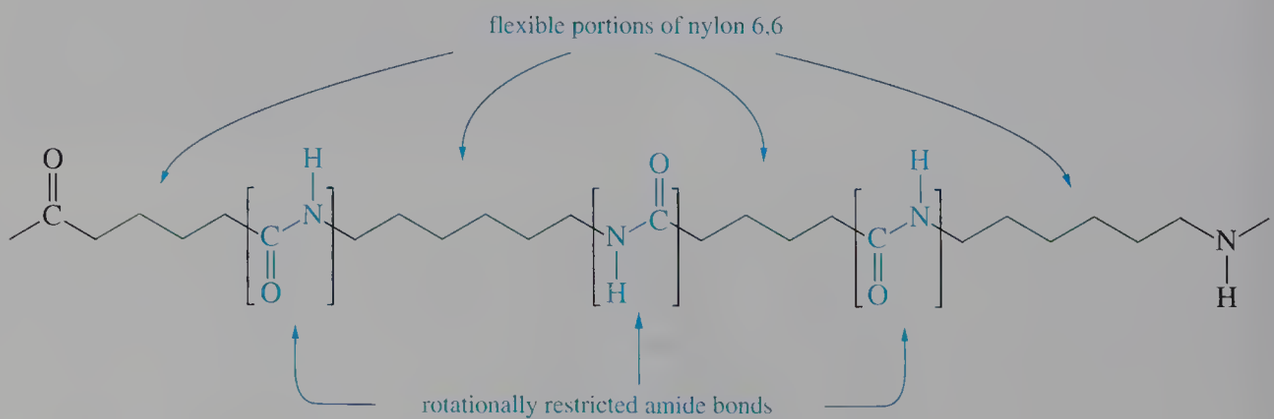


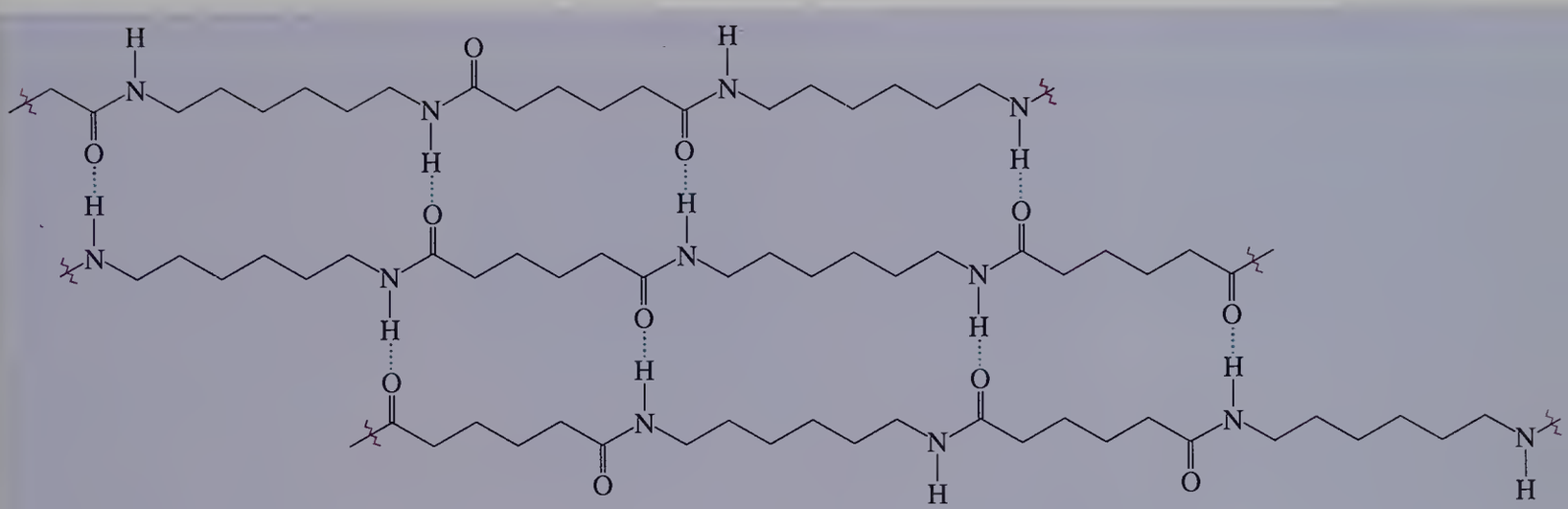
FIGURE 29.3 Branching in Low-Density Polyethylene
The branches formed during the polymerization process prevent the polymer from close packing. The London forces are smaller than in HDPE. The more open structure is also less dense.

Structural units such as aromatic rings have polarizable electrons that create strong London forces. Hence, polymers with aromatic rings have higher tensile strength than polymers with alicyclic units because there are strong London forces between aromatic rings in neighboring polymer chains. The aromatic rings also reduce the flexibility of the polymer chain and the number of possible conformations. Chains of sp^3-hybridized carbon atoms in polymers such as polyethylene or nylon 66 are more flexible. They can exist in gauche and anti conformations around each carbon–carbon bond. The allowed motions of the chains affect the properties of the polymer.

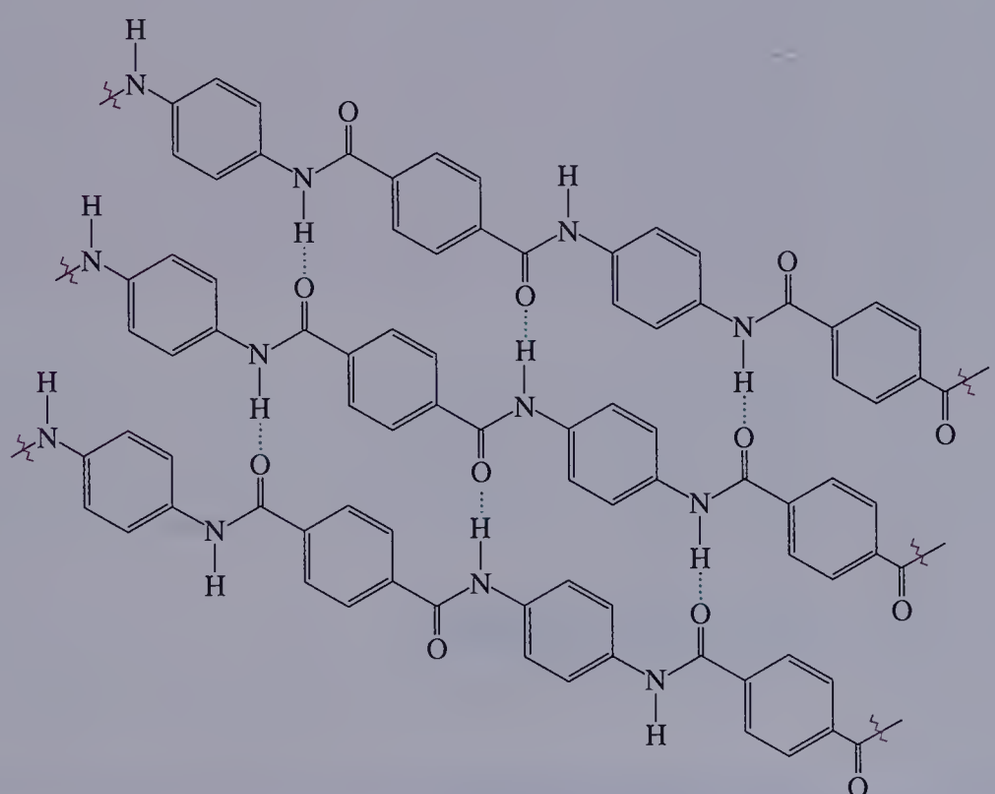


Hydrogen Bonding and Properties

We noted that intermolecular hydrogen bonding dramatically affects the properties of naturally occurring macromolecules such as structural proteins and cellulose. Some synthetic polymers also have extensive hydrogen bonding between polymer chains. The substantial strength of polyamides such as nylon 66 and Kevlar is due to hydrogen bonding. The amount of hydrogen bonding in nylon 66 is affected by the flexibility of the chain and the conformation around the carbon–carbon bonds. The maximum number of hydrogen bonds is formed only if nylon 66 is in the all-anti conformation (Figure 29.4). Kevlar, used in bulletproof vests, is extensively hydrogen bonded because the aromatic ring and the amide bond restrict the conformation to the one best suited to form the maximum number of hydrogen bonds (Figure 29.4).



nylon



kevlar

FIGURE 29.4 Hydrogen Bonds in Polyamides

Crystallinity

Crystalline structures are a common characteristic of ionic and covalent compounds. In these crystals, identical species are arranged in a precise, repeating manner. Polymers are not pure samples of a single molecular species. Since they are mixtures of high molecular weight molecules, they don't form true crystalline solids. An accumulation of intermolecular interactions within regions of a polymer causes a phenomenon known as crystallinity. The number and arrangement of such crystalline domains affect the properties of polymers. Crystalline regions—called crystallites—are dispersed between amorphous, noncrystalline areas (Figure 29.5).

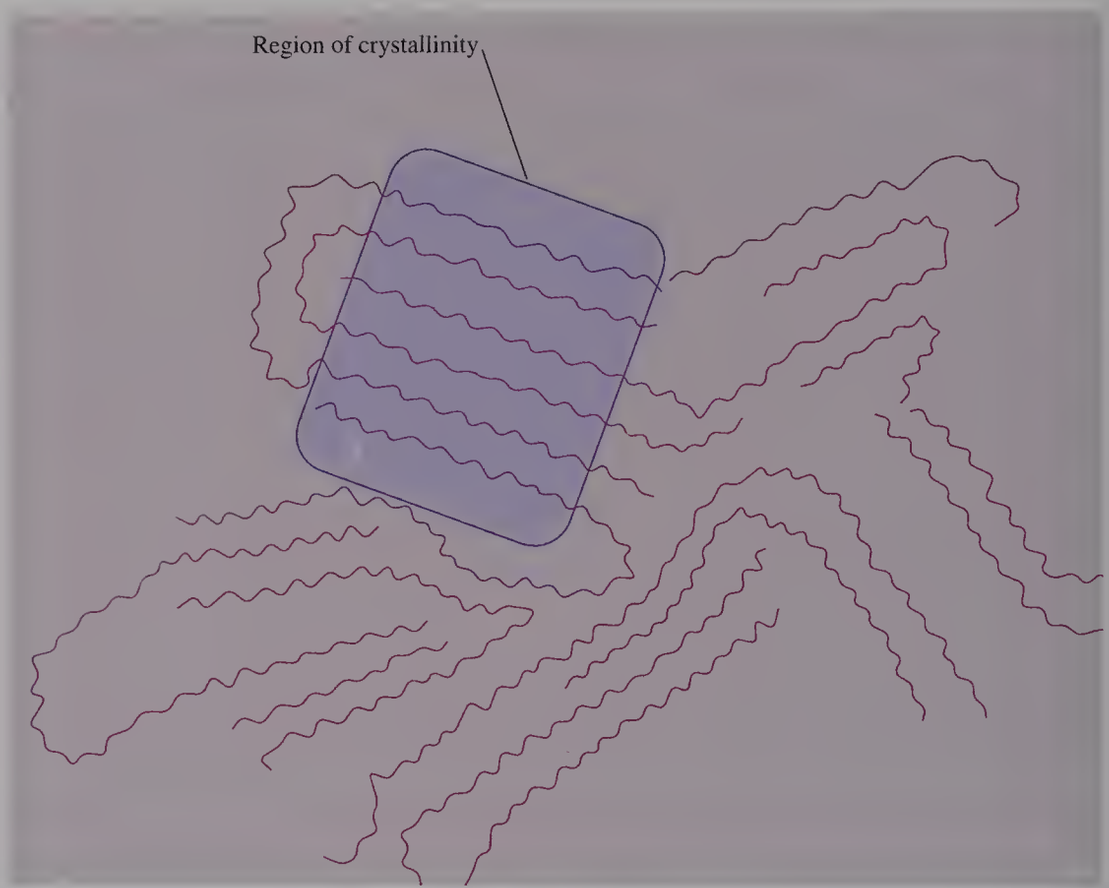


FIGURE 29.5
Crystallinity in Polymers

Crystalline regions can form when portions of the chains are oriented to allow intermolecular hydrogen bonds. The crystallinity of a polymer is also influenced by dipole–dipole interactions among polar functional groups. Even hydrocarbon chains can form crystalline regions. In this case, many relatively weak London forces provide the cumulative attractive forces that maintain the crystalline structure.

Problem 29.1

There are three isomeric benzenedicarboxylic acids. Which one should produce the most crystalline polymer in a reaction with ethylene glycol to give a polyester?

Problem 29.2

How would the properties of an addition polymer formed from 3-methyl-1-pentene differ from those of a polymer formed from propene?

Sample Solution

The polymer of 3-methyl-1-pentene has large branched *sec*-butyl groups off the main chain, whereas propene has relatively small methyl groups as branches. As a result, the polymer of 3-methyl-1-pentene has a more open structure. The bulkier chains cannot pack closely, and the intermolecular forces between chains are smaller. The polymer of 3-methyl-1-pentene should have a lower melting point and be a more flexible material.

29.3 Classification of Polymers

Polymers can be classified by macroscopic physical properties. The three major classes are elastomers, plastics, and fibers.

Elastomers

Elastomers are elastic materials that regain their original shape if they are distorted. Some common elastomers are rubber, a naturally occurring polymer of isoprene, and neoprene, a synthetic polymer of 2-chloro-1,3-butadiene. These elastomers contain carbon–carbon double bonds separated by intervening units containing two sp^3-hybridized carbon atoms (Figure 29.6). An elastomer's properties depend on both the groups bonded to the sp^3-hybridized carbon atoms and the geometry of the polymer chain around the double bond.

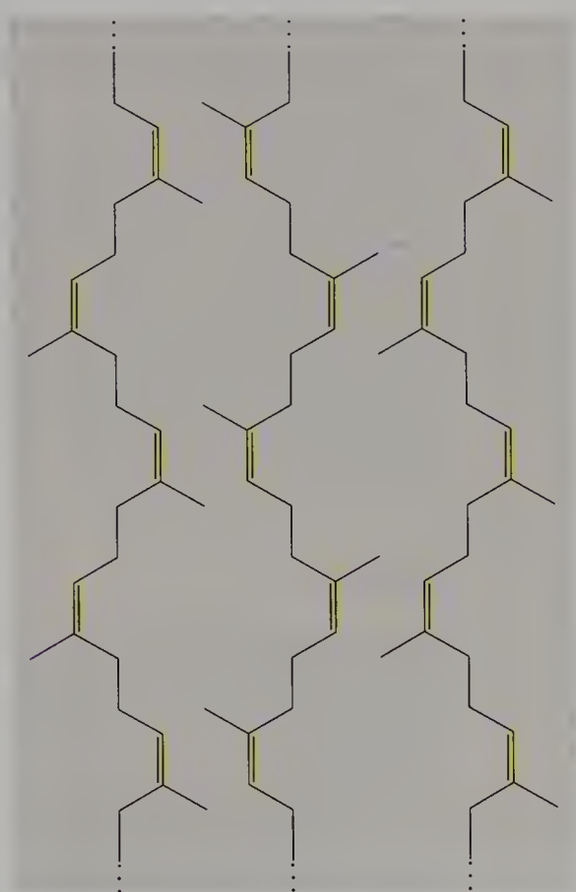


FIGURE 29.6 Structure of an Elastomer

The polyisoprene chains are flexible about the methylene groups. The all-trans conformation is shown, but other conformations are possible. The London forces between the chains are not large.

Elastomers are amorphous materials. The individual chains of the polymers are random coils that are tangled in an irregular way. The coils "straighten out" when they are stretched. When the force is released, the elastomer returns to its coiled state because the intermolecular forces are greatest in this arrangement.

The flexibility of an individual chain of an elastomer depends on the structure of the intervening unit of sp^3-hybridized carbon atoms. Some rotation can occur around the σ bonds. The double bonds provide rigidity because they restrict rotation around π bonds. Polymer chains of *E* and *Z* configurations are both known. For example, natural rubber has a *Z* configuration, whereas gutta-percha, an industrial polymer of isoprene, has an *E* configuration (Figure 29.6). This stereochemical difference is reflected in the properties of the two polymers. Rubber is an elastomer, but gutta-percha is less flexible. In gutta-percha the trans double bonds gives a zigzag arrangement resembling that of saturated fatty acids (Section 24.2). We recall that the regularity of the zigzag chains of fatty acids allows adjacent chains to nestle together, resulting in large London forces. Similar large forces exist in gutta-percha. Natural rubber has a "bent" chain similar to that of an unsaturated fatty acid. This arrangement of atoms gives a more open, less regular relationship among polymer chains. As a result, the polymer chains are not closely packed, and they can slide past one another as the elastomer is distorted.

Plastics

In polymer chemistry, the term *plastic* is used for those polymers that harden upon cooling and can be molded or extruded into shapes that remain after cooling. **Thermoplastics** are polymers that reversibly soften when heated, becoming sufficiently fluid to be molded. **Thermosetting polymers** can be molded when they are first prepared. However, after being heated they "set," hardening irreversibly. If heated to a high temperature, thermosetting polymers decompose rather than melt.

The difference between thermoplastics and thermosetting polymers is related to cross-linking. The polymer chains of thermoplastics are not cross-linked. When a thermoplastic is heated, the kinetic energy of the polymer chains increases, overcoming the intermolecular forces and causing the polymer to melt. Polyethylene is a thermoplastic in which the London forces between hydrocarbon chains are the only intermolecular forces. Thermosetting polymers have extensive cross-links between polymer "chains" that result in much larger polymer molecules. Bakelite is a thermosetting polymer (Section 27.6). The only way that the structure of this material can be disrupted is by cleaving covalent bonds. This process irreversibly decomposes the material.

Fibers

Some thermoplastics are prepared as thin filaments that can be spun into fibers similar to natural fibers. The length of the polymer molecule must be at least 500 nm, which corresponds to a minimum average molecular weight of 10^4. The structure of the polymer chains must also provide sufficiently strong intermolecular forces to give the fiber an adequate tensile strength.

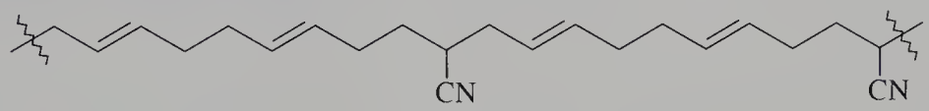
Filaments of thermoplastics are prepared by two methods. If the thermoplastic is stable in the molten state, it may be passed through tiny pores in a die called a spinneret and then cooled. For less stable thermoplastics the polymer is dissolved in a volatile solvent and forced through the spinneret. The solvent evaporates and a filament precipitates. Regardless of the method of formation, the fiber is then drawn out to several times its length after it has cooled. The **cold drawing** orients the molecules along the axis of the fiber. The resultant intermolecular forces between polymer molecules increase the tensile strength of the fiber.

Problem 29.3

What type of plastic is best suited to make the handles for cooking utensils for the home? What type of plastic is most likely to be used for the frames of eyeglasses?

Problem 29.4

Assign the polymer represented by the following structure to one of the three classes of polymers. Identify a compound whose physical properties it most closely resembles.



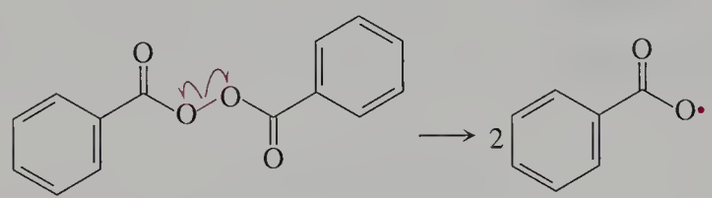
Sample Solution

The polymer is an elastomer. The sp^3-hybridized carbon atoms between double bonds provide some flexibility to the elastomer. However, the trans arrangement of the double bond, which resembles that of gutta-percha, allows chains to pack efficiently and leads to less flexibility in the elastomer.

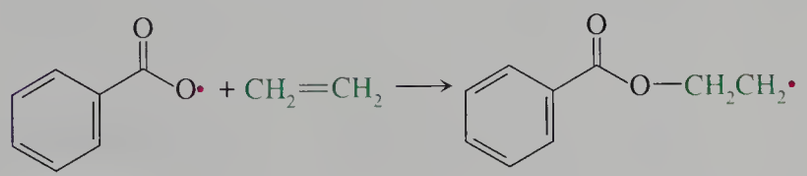
29.4 Methods of Polymerization

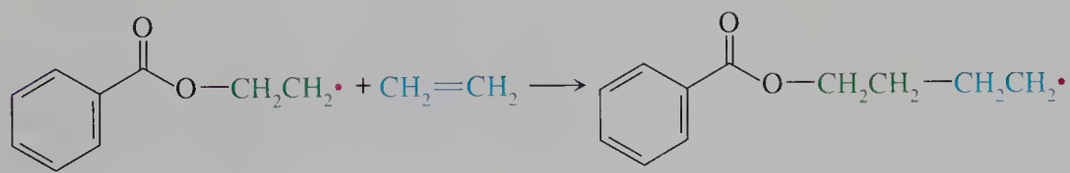
Polymers can be divided into two broad classes called addition polymers and condensation polymers. **Addition polymers** result from the successive addition reactions of one alkene or a mixture of alkenes by radical, cationic, or anionic mechanisms. **Condensation polymers** result from condensation reactions of monomers that contain two or more functional groups such as an alcohol and a carboxylic acid or an amine and a carboxylic acid. These functional groups react in condensation reactions to eliminate a small molecule such as water. Condensation polymerization reactions are often carried out at high temperatures so that the eliminated molecule evaporates, helping drive the reaction to completion.

Addition polymers are also called **chain growth polymers**. The polymer chain grows when the reactive intermediate formed in an initiation step adds to another monomer unit. The initiating species may be a radical, carbocation, or carbanion. For example, dibenzoyl peroxide yields a benzoyl radical.



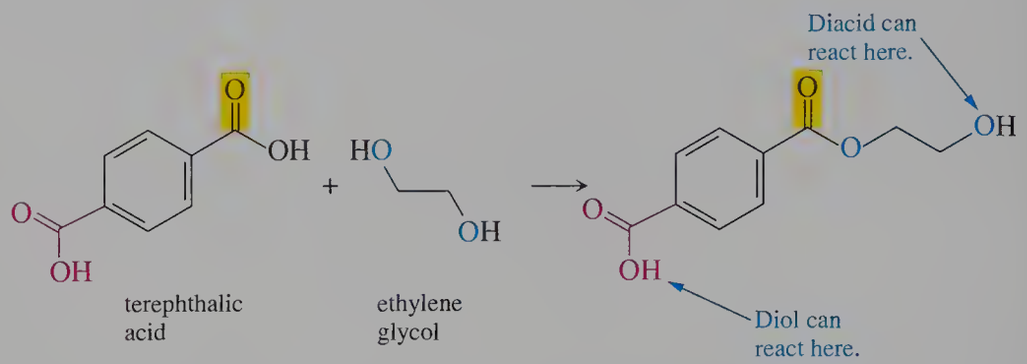
This radical reacts with a monomer to give another radical that then reacts with another unit of monomer.





The successive additions of monomers give a growing chain that always has a reactive end. The number of polymer chains formed therefore depends on the concentration of intermediates initially formed. A monomer cannot react until it encounters one of the growing chains with a reactive site.

Condensation polymers are also called **step-growth polymers**. In reactions between two units, such as a diol and a diacid, a stable ester forms between one alcohol site and one acid site. The new ester still has an alcohol site and an acid site at the ends of the molecule. Monomers can continue to react in condensation reactions with this product.



However, subsequent condensation reactions are not restricted to the ends of the growing polymer chain. The monomers in the reaction mixture can continue to react with each other randomly to start additional chains. So, the monomers in a step-growth polymerization generate many low molecular weight oligomers rather than a smaller number of steadily growing, high molecular weight chains. Formation of true polymers occurs only after the monomer is used up. At this point large increases in the chain length result from the reaction of the ends of the oligomers with each other. Thus, in step-growth polymerization, the polymer is formed in "blocks" that result in substantially higher molecular weight product than an addition polymer.

29.5 Addition Polymerization

We recall that addition polymerization occurs by a chain reaction in which one carbon–carbon double bond adds to another (Section 7.20). For free radical polymerization, an initiation step forms a radical that adds to the alkene to give the intermediate required in the chain propagation step. Now let's consider chain termination.

Termination Steps

The monomer continues to react with the end of the growing polymer chain throughout an addition polymerization reaction until the reactive intermediate is destroyed in a termination reaction. Disproportionation and dimerization are two possible termination reactions. In disproportionation, a hydrogen atom at a carbon atom α to the radical center is abstracted by a radical in another chain. This produces a double bond in one polymer molecule, and the other polymer molecule becomes saturated. Because no new radical intermediates are formed, the propagation steps are terminated.

$$2\,R{-}(CH_2CH_2)_nCH_2CH_2{\cdot} \longrightarrow R{-}(CH_2CH_2)_nCH{=}CH_2 + R{-}(CH_2CH_2)_nCH_2CH_2{-}H$$

In the dimerization reaction, two radicals combine to form an even longer polymer chain. Again, the destruction of radicals prevents propagation.

$$2\,R{-}(CH_2CH_2)_nCH_2CH_2{\cdot} \longrightarrow R{-}(CH_2CH_2)_nCH_2CH_2{-}CH_2CH_2(CH_2CH_2)_n{-}R$$

The probability that the reactive sites of two growing polymer chains will react in either of these bimolecular termination reactions is very small. A bimolecular reaction of one chain with a monomer molecule, which is present in higher concentration and consumed throughout the reaction, is more likely.

Regulation of Chain Length

The average molecular weight of the addition polymer is controlled by the number of times the propagation steps occur before the chain is terminated. However, the length of the chain can also be controlled by using either chain-transfer agents or inhibitors.

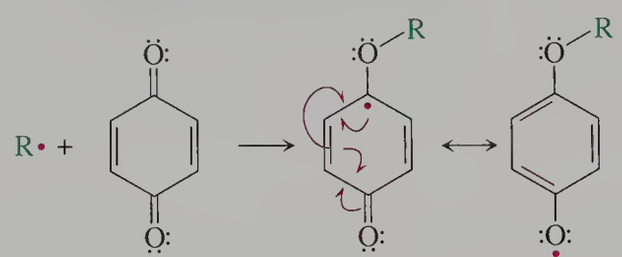
Chain transfer agents control the chain length of a polymer by interrupting the growth of one chain and then initiating the formation of another chain. Thiols are common chain transfer agents.

$$R{-}CH_2CH_2{\cdot} + R'{-}S{-}H \longrightarrow \underbrace{R{-}CH_2CH_2{-}H}_{\text{one terminated chain}} + R'{-}S{\cdot}$$

$$R{-}S{\cdot} + CH_2{=}CH_2 \longrightarrow \underbrace{R{-}S{-}CH_2{-}CH_2{\cdot}}_{\text{initiation of another chain}}$$

A chain transfer reagent must be sufficiently reactive to transfer a hydrogen atom, but the resulting radical must be reactive enough to add to a double bond. The polymerization continues, and monomer continues to be consumed. However, the average molecular weight of the product is smaller because more chains are formed by the chain transfer process.

Inhibitors react with the radical site of a growing polymer chain to give a less reactive radical. Benzoquinone is a typical inhibitor used in free radical polymerization reactions.

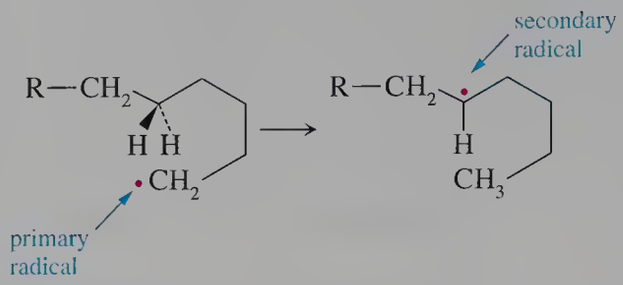


The resonance-stabilized radical is less reactive and does not effectively participate in chain-propagation steps. It eventually is destroyed by disproportionation or dimerization reactions.

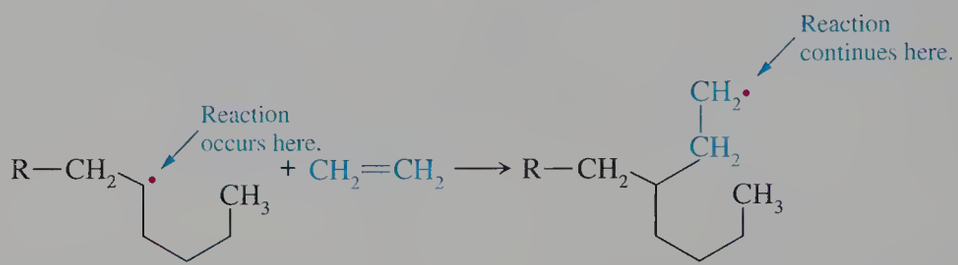
Chain Branching

In practice, the linear polymer normally indicated for alkenes is not the major product of the free radical process. (Cationic polymerization is generally used to prepare linear addition polymers of alkenes.) The product chains have many alkyl branches, which most often are the four-carbon-atom butyl groups produced by **short chain branching**. These products are the result of an intramolecular hydrogen abstraction

by way of a six-membered transition state that generates a secondary radical from a primary radical.



The polymerization continues at the new radical site, and a butyl group branch is located on the chain.



Large chain branching occurs by a random process. Intermolecular hydrogen atom abstraction can occur between the terminal radical of one chain and any of the hydrogen atoms located in another chain. In this case, one chain is terminated and the polymerization continues at a site within the other chain. The length of the resulting branch depends on the site of hydrogen abstraction.

Short chain branching is more common than long chain branching because intramolecular reactions are more probable than intermolecular reactions. We recall that the ΔS°_{rxn} is more negative for a bimolecular process than for an intramolecular process. Chain branching also occurs for other polymers, such as polypropylene and polystyrene.

Problem 29.5

Draw a representation of the reacting end of a polystyrene. What structural feature should exist in a chain terminated by a dimerization reaction?

29.6 Copolymerization of Alkenes

The addition polymers that we've discussed are homopolymers made up of repeating units derived from a single unsaturated monomer. **Copolymers** incorporate two different monomers in the polymer chain. They are formed in reactions of a mixture of two monomers. Copolymerization of various combinations of monomers provides many more possible structures and a greater variety of materials that might have desirable physical properties than homopolymerization..

The structure of a copolymer depends on the structure of the radical at the end of the chain and the structure of the monomer that might add. The polymer formed results from kinetically controlled processes. Let's consider each of the following possible kinetic results for combinations of alkenes A and B.

1. A adds A at a rate significantly faster than it adds B; B adds B at a rate significantly faster than it adds A.

2. A adds B at a rate significantly faster than it adds A; B adds A at a rate significantly faster than it adds B.
3. A can add either A or B at comparable rates; B can add either A or B at comparable rates.

For the first case, no copolymer forms, and a mixture of homopolymers results. This process has no commercial application. For example, although styrene and 2-methyl-1,3-butadiene (isoprene) each readily polymerize to form homopolymers, they do not form a copolymer.

$$n\,A + n\,B \longrightarrow \underset{\text{(a mixture of homopolymers)}}{-A-A-A-A-A-A- + -B-B-B-B-B-B-}$$

For the second case, a chain containing an alternating sequence of monomers results.

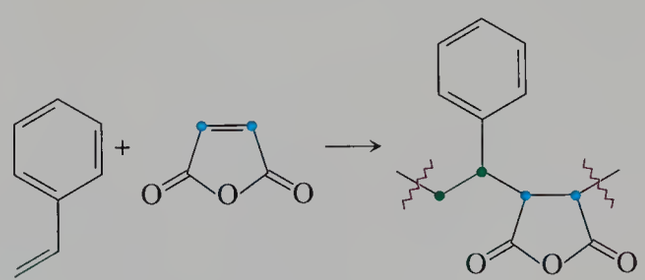
$$n\,A + n\,B \longrightarrow \underset{\text{(an alternating copolymer)}}{-A-B-A-B-A-B-A-B-A-B-}$$

For the third case, random polymers form. The exact composition depends on the reaction conditions and on the concentrations of the two monomers.

$$n\,A + n\,B \longrightarrow \underset{\text{(a random copolymer)}}{-A-B-A-A-B-A-B-B-B-A-B-A-A-B-}$$

Few pairs of monomers give totally random copolymers. In fact, monomers are usually selected to avoid random copolymers. Monomers are chosen so that one monomer at the end of growing polymer chain prefers to react with the other monomer in the mixture, and vice versa. In short, it is desirable to have a monomer at the end of a chain that reacts preferentially with the other monomer in the reaction mixture. But some random distribution of monomers always occurs.

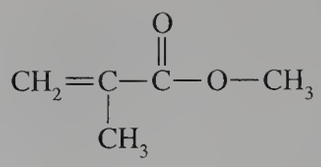
It is difficult to form perfect alternating copolymers. However, the reaction of styrene with maleic anhydride produces a nearly perfect alternating copolymer.



styrene maleic anhydride

Maleic acid reacts with itself very slowly, and its homopolymer is difficult to form. Styrene readily reacts to form a homopolymer. However, a styrene group at the end of a growing polymer chain reacts faster with maleic anhydride than with styrene. After the addition of styrene to maleic anhydride, a radical is produced that does not react with maleic anhydride. As a result, the next alkene that is added is styrene. Monomers that provide perfect alternating copolymers are highly desirable because the product can be reproduced.

The amount of alternation compared to random sequencing in copolymers depends on two selectivity ratios. Consider the copolymerization of styrene and methyl 2-methylpropenoate.



methyl 2-methylpropenoate

When styrene is at the end of the chain, it reacts with methyl 2-methylpropenoate rather than another styrene by about a 2:1 ratio. When methyl 2-methylpropenoate is at the end of the chain, it reacts with styrene rather than methyl 2-methylpropenoate by about a 2:1 ratio. These selectivity ratios tend to give an alternating copolymer. However, some repetition of one monomer or the other is still likely.

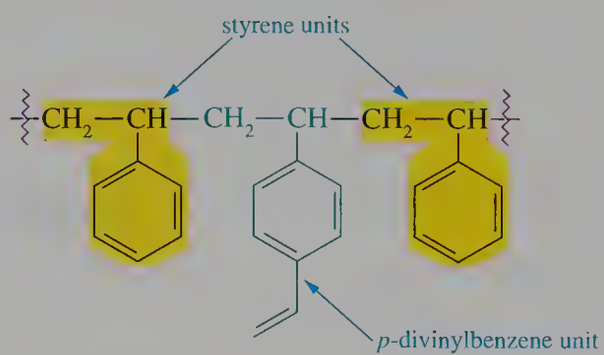
Problem 29.6

Styrene and acrylonitrile ($CH_2{=}CH{-}C{\equiv}N$) form an alternating copolymer that is used in the lenses of automobile headlights. Draw a representation of the copolymer.

29.7 Cross-linked Polymers

Atoms bonded between polymer chains are called cross-links. They form during polymerization of the monomers or in separate reactions after formation of the polymer.

p-Divinylbenzene has two alkene functional groups, each of which can become part of a different polymer chain by an addition polymerization reaction. One alkene group of *p*-divinylbenzene is incorporated in a chain whose major components are styrene units.

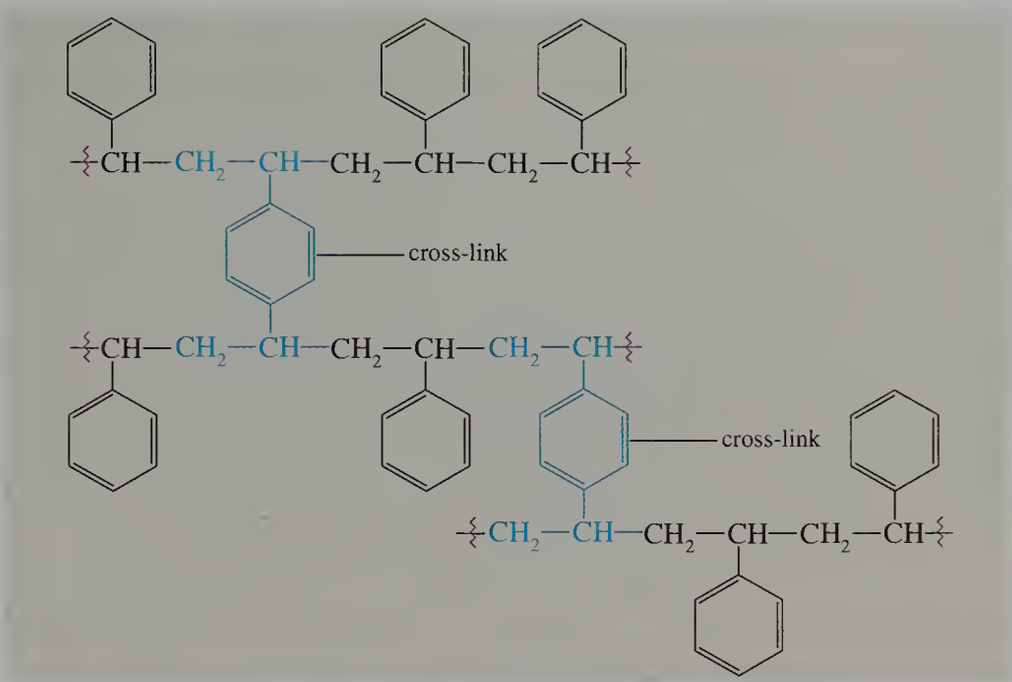


At some point in the reaction, the other alkene group reacts in a chain propagation process that develops a second chain. Thus, divinylbenzene becomes part of each polymer chain and forms a link between the two chains (Figure 29.7). The degree of cross-linking and the space between the divinylbenzene units depend on the amounts of two monomers used.

The importance of cross-links in determining the properties of a polymer was accidentally discovered by Charles Goodyear in his study of the properties of rubber. Natural and synthetic rubbers can be used to make rubber bands, but are too soft and tacky for many applications such as tires. The resilience of rubber decreases when it is heated because the polyisoprene chains slide past each other more easily when stretched at higher temperatures. When tension is released, natural rubber does not regain its original structure.

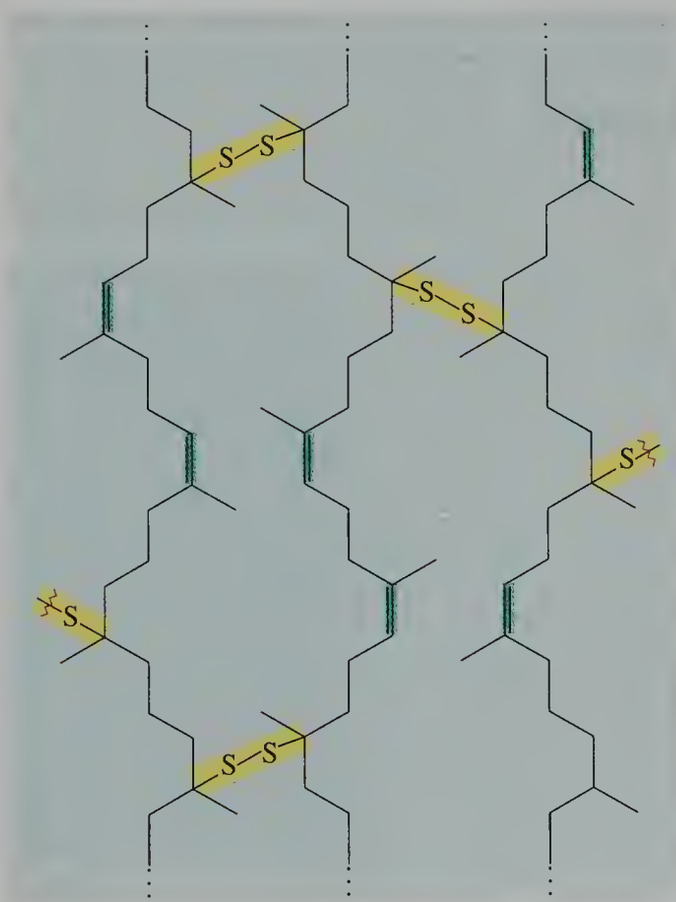
In 1839 Charles Goodyear found that heating natural rubber with a small amount of sulfur produces a material with different properties. He called this process **vulcanization**. The sulfur reacts with the polyisoprene to replace some

FIGURE 29.7 Cross-links in Addition Polymerization



C—H bonds with disulfide bonds. As a result, the polymer chains become connected by cross-links that may contain one, two, or more sulfur atoms (Figure 29.8). These cross-links increase the rigidity of the rubber because more of the chains are linked into a larger molecule. The freedom of movement of one chain relative to another is diminished. After distortion, the vulcanized rubber returns to its original molded shape. The amount of sulfur—3 to 10% by weight—controls the flexibility and hardness of the rubber.

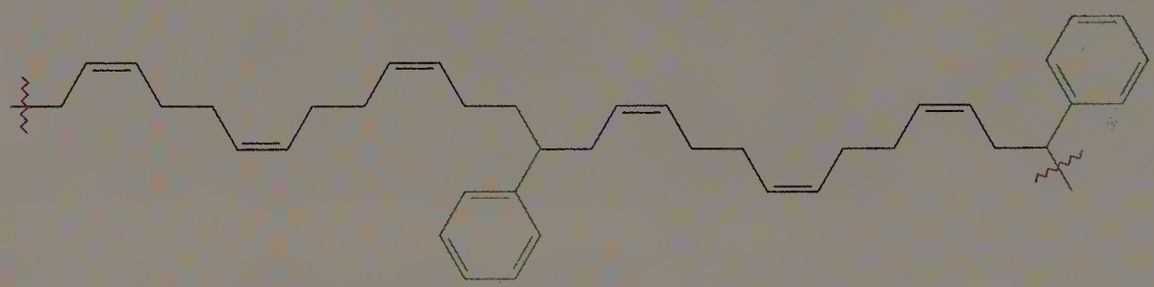
FIGURE 29.8 Structure of Vulcanized Rubber
The disulfide bridges are shown between the tertiary centers, but bridges may be formed at the secondary methylene groups.



Copolymers in Automobiles

The most important synthetic rubber produced in the United States is a copolymer of styrene and butadiene called SB. About 1.5 million tons of SB are produced annually for use in automobile tires. The elastomer with the best properties has a 1:3 ratio of styrene to butadiene. The remaining double bond in the butadiene unit of the polymer can be cross-linked by vulcanization.

A copolymer of three monomers—acrylonitrile, butadiene, and styrene—known as ABS can be molded to form a variety of products. About one-half million tons are produced annually in the United States. In addition to the large quantities used to make instrument panels, grills, and exterior trim for automobiles, ABS is used to make housings for appliances, power tools, and television cabinets.

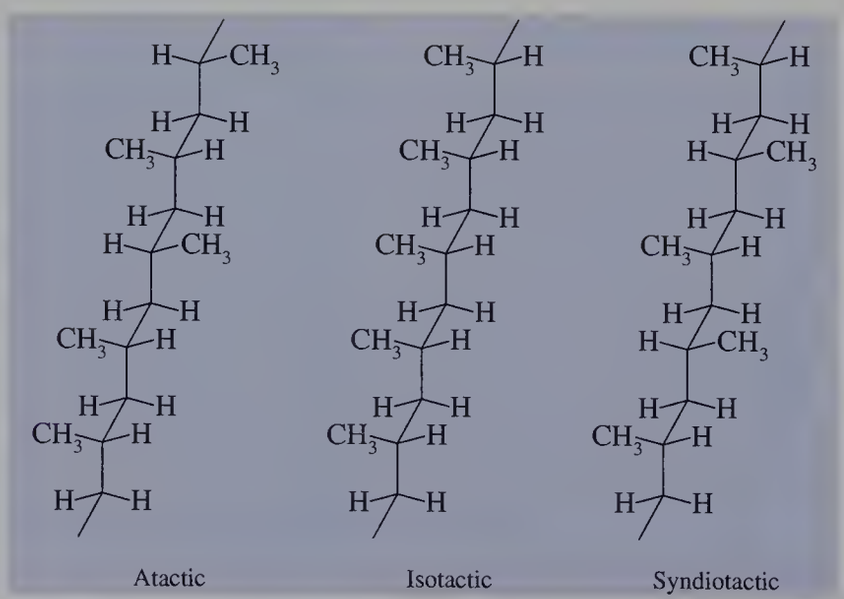


representation of an SB polymer (1:3 ratio)

29.8 Stereochemistry of Addition Polymerization

Addition polymerization of some alkenes generates stereogenic centers along the entire backbone of the polymer. The relationship of these centers to one another affects the physical properties of the polymer. Consider the polymer formed from propene. If the methyl groups are all on the same side of the backbone of the zigzag chain, the polymer is **isotactic**. If the methyl groups are in a regular alternating sequence on opposite sides of the backbone, the polymer is **syndiotactic**. If the methyl groups are randomly oriented, the polymer is **atactic**. The three forms of polypropylene are shown in Figure 29.9.

FIGURE 29.9
Stereochemistry of Addition Polymers



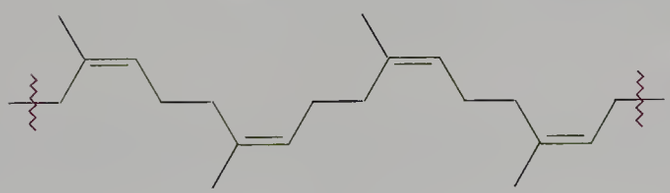
The regularity of structure of isotactic and syndiotactic polymers is responsible for substantial areas of crystallinity. Both types of polymers have high melting points, so they can be used to manufacture objects that will be exposed to boiling water.

Atactic polymers form from radical chain polymerization. These polymers have branches that result from hydrogen abstraction processes. Both isotactic and syndiotactic forms of polymers are produced with catalysts designed by K. Ziegler of Germany and G. Natta of Italy. These catalysts yield polymers with no chain branching. The development of methods to form stereochemically regular linear polymers revolutionized polymer science.

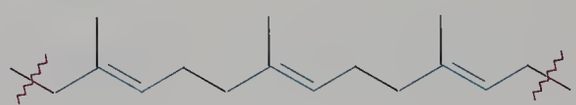
The Ziegler–Natta catalysts are organometallic compounds that contain a transition metal. For example, triethylaluminum and titanium(III) chloride combine to give such a catalyst. The structure of the catalyst and its function in the polymerization process are beyond the scope of this text. However, each catalyst coordinates alkene monomers and allows them to react stereoselectively.

Diene Polymers

Conjugated dienes can form addition polymers by a 1,4-addition reaction. The remaining double bond of each monomer unit occurs at every fourth carbon atom along the chain. Natural rubber, for example, is a polymer of 2-methyl-1,3-butadiene (isoprene) with cis stereochemistry at all of the double bonds. The polymer is obtained from the latex synthesized under the bark of some trees that grow in southeast Asia. The isomeric gutta-percha is a trans isomer of natural rubber that is produced by trees of a different genus. As usual, biosynthetic reactions yield products formed in stereospecific reactions. Both species use isopentenyl pyrophosphate as a starting material, but the enzyme catalysts differ.



natural rubber
(all cis)



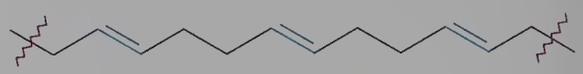
gutta-percha
(all trans)

The different properties of natural rubber and gutta-percha reflect both the geometries around the double bonds and the molecular weights. The molecular weight of natural rubber is about 100,000, whereas that of gutta-percha is less than 10,000. As a result of the cis arrangement of the chain in natural rubber, the adjacent molecules cannot fit close to one another. Natural rubber has random coils that can be stretched out when the material is pulled. After the tension is released, the material returns to its original structure. Gutta-percha molecules, on the other hand, can pack closer because the trans arrangement of the double bonds and the favored anti conformation around the saturated carbon atoms provide a chain with a regular zigzag arrangement. So gutta-percha is a highly crystalline, hard, inflexible material. It is used in covers for golf balls and in casings for electrical cables.

Early attempts to polymerize isoprene in industrial processes to prepare synthetic rubber were not successful because the reactions were not stereospecific. However, a variety of Ziegler–Natta catalysts are now available. One catalyst that contains titanium stereospecifically gives polyisoprene with cis double bonds, and another catalyst containing vanadium gives polyisoprene with trans double bonds.

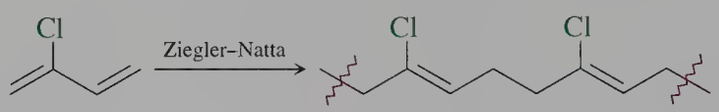
1,3-Butadiene can also be stereospecifically polymerized to give either of two isomeric polymers. The stereochemistry depends on the conditions of the reaction and the Ziegler–Natta catalyst used.

cis-poly(1,3-butadiene)



trans-poly(1,3-butadiene)

The polymerization of 2-chloro-1,3-butadiene was one of the reactions considered by U.S. industry to replace rubber made from natural sources located in areas of the world that could be cut off in a crisis such as war. This diene structurally resembles isoprene, with a chlorine atom replacing the methyl group of isoprene. Free radical polymerization gives a mixture of cis and trans double bonds as well as a mixture of 1,2- and 1,4-addition products. Polymerization of 2-chloro-1,3-butadiene using a Ziegler–Natta catalyst yields neoprene, a compound with trans double bonds.



Neoprene

Neoprene resists oxidizing agents better than natural rubber. Neoprene is therefore used to manufacture materials such as gaskets and industrial hoses.

Problem 29.7

The free radical polymerization of 1,3-butadiene yields some sections of the polymer that contain a vinyl group. Explain the origin of this group.

Sample Solution

The presence of a vinyl group bonded to the main chain means than the other vinyl group of 1,3-butadiene is incorporated in the chain. Thus, the polymerization of this unit involves a 1,2-addition similar to that of a simple alkene.

Problem 29.8

Draw the structure of the product of ozonolysis of *trans*-poly(1,3-butadiene) under oxidation workup conditions.

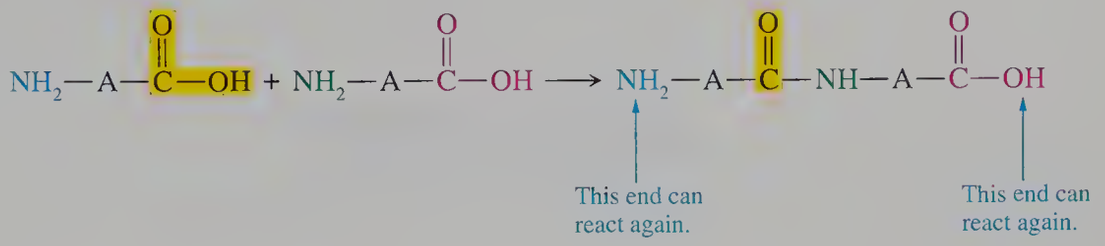
29.9 Condensation Polymers

A condensation reaction is a reaction between two reactants that yields one larger product and a second, smaller product such as water. This type of reaction has been illustrated in the reactions of many functional groups containing oxygen or nitrogen. Products of condensation reactions include ethers, acetals, esters, imines, and amides.

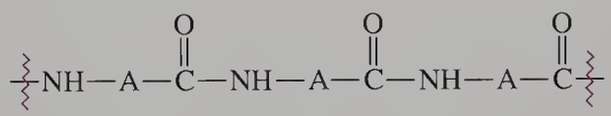
Types of Monomers

We now consider condensation reactions that yield polymers. Two functional groups are required in a monomer so that after one functional group reacts, the other is available to link to another monomer. The functional groups in monomers may be arranged in two ways for condensation polymerization.

A single compound may contain two different functional groups such as an amino group and a carboxylic acid group. Reaction of the amino group of one molecule with the carboxylic acid of another molecule gives an amide that still has a free amino group and a free carboxylic acid group, which can continue to react to form a polymer. The generalized reaction is

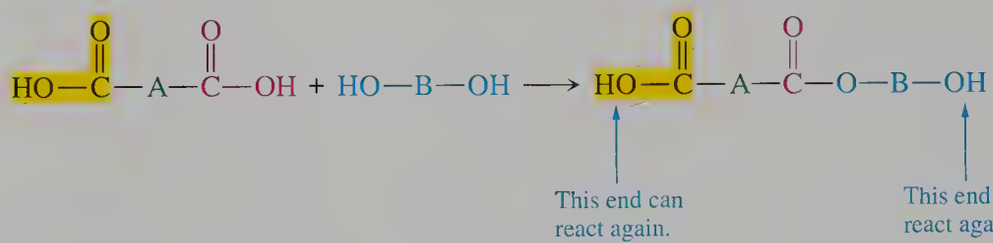


Continued reaction of the carboxylic acid end with the amino group of another monomer or of the amino group end with the carboxylic acid group of another monomer yields a homopolymer.

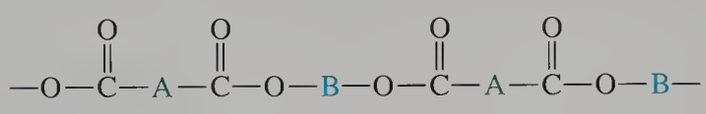


(a homopolymer of an amino acid)

Condensation reactions also result from the copolymerization of two monomers. Each monomer contains two of the same functional group. Examples include the reaction of a monomer that is a dicarboxylic acid with a monomer that is a diol. The functional groups on one monomer can only react with the functional groups on the other monomer. The generalized reaction is



Continued reaction of the carboxylic acid end with the hydroxyl group of the diol monomer or of the hydroxyl group end with the carboxylic acid group of the dicarboxylic acid monomer yields a copolymer.



(an alternating copolymer)

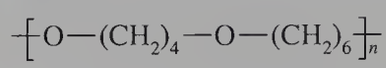
A monomer can contain two different functional groups, but such monomers are not widely used. First, these monomers are more difficult to prepare without uncontrolled polymerization during their synthesis. Second, the monomer can only be used in one possible polymerization reaction. Condensation polymers formed from two different monomers are more common. The synthesis of each monomer is usually straightforward and less expensive. Each monomer can be used in reactions with other monomers. For example, any of a series of dicarboxylic acids can react with any of another series of diols.

The reactants and the condensation reaction selected must give high yields of a product with few side reactions. The experimental conditions must also allow the

reaction to be carried out on a large scale in a continuously operating industrial plant without "workup" conditions. We recall that an ester can be prepared in the laboratory using an acid chloride and an alcohol or by the Fischer esterification method. Each process has limitations when used in industrial laboratories. Although acid chlorides give high yields, they are very reactive compounds and are difficult to handle. The Fischer esterification is an equilibrium process that requires "driving" the reaction to completion using excess reagent or by removing products.

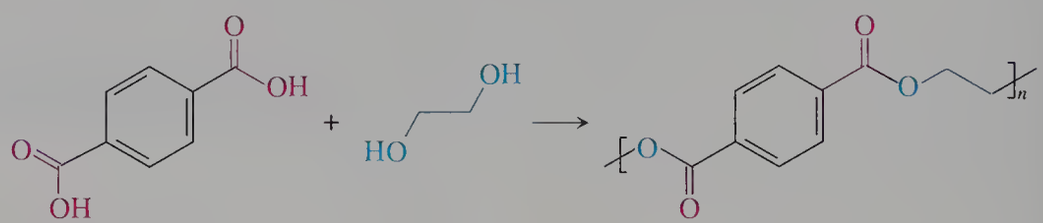
Problem 29.9

Can the disodium salt of 1,4-butanediol be used with 1,6-dibromohexane to yield a polyether represented by the following formula?



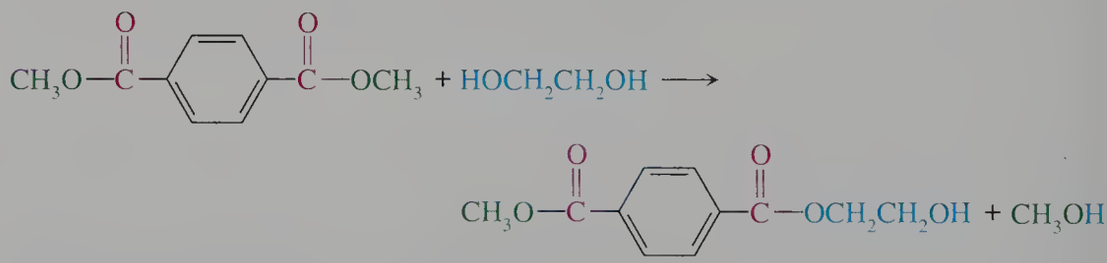
29.10 Polyesters

Polyesters account for approximately 40% of the synthetic fibers produced in the United States. Poly(ethylene terephthalate), also known as PET, is the major polyester. It is a copolymer of ethylene glycol and terephthalic acid.



terephthalic acid ethylene glycol PET

PET and all other polyesters are produced industrially by transesterification reactions. PET is prepared by the reaction of dimethyl terephthalate with ethylene glycol at 150 °C. Neither reactant is volatile at this temperature, but the second product is methanol, which boils at 65 °C. As methanol forms, it is continuously vaporized from the reaction mixture, driving the polymerization reaction to completion.

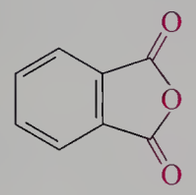


PET is produced as a fiber known as Dacron, which is used in products as common as clothing and as esoteric as tubes used to replace blood vessels. Human tissue can grow into and around Dacron, incorporating the polymer as part of the structure of the human body.

PET is also used to form a film called Mylar, which can be produced in thin sheets. It is used to make magnetic recording tape. Thicker versions of Mylar are used in compact discs.

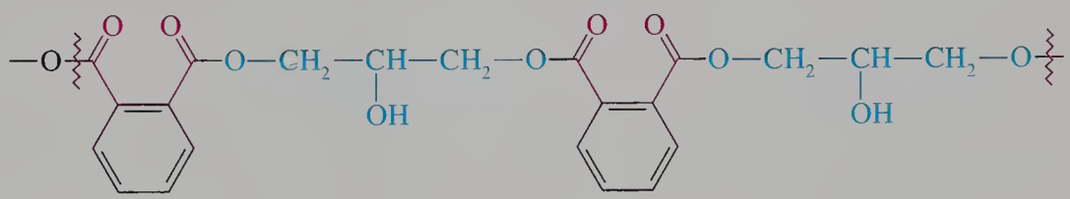
Cyclic anhydrides such as phthalic anhydride and maleic anhydride also react

with glycols to form polyesters. The anhydride is a bifunctional molecule that reacts with the bifunctional glycol to give linear alternating copolymers.



phthalic anhydride

However, when a triol reacts with an anhydride, a cross-linked polymer results. For example, the reaction of phthalic anhydride with 1,2,3-propanetriol (glycerol) initially occurs regioselectively with the primary hydroxyl groups to give a linear polymer.



Reaction of phthalic anhydride with the secondary hydroxyl groups is so slow that continued polymerization can be carried out as a second step. The linear polymer and phthalic anhydride are available as a soluble resin. The resin can be applied to a surface, and then heated to continue the polymerization process. The resulting cross-linked polymer is an insoluble, hard, thermosetting plastic called glyptal (Figure 29.10).

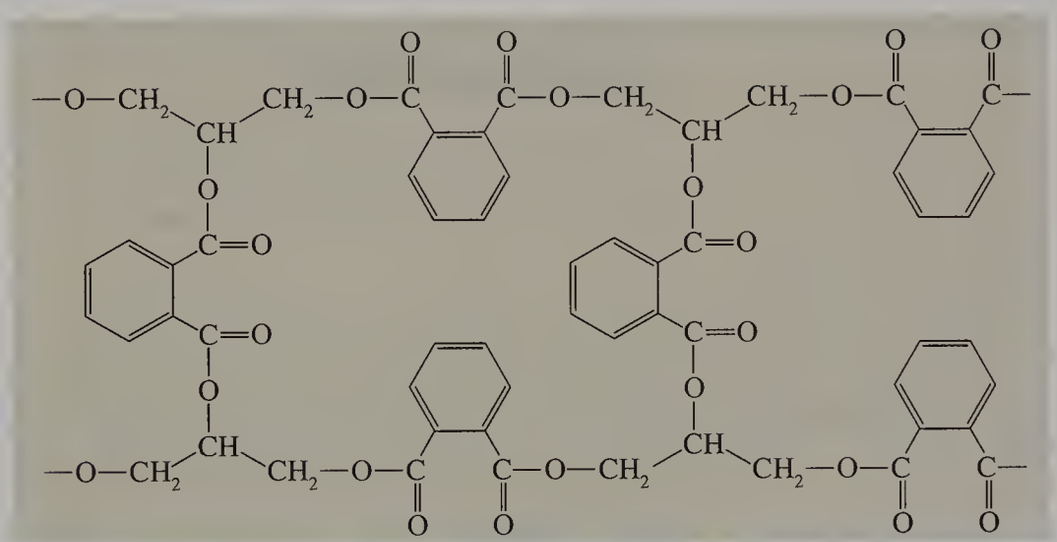


FIGURE 29.10 Cross-links in a Condensation Polymer
The reaction of 2 moles of 1,2,3-propanetriol and 3 moles of phthalic anhydride gives a cross-linked polymer called a glyptal.

Problem 29.10

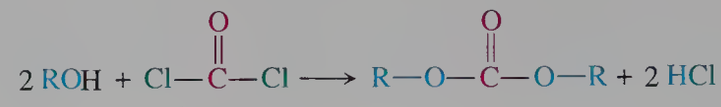
Poly(ethylene terephthalate) is melted and spun into fibers at 270 °C. Explain why the surrounding air must be "dry" while the polymer is hot.

29.11 Polycarbonates

Carbonates are esters of carbonic acid. However, because carbonic acid is unstable, carbonates cannot be produced from carbonic acid and an alcohol.

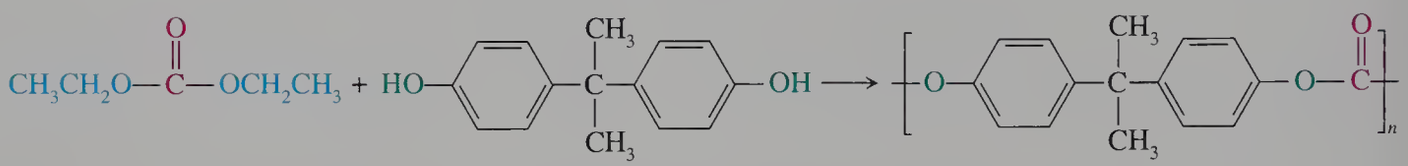
carbonic acid (a dialkyl carbonate)

Dialkyl carbonates can be made from the reaction of alcohols with phosgene, a highly toxic gas. The second chlorine atom of phosgene increases the electrophilicity of the carbonyl carbon atom. As in the reaction of an alcohol with an acid chloride, a base is required to neutralize the HCl by-product.



phosgene

Although a polymeric carbonate could be produced in the reaction of a diol with phosgene, these products are usually obtained by a transesterification reaction with a dialkyl (or diaryl) carbonate. The reaction of diethyl carbonate with a phenol called bisphenol A gives a polycarbonate known as Lexan.



bisphenol A Lexan

Lexan has very high impact strength and is strong enough to be used in crash helmets. It is also used to manufacture telephone housings. Because Lexan can be produced as a clear colorless polymer, it is used in bulletproof windshields and in the visors of astronauts' helmets.

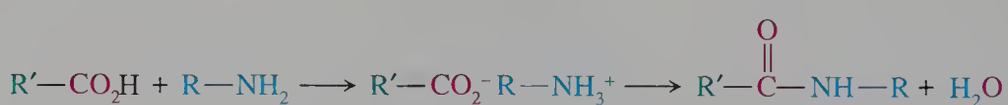
Problem 29.11

Lexan can be prepared using diphenyl carbonate rather than diethyl carbonate. Which reaction is thermodynamically more favorable?

29.12 Polyamides

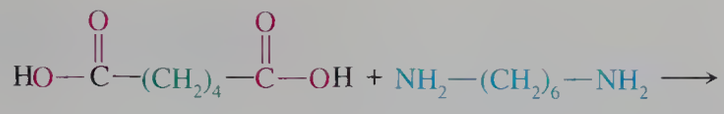
We recall that amides are best made by the reaction of acid chlorides and amines. Therefore, polyamides can be made by reaction of a monomer with two acid chloride functional groups and a monomer with two amine groups. However, the high reactivity of acid chlorides with nucleophiles such as water requires special precautions to preserve this reagent. Thus, these compounds are not much used in industrial laboratories.

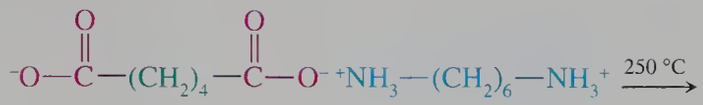
An alternate method for the synthesis of amides is the direct heating of an amine with a carboxylic acid. The first product is an ammonium salt, which loses water when heated to form the amide.



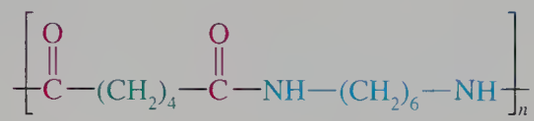
Polyamides can be made from the reaction of diacids with diamines. A diammonium salt is formed by proton transfer reactions. When the salt is heated to 250 °C, water is driven off and a polyamide forms.

Nylon is a common name for polyamides. The most common polyamide is formed by the reaction of adipic acid, a six-carbon, diacid, and 1,6-hexanediamine (hexamethylene diamine), a six-carbon diamine. The ammonium salt formed is called a nylon salt.





nylon salt

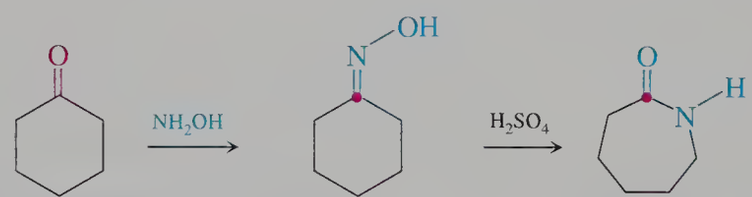


nylon 6,6

This nylon is called nylon 6,6 (or nylon 66) to indicate that the polyamide is made by the reaction of a six-carbon diamine and a six-carbon diacid.

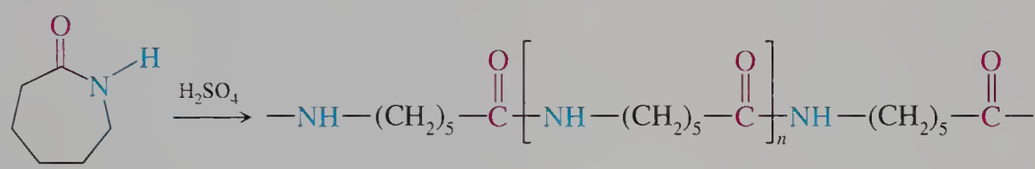
A polyamide can be produced from a single monomer containing both an amine and a carboxylic acid. However, a related cyclic structure called a lactam can also be converted into a polyamide. When the lactam ring is hydrolyzed, an amino acid is produced that can be polymerized.

6-Aminohexanoic acid lactam (ε-caprolactam) is obtained in two steps starting from cyclohexanone. The ketone is converted into an oxime, then the oxime is converted into ε-caprolactam by treatment with sulfuric acid. The second step, called the Beckmann rearrangement, involves cationic intermediates and a skeletal rearrangement.



cyclohexanone cyclohexanone oxime ε-caprolactam

When ε-caprolactam is heated with a catalytic amount of a nucleophile such as water, the nucleophile attacks the carbonyl carbon atom and opens the ring. The amino group of the resulting amino acid is nucleophilic and reacts with another molecule of the lactam. Subsequent reaction of the amino group of the dimer with the lactam yields a trimer. Continued reaction yields a six-carbon homopolymer called nylon 6. The molecular weight of the polymer formed is approximately 6000.



nylon 6

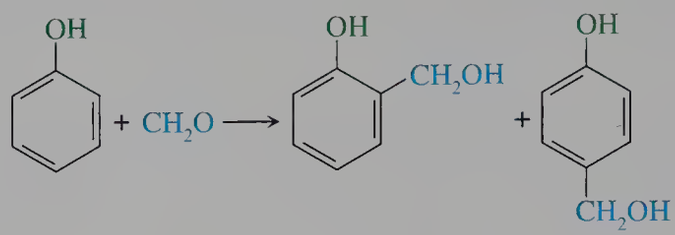
Nylons are used in many products. As a fiber, nylon is used in clothing, rope, tire cord, and parachutes. Because nylon has a high impact strength and resistance to abrasion, it can even be used to make bearings and gears.

Problem 29.12

Nylon 6,10 is prepared by reaction of a diamine and a diacid chloride. Draw the structures of the reactants.

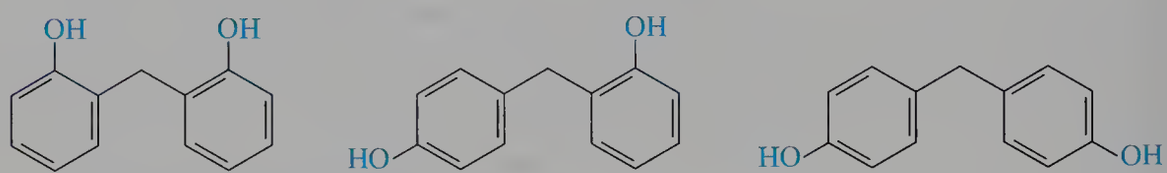
29.13 Phenol–Formaldehyde Polymers

Bakelite, a copolymer of phenol and formaldehyde, was the first commercial polymer. It was prepared in 1907 by Leo Bakeland. The chemistry of this reaction was described in Section 27.6. The first step is an addition reaction of a phenolate to formaldehyde to give either of two isomeric hydroxymethylphenols.



hydroxymethylphenols

Subsequent alkylation of phenol by the benzylic carbon atom gives several possible bis(hydroxyphenyl)methanes that have a methylene group bonded between two ortho positions, two para positions, or an ortho and a para position. The reaction results in an elimination of water and thus is a condensation process.



bis(hydroxyphenyl)methanes

Continued condensation yields a branched oligomer that is produced as a Bakelite resin (Figure 29.11). This low-melting oligomer is then heated in a mold to give a thermosetting polymer with many more cross-links.

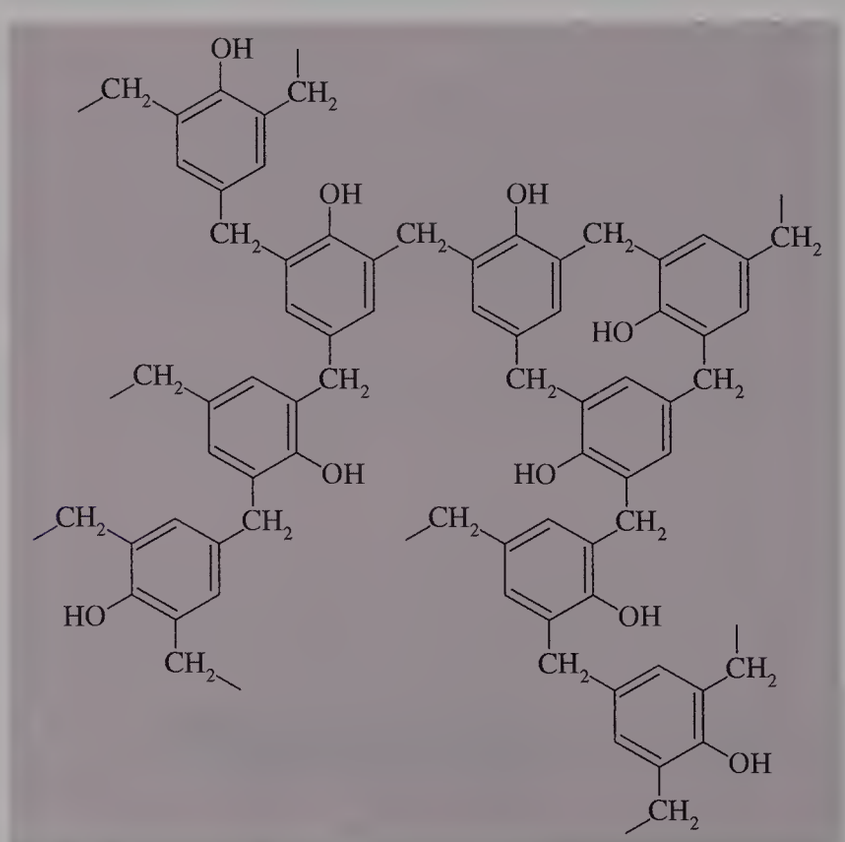


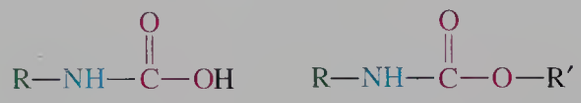
FIGURE 29.11 Cross-links in Thermosetting Plastic

Problem 29.13

Explain why phenol and acetone do not form a condensation polymer.

29.14 Polyurethanes

A urethane is an ester of a carbamic acid. We recall that a carbamic acid, the intermediate in a Hofmann rearrangement, is unstable and decomposes to an amine and carbon dioxide. Therefore, urethanes cannot be made by esterification of a carbamic acid.

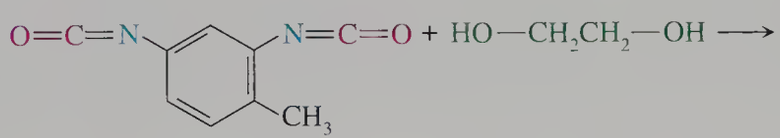


(a carbamic acid) (a urethane)

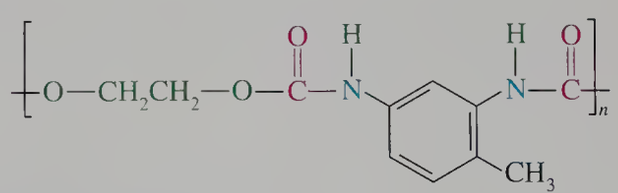
We recall that the identity of the isocyanate intermediate in the Hofmann rearrangement is established by the reaction with an alcohol to give a urethane (Section 25.9). Isocyanates can be prepared by other methods not discussed in this text. They react quantitatively and rapidly with an alcohol or phenol to give carbamate esters.

(an isocyanate)

Polyurethane can be prepared by the reaction of a diisocyanate with a diol. The major diisocyanate used is toluene diisocyanate, which has the isocyanate groups at positions ortho and para to the methyl group. When ethylene glycol is added to the diisocyanate, a typical condensation polymerization occurs to give a polyurethane.



toluene diisocyanate



(a polyurethane)

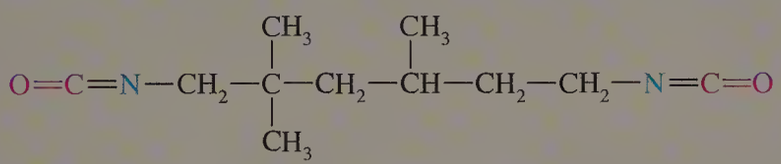
The major use of polyurethanes is in foams. Gases are blown into the liquid polymer to produce bubbles that are trapped as the material cools. When the resulting material is spongy, it is used for cushions. If monomers are selected to give cross-links, the more rigid foams that form are used for thermal insulation in building construction.

Fibers of polyurethanes can be made by using oligomeric ethers with a ter-

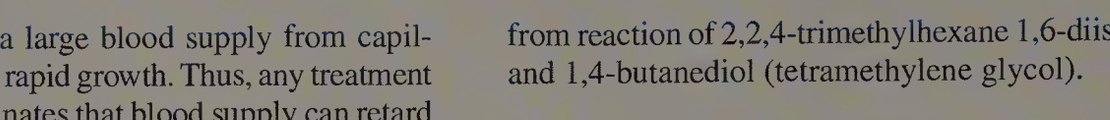
Polyurethanes in Treatment of Cancer

Solid tumors require a large blood supply from capillaries to maintain their rapid growth. Thus, any treatment that decreases or eliminates that blood supply can retard the growth of solid tumors in organs for which surgery is difficult. In 1994 a potential use of polymers to block tumor-feeding capillaries was developed. A polyurethane that is soluble in ethanol is injected through a catheter that has been threaded along the patient's arteries to the site of the tumor. Because the polyurethane is insoluble in aqueous tissue fluids such as blood, it precipitates as particles that are sufficiently large to lodge in the capillaries that supply blood to the tumor. Eventually the polyurethane will hydrolyze and the monomers can be eliminated from the body.

One polyurethane used to "starve" tumors is formed from reaction of 2,2,4-trimethylhexane 1,6-diisocyanate and 1,4-butanediol (tetramethylene glycol).

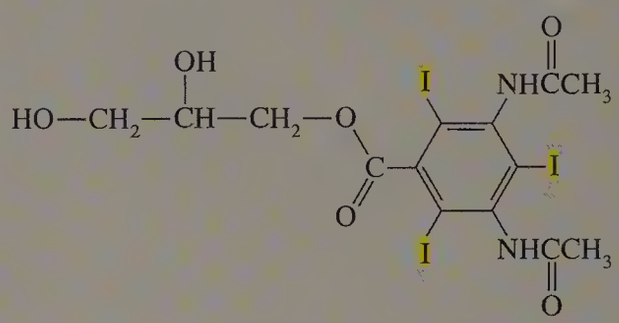


2,2,4-trimethylhexane 1,6-diisocyanate

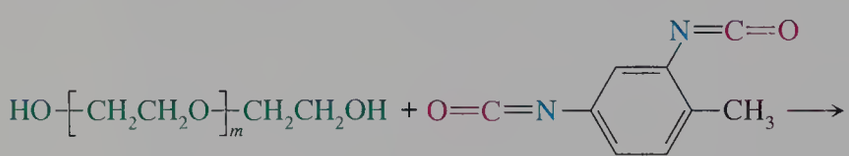


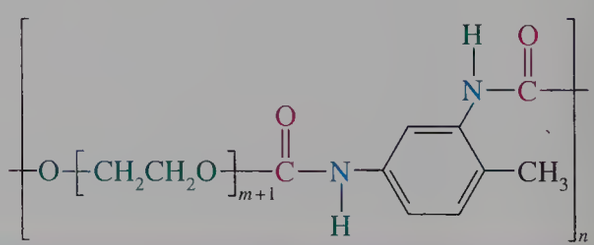
1,4-butanediol (tetramethylene glycol)

Some quantity of a second diol is used to provide a method of monitoring the delivery of the polyurethane to the site of the cancer. The 1-glyceryl ester of 3,5-diacetamido-2,4,6-triiodobenzoic acid is a diol that when incorporated in the polyurethane can be "seen" because the iodine atoms can be detected by X-rays.



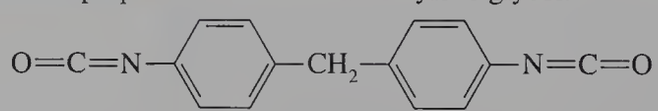
minal hydroxyl group. The oligomer located between the ester linkages makes the polymer an elastomer. Polyurethane fibers are used in Spandex and Lycra.





Problem 29.14

Methanediphenyl diisocyanate (MDI) is used to prepare a polyurethane. Draw the structure of a polyurethane prepared from MDI and ethylene glycol.



MDI

EXERCISES

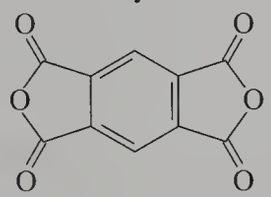
Properties of Polymers

29.1 Explain why the polymer of 2-methylpropene is a sticky elastomer with few crystalline domains.

29.2 How would the properties of the polymer of the following diamine and adipic acid differ from those of nylon 6,6?

$$CH_3—NH—(CH_2)_6—NH—CH_3$$

29.3 Explain how 1,2,4,5-benzenetetracarboxylic acid dianhydride could be used to make a thermosetting polyester.



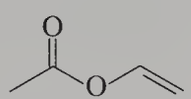
29.4 How would the properties of the copolymer of 1,4-butanediol with terephthalic acid differ from those of PET?

29.5 Why is neoprene less susceptible to oxidation than polyisoprene?

29.6 Explain why Teflon, a polymer of tetrafluoroethylene, is not sensitive to oxidation.

Addition Polymers

29.7 Vinyl acetate is used to make a polymer used in chewing gum. Draw a bond-line representation of the polymer.



29.8 Draw a bond-line structure of polyvinyl alcohol. Explain why the polymer is prepared by the hydrolysis of polyvinyl acetate.

29.9 What monomer is required to prepare the following polymer?

$$—CFCl—CF_2—CFCl—CF_2—CFCl—CF_2—CFCl—CF_2—$$

29.10 Hexafluoropropene is a monomer used to prepare a polymer called Viton. Draw a representation of the polymer.

29.11 Draw the structure of the ozonolysis product of natural rubber under oxidative workup conditions.

29.12 The polymer formed from a compound with molecular formula C_6H_{10} undergoes ozonolysis to give 2,5-hexanedione. What is the structure of C_6H_{10}?

Chain Transfer Reactions

29.13 Draw the structure of the branch formed by a short chain transfer reaction in the formation of polystyrene.

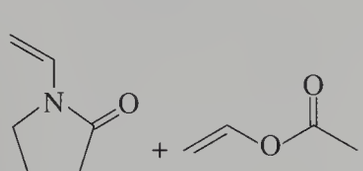
29.14 Explain why formation of a polymer of 1-hexene under free radical conditions would produce some molecules with methyl groups bonded to the main chain.

Copolymers

29.15 Draw a representation of an alternating polymer of isoprene and 2-methylpropene.

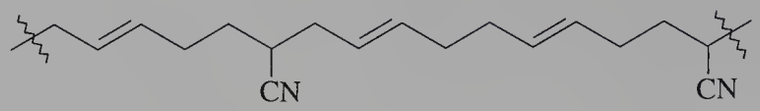
29.16 Styrene and 1,3-butadiene form a random polymer. What is the probability that a 1,3-butadiene unit will react with a growing polymer chain with styrene at its end?

29.17 Some hair sprays contain a solution of a copolymer made from the following monomers. Draw a representation of the polymer. Why does the copolymer hold hair in place?



29.18 Saran is a copolymer of vinylidene chloride ($CH_2{=}CCl_2$) and a smaller amount of vinyl chloride. Draw a representation of the polymer.

29.19 Nitrile rubber, which is used to make automotive hoses, has the following structure. What monomers are used to produce the polymer?



29.20 Draw a section of a copolymer of acrylonitrile, styrene, and 1,3-butadiene, which is used as a synthetic rubber.

Cross-linked Polymers

29.21 What is the difference between the number of cross-links in the rubber used in tires and the rubber used in gloves?

29.22 Draw a representation of the polyester formed from butenedioic anhydride (maleic anhydride) and 1,2-propanediol. Explain how this polymer could be cross-linked by reacting it with styrene.

Stereochemistry of Polymerization

29.23 Which of the following alkenes can be polymerized to give isotactic and syndiotactic structures?
(**a**) 1-chloroethene (**b**) 1,1-dichloroethene (**c**) 2-methylpropene (**d**) styrene

29.24 Are syndiotactic or isotactic forms of polypropylene optically active?

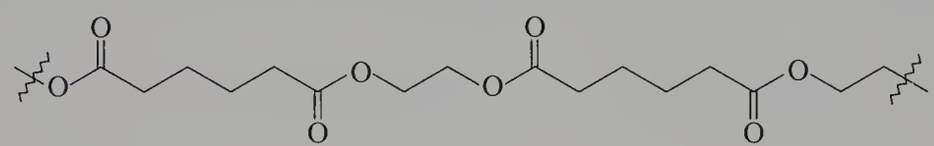
29.25 3-Methyl-1-pentene reacts with a Ziegler–Natta catalyst to give an isotactic polymer. What relationship exists between the alkyl groups on the polymer chain?

29.26 Ethylene and *cis*-2-butene form a syndiotactic copolymer in a reaction catalyzed by a vanadium catalyst. Draw a representation of the polymer.

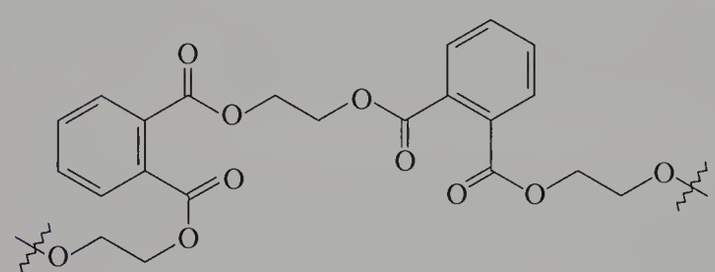
Condensation Polymers

29.27 What monomers are required to prepare the following polymers?

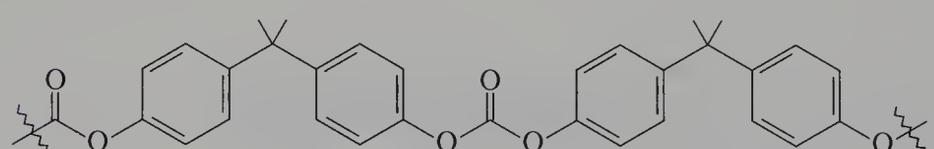
(**a**)



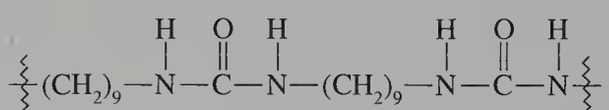
(**b**)



(**c**)

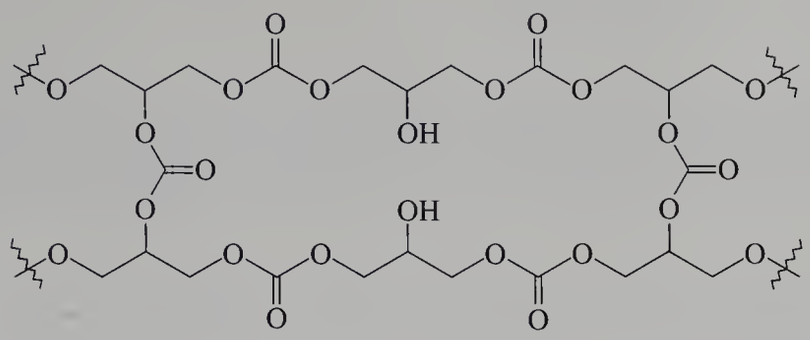


(**d**)

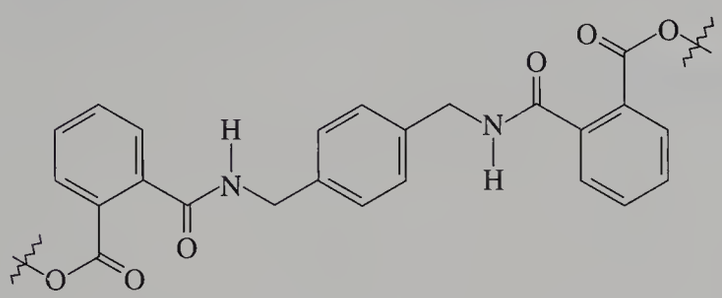


29.28 What monomers are required to prepare the following polymers?

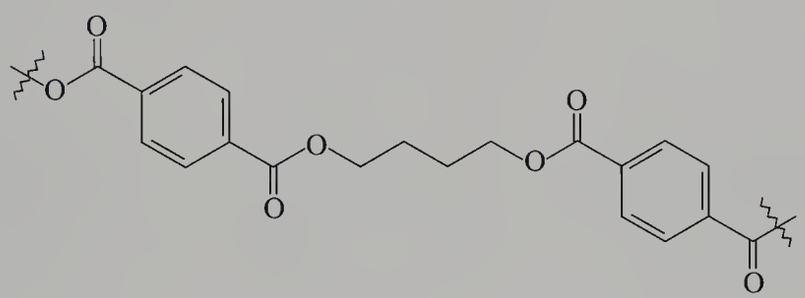
(a)



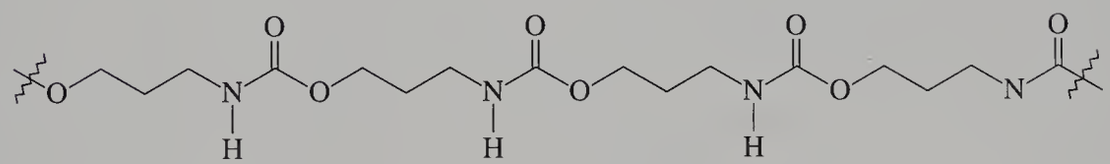
(b)



(c)



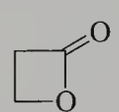
(d)



Polyesters

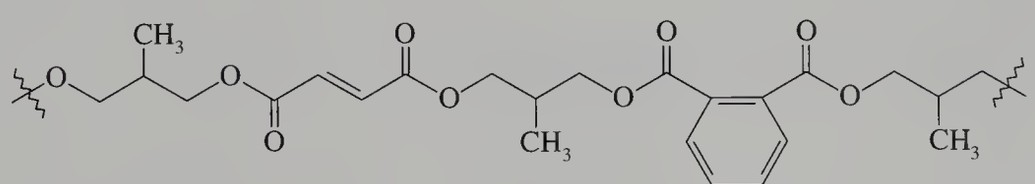
29.29 A homopolymer of lactic acid can be used to make body implants. Write a bond-line representation of the polymer.

29.30 A polymer of β-propiolactone is obtained by using a catalytic amount of hydroxide ion. Draw the structure of the polymer. Why does the polymerization reaction continue?



29.31 Kodel is a polymer of terephthalic acid and *trans*-di-1,4-(hydroxymethyl)cyclohexane. Draw a representation of the polymer.

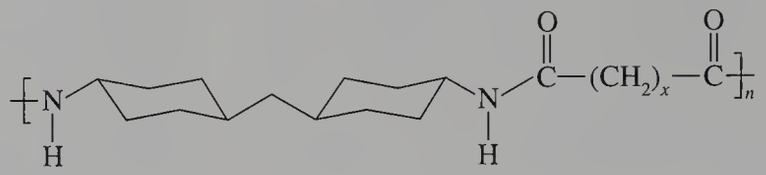
29.32 What monomers are used to prepare the following polyester? Identify an unusual feature of this polyester.



Polyamides

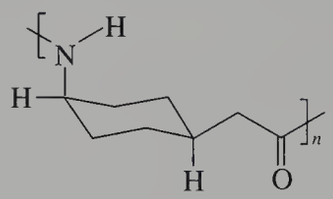
29.33 Draw a representation of each of the following polymers.
(**a**) nylon 6,10 (**b**) nylon 11 (**c**) nylon 4,6

29.34 The following structure represents a group of polyamides called Qiana. The value of x is 8, 10, or 12. What are the component monomers? What is the significance of the value of x?



29.35 Is it likely that nylon 11 could be prepared from a lactam?

29.36 A polyamide contains the following structural unit, which is prepared from the reaction of a lactam. Draw the structure of the lactam.



Polyethers

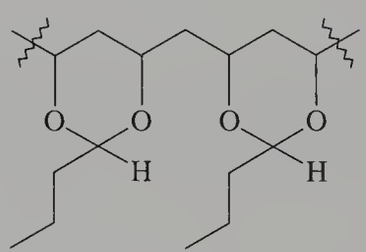
29.37 Carbowax is a polyether named polyethylene glycol. Why is ethylene oxide used to prepare this polymer?

29.38 Polymerization of (*S*)-2-methyloxirane catalyzed by a Lewis acid in ether yields an optically inactive polymer. Use of solid sodium hydroxide as a catalyst gives an optically active polymer. Account for the difference in the two reactions.

29.39 A polyether oligomer of tetramethylene glycol is produced by an acid-catalyzed ring opening of tetrahydrofuran. Write the steps that account for the formation of the oligomer.

$$+(CH_2)_4-O+_n$$

29.40 Poly(vinylbutyral) is used in automobile windshield glass. How is this polymer prepared starting from polyvinyl acetate?



poly(vinyl butyral)

Polyurethanes

29.41 Explain why the addition of glycerol to the polymerization of toluene diisocyanate and ethylene glycol produces a stiffer foam.

29.42 An oligomer of tetramethylene glycol $H-O+(CH_2)_4-O+_nH$ reacts with toluene diisocyanate to form a polyurethane called Lycra. Draw a representation of the polyurethane.

Appendix A: Heats of Formation (kJ mole^{-1})

Alkanes

methane	−74.48
ethane	−83.85
propane	−104.68
butane	−126.78
2-methylpropane	−134.18
pentane	−146.94
2-methylbutane	−153.55
hexane	−166.94
2-methylpentane	−174.68
3-methylpentane	−172.0
heptane	−187.65
2-methylhexane	−194.72
3-methylhexane	−191.3
octane	−208.82
2-methylheptane	−215.35
3-methylheptane	−212.5
nonane	−228.86
2-methyloctane	−235.85
3-methyloctane	−233.7
decane	−249.55
2-methylnonane	−256.52
3-methylnonane	−254.4

Cycloalkanes

cyclopropane	+53.3
cyclobutane	+28.4
cyclopentane	−77.10
cyclohexane	−123.19
cycloheptane	−118.1
cyclooctane	−124.4
cyclononane	−132.6
cyclodecane	−154.3
cycloundecane	−179.4
cyclododecane	−230.1
cyclotridecane	−246
cyclotetradecane	−301
cyclopentadecane	−323

Substituted Cycloalkanes

methylcyclopentane	−105.8
methylcyclohexane	−154.7
ethylcyclohexane	−171.4
trans-1,2-dimethylcyclopropane	−3.2
cis-1,2-dimethylcyclopropane	+0.7
trans-1,2-dimethylcyclopentane	−32.7
cis-1,2-dimethylcyclopentane	−31.0
trans-1,3-dimethylcyclopentane	−31.9
cis-1,3-dimethylcyclopentane	−32.5
trans-1,2-dimethylcyclohexane	−171.6
cis-1,2-dimethylcyclohexane	−179.5
trans-1,3-dimethylcyclohexane	−184.2
cis-1,3-dimethylcyclohexane	−176.2
trans-1,4-dimethylcyclohexane	−176.2
cis-1,4-dimethylcyclohexane	−184.2

Alkenes

ethene	+52.5
propene	+20.0
cis-2-butene	−7.1
trans-2-butene	−11.4
2-methylpropene	−16.9
cis-2-pentene	−27.6
trans-2-pentene	−31.9
2-methyl-1-butene	−35.3
2-methyl-2-butene	−41.8
3-methyl-1-butene	−27.6

Cycloalkenes

cyclopentene	+33.9
cyclohexene	−5.0
cycloheptene	−9.2
1-methylcyclohexene	−43.1
cyclooctene	−27.2

Dienes

propadiene	+190.5
1,2-butadiene	+162.3
1,3-butadiene	+110.3
2-methyl-1,3-butadiene	+75.5
cis-1,3-pentadiene	+81.4
trans-1,3-pentadiene	+76.1
1,4-pentadiene	+105.6
1,3-cyclopentadiene	+133

Alkynes

propyne	185.0
1-butyne	165.7
2-butyne	147.7
1-pentyne	144.0
2-pentyne	128.6
3-methyl-1-butyne	136.1
1-hexyne	123.4
1-heptyne	102.8
1-octyne	82.2
1-nonyne	61.7
1-decyne	41.1

Aromatic Hydrocarbons

benzene	+82.6
toluene	+50.4
o-xylene	+19.1
m-xylene	+17.3
p-xylene	+18.0
ethylbenzene	+29.9
styrene	+147.9
naphthalene	+150.3
anthracene	+230.9
phenanthrene	+207.5

Alcohols

methanol	−201.5
ethanol	−235.2
1-propanol	−255.1
2-propanol	−272.8
1-butanol	−275.0
2-butanol	−292.9
2-methyl-1-propanol	−283.9
2-methyl-2-propanol	−312.5
cyclopentanol	−242.4
cyclohexanol	−285.9

Ethers

dimethyl ether	−184.1
diethyl ether	−252.1
ethylene oxide	−52.6
tetrahydrofuran	−184.2
furan	−34.9

Aldehydes and Ketones

methanal	−108.6
ethanal	−166.1
propanal	−185.6
propanone	−217.3
butanal	−204.8
2-methylpropanal	−215.8
2-butanone	−238.7
cyclopentanone	−192.1
cyclohexanone	−225.7
benzaldehyde	−36.7
acetophenone	−86.7

Acids and Esters

methanoic acid	−378.7
ethanoic acid	−432.8
methyl methanoate	−355.5
methyl ethanoate	−411.9
ethyl ethanoate	−444.1

Amines

methylamine	−23.0
ethylamine	−47.4
propylamine	−70.2
isopropylamine	−83.8
butylamine	−92.0
isobutylamine	−98.7
tert-butylamine	−120.9
pyrrole	+108.3
pyrrolidine	−3.4
pyridine	+140.4
piperidine	−47.2

Sulfur Compounds

methanethiol	−22.9
ethanethiol	−46.3
dimethyl sulfide	−37.5
dimethyl disulfide	−23.4
dimethyl sulfoxide	−150.9
thiophene	+115.4

Appendix B: pK_a Values

Inorganic Acids

arsenic (H_3AsO_4)	2.25, 6.77, 11.6
boric (H_3BO_3)	9.14, 12.7, 13.8
carbonic (H_2CO_3)	6.37, 10.25
hydrobromic (HBr)	–9
hydrochloric (HCl)	–7
hydrocyanic (HCN)	9.31
hydrofluoric (HF)	3.45
hydrogen sulfide (H_2S)	7.04, 12.0
hypochlorous (HOCl)	4.53
nitric (HNO_3)	–1.3
nitrous (HNO_2)	3.37
phosphoric (H_3PO_4)	2.12, 7.21, 12.7
pyrophosphoric ($H_4P_2O_7$)	0.85, 1.49, 5.77, 8.22
sulfuric (H_2SO_4)	–5.2, 2.0
sulfurous (H_2SO_3)	1.81, 6.91

Acyclic Carboxylic Acids

HCO_2H	3.75
CH_3CO_2H	4.72
$CH_3CH_2CO_2H$	4.87
$CH_3(CH_2)_2CO_2H$	4.82
$(CH_3)_2CHCO_2H$	4.84
$CH_3(CH_2)_3CO_2H$	4.81
$(CH_3)_3CCO_2H$	5.03
$HC{\equiv}CCO_2H$	1.9
$CH_3C{\equiv}CCO_2H$	2.6
$CH_2{=}CHCO_2H$	4.2

Substituted Acetic Acids

FCH_2CO_2H	2.59
$ClCH_2CO_2H$	2.86
$BrCH_2CO_2H$	2.90
ICH_2CO_2H	3.18
Cl_2CHCO_2H	1.22
Cl_3CCO_2H	0.64
F_3CCO_2H	0.23
$NO_2CH_2CO_2H$	1.3
$NCCH_2CO_2H$	2.5
$HSCH_2CO_2H$	3.5
$HOCH_2CO_2H$	3.7
$CH_3OCH_2CO_2H$	3.6

Benzoic Acids

benzoic	4.2
m-aminobenzoic	4.8
p-aminobenzoic	4.9
o-bromobenzoic	2.8
m-bromobenzoic	3.9
o-chlorobenzoic	2.9
m-chlorobenzoic	3.8
p-chlorobenzoic	4.0
o-nitrobenzoic	2.2
m-nitrobenzoic	3.5
p-nitrobenzoic	3.4
o-methylbenzoic	3.9
m-methylbenzoic	4.3
p-methylbenzoic	4.4
o-methoxybenzoic	4.1
m-methoxybenzoic	4.1
p-methoxybenzoic	4.5

Dicarboxylic Acids

oxalic	1.27, 4.27
malonic	2.85, 5.7
succinic	4.20, 5.64
glutaric	4.35, 5.42
adipic	4.41, 5.41
pimelic	4.51, 5.42
suberic	4.52, 5.41
azeleic	4.54, 5.41
sebacic	4.55, 5.40

Alcohols

CH_3OH	15.5
CH_3CH_2OH	15.9
$(CH_3)_2CHOH$	18.0
$(CH_3)_3COH$	19.0
$ClCH_2CH_2OH$	14.3
Cl_2CHCH_2OH	12.9
CF_3CH_2OH	12.4
$CF_3CH_2CH_2OH$	14.6
$(CF_3)_3COH$	4.7
$C_6H_5CH_2OH$	15.4
$CH_2{=}CHCH_2OH$	15.5

Phenols

phenol	10.0
o-bromophenol	8.4
m-bromophenol	8.9
p-bromophenol	9.2
o-chlorophenol	8.4
m-chlorophenol	9.0
p-chlorophenol	9.4
2,4-dichlorophenol	7.8
2,4,6-trichlorophenol	6.2
p-cyanophenol	8.0
o-methoxyphenol	10.0
m-methoxyphenol	9.6
p-methoxyphenol	10.2
o-methylphenol	10.3
m-methylphenol	10.1
p-methylphenol	10.3
o-nitrophenol	7.2
m-nitrophenol	8.4
p-nitrophenol	7.2
3,4-dinitrophenol	3.5
2,4-dinitrophenol	4.1
2,4,6-trinitrophenol	0.3
p-trifluoromethylphenol	8.7

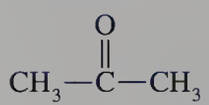
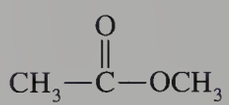
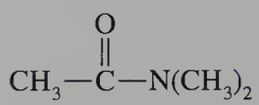
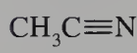
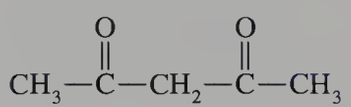
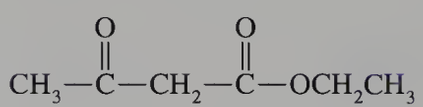
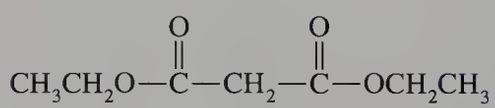
Sulfur Compounds

methanesulfonic acid	−1.8
thiophenol	6.6
methanethiol	10.3
dimethyl sulfoxide	35
dimethyl sulfone	28

Hydrocarbons

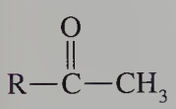
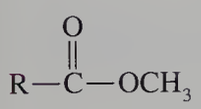
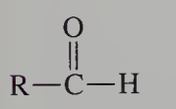
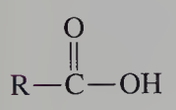
ethane	50
ethylene	44
acetylene	25
benzene	43
toluene	41
diphenylmethane	34
triphenylmethane	32
cyclopentadiene	15

α-Hydrogen Atoms

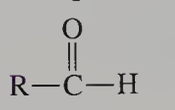
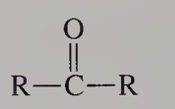
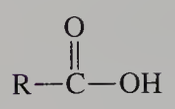
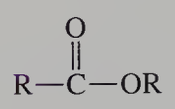
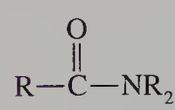
	19
	25
	30
	25
	19
	11
	19

Appendix C: Chemical Shifts (ppm)

^{1}H NMR

$(CH_3)_4Si$	0.0
ROH	1.0–6.0
RNH_2	1.0–3.0
RCH_3	0.8–1.0
R_2CH_2	1.2–1.4
R_3CH	1.4–1.7
$R_2C{=}CRCH_2R$	1.6–1.9
$RC{\equiv}CCH_3$	1.9–2.1
$RC{\equiv}CH$	2.5–3.1
$ArCH_3$	2.2–2.5
$R_2C{=}CH_2$	4.5–5.0
Ar—H	6.5–8.5
	2.0–2.5
RCH_2OH	3.3–4.0
RCH_2OCH_3	3.3–3.9
	3.4–3.8
	9.4–9.8
	10–12
RCH_2—Cl	3.6–3.8
RCH_2—Br	3.4–3.6

^{13}C NMR

$(CH_3)_4Si$	0.0
R_3CH	0–40
R_2CH_2	15–55
R_3CH	20–60
$R_2C{=}CR_2$	100–150
$RC{\equiv}CR$	65–85
ArH	110–160
$R_2C{=}CH_2$	4.5–5.0
RCH_2—Cl	35–80
RCH_2—Br	25–65
	190–210
	190–210
	160–190
	160–190
	150–185

Appendix D: Characteristic Infrared Absorptions (cm^{-1})

Hydrocarbons

C—H stretching	
alkane	3000–2850
alkene	3100–3000
alkyne	3300
C—H bending	
alkene	
monosubstituted	995–985, 910–905
cis	690
disubstituted	895–885
trans	980–965
trisubstituted	840–790
aromatic	
5 adjacent hydrogens	770–730
4 adjacent hydrogens	770–735
3 adjacent hydrogens	810–750
2 adjacent hydrogens	860–800
1 hydrogen	900–860
C—C stretching	
alkene (unconjugated)	1670–1630
alkyne	2140–2100

Ketone Carbonyl Stretch

acyclic	1715–1710
α,β-unsaturated	1685–1665
aryl conjugated	1700–1680
cyclic	
6-membered ring	1710
5-membered ring	1745
4-membered ring	1780

Aldehyde Carbonyl Stretch

saturated	1725–1720
α,β-unsaturated	1705–1680
aryl conjugated	1715–1695

Ester Carbonyl Stretch

saturated	1750–1735
α,β-unsaturated	1730–1715
cyclic	
6-membered ring	1750–1700
5-membered ring	1780–1760
4-membered ring	1820

Carboxylic Acid Carbonyl Stretch

saturated	1725–1700
α,β-unsaturated	1715–1690
aryl conjugated	1700–1680

Acid Derivatives

acyl chloride (carbonyl)	1800
amide (carbonyl)	1655
nitriles (C≡N)	2250–2200

O—H, S—H, and N—H Groups

alcohols	3400–3200
carboxylic acids	3600–2400
thiols	2600–2550
amines	3375–3200

Appendix E: Summary of Synthetic Methods

Synthesis of Alkanes, Cycloalkanes, and Aromatic Hydrocarbons

1. Catalytic hydrogenation of alkenes (6.9)
2. Catalytic hydrogenation of alkynes (11.6)
3. Catalytic hydrogenation of aromatic compounds (13.11)
4. Protonation of Grignard reagents (8.8)
5. Addition of carbenoids to alkenes (7.7)
6. Friedel–Crafts alkylation of aromatic compounds (14.2)
7. Wolff–Kishner or Clemmensen reduction of aldehydes or ketones (14.8, 18.5)
8. Reduction of aryldiazonium salts with hypophosphorous acid (14.8)
9. Catalytic reduction of aryl ketones (13.11)
10. Substitution reaction of alkyl halide with lithium dialkyl cuprates (8.8)
11. Reduction of thioacetals (19.9)

Synthesis of Alkenes

1. Acid-catalyzed dehydration of alcohols (8.20)
2. Dehydrohalogenation of alkyl halides (8.18)
3. Catalytic reduction of alkynes (11.6)
4. Reduction of alkynes with lithium in liquid ammonia (11.6)
5. Hofmann elimination of quaternary ammonium hydroxides (25.15)
6. Wittig reaction of aldehydes or ketones (19.11)

Synthesis of Alkynes

1. β elimination of dihaloalkanes or vinyl halides (11.8)
2. Alkylation of alkynides with alkyl halides (8.8, 11.8)

Synthesis of Alkyl Halides

1. Polar addition of hydrogen halides to alkenes (7.2)
2. Peroxide-induced addition of hydrogen halides to alkenes (7.11)
3. Addition of halogens to alkenes (7.6)
4. Reaction of alcohols with hydrogen halide (8.14)
5. Reaction of alcohols with thionyl chloride or phosphorus tribromide (8.15, 16.3)
6. Allylic or benzylic halogenation (12.5)
7. α halogenation of aldehydes, ketones, or carboxylic acids (23.5, 23.14)

Synthesis of Aryl Halides

1. Direct halogenation using Lewis acid catalyst (14.2)
2. Reaction of aryldiazonium salts with copper(I) halide (14.8)

Synthesis of Alcohols

1. Acid-catalyzed hydration of alkenes (7.5)
2. Oxymercuration–demercuration of alkenes (16.8)
3. Hydroboration–oxidation of alkenes (16.8)
4. Reduction of aldehydes or ketones (16.9, 18.5)
5. Reduction of carboxylic acids (21.7)
6. Reduction of esters (16.9, 22.8)
7. Reaction of Grignard reagent with aldehydes or ketones (16.10)
8. Reaction of Grignard reagent with esters (22.10)
9. Reaction of Grignard reagent with ethylene oxide (17.10)
10. Reaction of alkynide ion with aldehyde or ketone (16.10)

Synthesis of Glycols

1. Ring opening of epoxides (17.10)
2. Reaction of alkenes with potassium permanganate or osmium tetroxide (7.9)

Synthesis of Ethers

1. Alkoxylation of alkyl halides with alkoxides or phenoxides (17.6, 27.4)
2. Alkoxymercuration–demercuration of alkenes (17.5)
3. Acid-catalyzed addition of alcohols to alkenes (17.4)
4. Acid-catalyzed dehydration of alcohols (17.4)
5. Acetal formation of aldehydes and ketones (19.7)
6. Aromatic ether by nucleophilic aromatic substitution (27.4)

Synthesis of Epoxides

1. Oxidation of alkenes with peroxy acids (7.8, 17.9)
2. Intramolecular Williamson synthesis from halohydrins (17.9)

Synthesis of Aldehydes

1. Oxidation of primary alcohols (16.4, 18.6)
2. Reduction of esters (18.6)
3. Reduction of acid chlorides (18.6, 22.8)
4. Hydroboration–oxidation of alkynes (18.6)
5. Ozonolysis of alkenes (7.10, 18.6)
6. Oxidative cleavage of glycols (16.5)
7. Reduction of nitriles (18.6)

Synthesis of Ketones

1. Oxidation of secondary alcohols (16.4)
2. Mercury(II)-catalyzed hydration of alkynes (11.7, 18.6)
3. Reaction of acid chlorides with lithium dialkylcuprates (18.6, 22.10)
4. Friedel–Crafts acylation of aromatic compounds (14.2, 18.6)
5. Ozonolysis of alkenes (7.10, 18.6)
6. Oxidative cleavage of glycols (16.5)
7. Acetoacetic ester synthesis (23.17)
8. Hydroboration–oxidation of alkynes (18.6)
9. Reaction of organolitihium reagents with carboxylic acids (18.6)

Synthesis of Carboxylic acids

1. Oxidation of primary alcohols (16.4, 18.5, 21.6)
2. Oxidation of aldehydes (18.5, 21.6)
3. Reaction of Grignard reagent with carbon dioxide (21.6)
4. Hydrolysis of esters (22.5)
5. Hydrolysis of amides (22.5)
6. Hydrolysis of acid chlorides (22.5)
7. Hydrolysis of nitriles (21.6, 22.5)
8. Ozonolysis of alkenes with oxidative workup conditions (7.10)
9. Ozonolysis of alkynes (11.5)
10. Haloform reaction of methyl ketones (21.6)
11. Malonic ester synthesis (23.17)

Synthesis of Esters

1. Acid catalyzed esterification of carboxylic acid with alcohol (21.12)
2. Alkylation of carboxylate salts with alkyl halides (21.12)
3. Alkylation of carboxylic acids with diazomethane (21.12)
4. Reaction of acid chlorides with alcohols (22.6)
5. Reaction of anhydrides with alcohols (22.6)

Synthesis of Acid Chlorides

1. Reaction of carboxylic acid with thionyl chloride (21.10)

Synthesis of Anhydrides

1. Reaction of carboxylic acids with dehydrating agent (21.11)
2. Reaction of carboxylate salt with acid chloride (21.11)

Synthesis of Amides

1. Reaction of acid chloride with amines (22.7, 25.13)
2. Reaction of amines with anhydrides (22.7)
3. Reaction of esters with amines (22.7)

Synthesis of Nitriles

1. Reaction of alkyl halides with cyanide ion (8.10)
2. Reaction of aryldiazonium ion with copper(I) cyanide (14.8)

Synthesis of Amines

1. Reduction of amides (22.8, 25.9)
2. Reduction of nitriles (22.8, 25.9)
3. Alkylation of amines using alkyl halides (25.8)
4. Reductive amination (25.9)
5. Gabriel synthesis (25.8)
6. Hofmann rearrangement (25.10)
7. Reduction of nitro compounds (14.8, 25.9)

Synthesis of Thiols and Sulfides

1. Thiols from alkyl halides (8.10, 16.11)
2. Sulfides from alkyl halides (17.11)

Formation of Carbon–Carbon Bonds

1. Reaction of alkyl halide with cyanide ion (8.10)
2. Reaction of alkynide ions with alkyl halides (8.8, 11.8)
3. Reaction of alkenes with carbenoids (7.7)
4. Wittig synthesis (19.11)
5. Cyanohydrin formation (19.2)
6. Friedel–Crafts alkylation and acylation reactions (14.2, 18.6)
7. Reaction of Grignard reagent with aldehydes or ketones (16.10)
8. Reaction of Grignard reagent with ethylene oxide (17.10)
9. Reaction of Grignard reagent with carbon dioxide (21.6)
10. Reaction of Grignard reagent with esters (22.10)
11. Reaction of lithium dialkylcuprates with acid chlorides (18.6, 22.10)
12. Aldol condensation (23.7)
13. Claisen condensation (23.15)
14. Malonic ester synthesis (23.17)
15. Acetoacetic acid synthesis (23.17)
16. Alkylation of ester enolates (23.6)
17. Alkylation of enamine (25.12)
18. Conjugate addition reactions of α,β-unsaturated carbonyl compounds (23.10)
19. Diels–Alder reaction (28.5)
20. Electrocyclic reactions (28.4)

Appendix F: Glossary

absolute configuration The spatial arrangement of atoms at a stereogenic center.

absolute specificity The ability of an enzyme to catalyze the reaction of only one substrate.

absorption spectroscopy A measure of the light absorption of a molecule as a function of wavelength, wavenumber, or frequency.

acetal A product formed from the reaction of 1 mole of an aldehyde and 2 moles of an alcohol, as in $RCH(OR)_2$.

acetoacetic ester synthesis Synthesis of substituted acetone derivatives by alkylation of acetoacetic esters followed by hydrolysis and decarboxylation.

acetyl coenzyme A Acetyl derivative of coenzyme A (a thiol); a central intermediate for metabolic processes.

acetylene The simplest alkyne, C_2H_2, but also commonly used to designate the class of alkynes.

acetylide The conjugate base (anion) of a terminal alkyne.

achiral compound A compound that can be superimposed on its mirror image.

acid A substance that is a proton donor (Brønsted–Lowry). A substance that is an electron pair acceptor (Lewis)

acid anhydride A compound formed by loss of water in the reaction of two molecules of an acid.

acid derivative Compound derived from carboxylic acids with atoms or groups of atoms replacing the —OH group.

acid dissociation constant A measure of the acidity of an acid in a reaction with water to produce the hydronium ion.

acid halide An acid derivative with a halogen atom replacing the hydroxyl group of a carboxylic acid.

acidic amino acids Amino acids that have more than one carboxyl group.

activating group A substituent on an aromatic ring that makes the ring more susceptible to attack by electrophiles.

activation energy The energy difference between reactants and the transition state that is the minimum required for a reaction to occur.

active site The region in an enzyme that has a unique arrangement of amino acid side shains required for catalytic activity.

active transport The movement of material across membranes from low concentration to high concentration.

acyclic compound A compound not containing any cyclic structure.

acylation Reaction attaching an acyl group to another structural unit.

acyl carrier protein The carrier of acyl groups in fatty acid biosynthesis.

acyl chloride Carboxylic acid derivative with the RCOCl functional group.

acyl group The carbonyl-containing portion of a compound such as an ester or amide.

acylium ion A reactive intermediate, $R—C{\equiv}O^+$, produced in Friedel–Crafts acylation reactions.

acyl transfer Reaction converting one acyl derivative into another.

1,2-addition An addition of two groups of atoms to adjacent carbon atoms as in an alkene, alkyne, or carbonyl compound.

1,4-addition An addition of two groups of atoms to carbon atoms with a 1,4 relationship, usually in a conjugated system of double bonds or carbonyl groups.

addition–elimination reaction A two-step mechanism for nucleophilic aromatic substitution or in the formation of an imine from a carbonyl compound.

addition polymer Polymer that forms from the addition of monomers to each other, usually involving double bonds.

addition reaction The incorporation of two groups of atoms into a molecule with a multiple bond such as an alkene or carbonyl compound; reaction in which two reactants combine to give a single product.

adenine A purine base found in both RNA and DNA.

adenosine diphosphate (ADP) Hydrolysis product of adenosine triphosphate consisting of ribose, adenine, and two phosphate groups.

adenosine monophosphate (AMP) Hydrolysis product of adenosine triphosphate consisting of ribose, adenine, and one phosphate group.

adenosine triphosphate (ATP) High-energy phosphate compound consisting of ribose, adenine, and three phosphate groups.

adipose tissue Another name for depot fat found in connective tissue.

aglycone The group bonded to the anomeric carbon atom of a glycoside.

alcohol A compound containing a hydroxyl group bonded to a saturated carbon atom.

alcohol dehydrogenase The enzyme that catalyzes the oxidation of ethanol to acetaldehyde and acetic acid in living cells.

aldaric acid A dicarboxylic acid prepared by oxidation to carboxylic acid groups at each end of a monosaccharide.

aldehyde A carbonyl compound whose carbonyl carbon atom is bonded to one hydrogen atom and either an alkyl or aryl group.

alditol A poly alcohol formed by reduction of an aldose or ketose.

aldol condensation Formation of α-hydroxy aldehyde or ketone or the related α,β-unsaturated carbonyl compound by reaction of two equivalents of carbonyl compounds.

aldonic acid A carboxylic acid obtained by oxidation of the aldehyde of an aldose.

aldose A carbohydrate containing an aldehyde group.

alkadiene A hydrocarbon containing two carbon–carbon double bonds.

alkali metals The elements of Group IA of the periodic table.

alkaline earth metals The elements of Group IIA.

alkane Hydrocarbon having only carbon–carbon single bonds and the molecular formula C_nH_{2n+2}.

alkene Hydrocarbon having a carbon–carbon double bond.

alkoxide ion Anion (RO^-) produced by loss of a proton from an alcohol.

alkoxy group A group, represented as RO—, present in ethers.

alkoxymercuration The addition of a mercuric salt to an alkene in an alcohol solution.

alkyl ammonium ion Derivative of ammonium ion in which one or more alkyl groups replace hydrogen, as in RNH_3^+.

alkyl group A group of carbon and hydrogen atoms that resemble an alkane but has one less hydrogen atom.

alkyl halide A derivative of an alkane of the type R—X.

alkyloxonium ion Positively charged species of the type ROH_2^+.

alkyne Hydrocarbon having a carbon–carbon triple bond.

allene The compound $CH_2{=}C{=}CH_2$ or a compound containing two cumulated double bonds.

allosteric effect A change in conformation at one site caused by a change in conformation at a second, spatially separated site.

allosteric regulation The noncompetitive inhibition causing conformational changes.

allyl group The $CH_2{=}CH{-}CH_2{-}$ group

allylic The saturated bonds at an atom adjacent to a carbon–carbon double bond.

alpha carbon atom The carbon atom immediately adjacent to the carbonyl carbon atom.

alpha elimination An elimination reaction in which the two groups of atoms eliminated are located on the same carbon atom.

amide The functional group with a nitrogen atom bonded to a carbonyl carbon atom.

amine derivative of ammonia in which one or more hydrogen atoms are replaced by alkyl or aryl groups.

amino The functional group $-NH_2$.

amino acid An amino-substituted carboxylic acid. In proteins the amino group is at the α position.

amino acid residue Amino acid components of a peptide or protein.

aminopeptidase Enzyme that sequentially hydrolyzes a peptide from the end that has the free amino group.

ammonium salt A tetravalent nitrogen species with a positive charge formed by protonation or alkylation of an amine.

amylopectin A component of starch that has branched chains of glucose.

amylose A component of starch that has a linear arrangement of glucose.

anabolic steroids Synthetic substances, related to testosterone, that promote muscle development.

androgens Male sex hormones; testosterone is one example.

angle strain The strain associated with bond angles that deviate from those associated with a particular type of hybrid bond.

angular (bent) molecule A planar molecule with three atoms arranged at an angle other than 180°.

anhydride An acid derivative containing an oxygen atom bridging two carbonyl carbon atoms.

anion Negatively charged ion that results from the gain of one or more electrons.

anomeric carbon atom The original carbonyl carbon atom of an aldose or ketose as contained in the cyclic form of the sugar.

anomers Stereoisomers that differ in configuration at the anomeric carbon atom.

antagonist Drug that opposes the effect of another compound

anti addition Addition of two groups to the opposite faces of a molecule.

antibonding molecular orbital A molecular orbital that is of higher energy than the isolated atomic orbitals used to form the orbital.

antibody Protein that recognizes and combines with a foreign substance.

anti conformation A conformation with a 180° dihedral (torsional) angle.

anti coplanar Groups having a 180° dihedral angle.

anti-Markovnikov addition Addition reaction with reagents that occurs with regioselectivity opposite that of Markovnikov addition.

annulene Acyclic compound containing a closed cycle of alternating single and double bonds.

aprotic solvent Solvent lacking easily exchangeable protons.

arene Hydrocarbon with an aromatic ring.

aromatic compound A benzene-like compound represented by a Lewis structure containing alernating single and double bonds.

aromaticity Stability associated with electron delocalization in an aromatic compound.

aryl group The part of an aromatic hydrocarbon remaining after a hydrogen atom is removed.

aryl halide A benzene (or other aromatic ring) derivative with one or more halogen atoms bonded to the ring carbon atoms.

asymmetric carbon atom Older term indicating a carbon atom bonded to four different atoms or groups of atoms.

atomic number A number equal to the number of protons in the nucleus of an atom of the element.

atomic orbital A region in space about a nucleus in which one or two electrons may be located.

atomic radius The radius of an atom, given in nanometers.

axial position A bond position that is perpendicular to the average plane of a molecule and parallel to the "axis" of the molecule.

base A proton acceptor or electron pair donor.

base dissociation constant A measure of the basicity of a base in a reaction with the hydronium ion giving the conjugate acid of the base.

basic amino acid Amino acid that has an extra amino group.

basic solution A solution with a lower concentration of hydronium ions than exists in pure water.

Benedict's solution An alkaline solution of cupric ion as a complex ion used as a test reagent for aldehydes or reducing sugars.

benzene Aromatic compound with the molecular formula C_6H_6.

benzyl carbon atom The carbon atom directly attached to a benzene ring.

benzyl group The carbon group remaining after a hydrogen is removed from the methyl group of toluene.

benzyne A reactive intermediate derived from benzene with two hydrogen atoms removed from adjacent carbon atoms.

beta elimination An elimination reaction in which the two groups of atoms eliminated are on adjacent atoms.

bilayer *See* lipid bilayer.

bimolecular A reaction with two structural units involved in the transition state.

biochemistry The study of the composition, structure, and reactions of substances in living systems.

boiling point The temperature at which the vapor pressure of a liquid equals atmospheric pressure.

bond angle The angle between two covalent bonds at a common atom in a molecule.

bond dissociation energy Energy required to homolytically break a bond in a molecule.

bonding A description of how atoms are held or fastened together in a molecule.

bonding electrons The electrons shared between atoms.

bonding molecular orbital A molecular orbital that is of lower energy than the isolated atomic orbitals used to form it.

bond length Distance between nuclei of two covalently bonded atoms.

bond-line structure A formula showing connections between atoms but not showing individual carbon or hydrogen atoms.

bond moment A measure of the polarity of a specific bond in a molecule.

branched alkane An alkane with an alkyl group bonded to a parent alkane.

branched chain A sequence of bonded atoms that have additional atoms attached to points within the chain.

bridged bicyclic compound A compound sharing two rings that are joined at nonadjacent atoms.

bridgehead atom An atom that is shared by two or more rings.

bromonium ion A halonium ion in which bromine is the halogen.

Brønsted–Lowry theory Acid–base theory describing acids as proton donors and bases as proton acceptors.

Cahn–Ingold–Prelog convention A method of describing the priorities of groups of atoms to define the absolute configuration of a chiral molecule.

carbanion A negative carbon ion with three bonds and an electron pair on a carbon atom.

carbene A divalent uncharged carbon-containing molecule such as $:CH_2$.

carbocation A carbon ion with three bonds and a positive charge on a carbon atom.

carbohydrate A polyhydroxy aldehyde or ketone or a compound that can be hydrolyzed to produce a polyhydroxy aldehyde or ketone.

carbonyl group A group consisting of a carbon atom and an oxygen atom joined by a double bond.

carboxylate group The anion formed by loss of a proton from a carboxylic acid, represented by RCO_2^-.

carboxylation Preparation of a carboxylic acid as in the reaction of carbon dioxide with a Grignard reagent.

carboxyl group The group $—CO_2H$ that is the functional group of carboxylic acids.

carboxylic acid Organic compound with the general molecular formula RCO_2H.

carboxypeptidase Enzyme that sequentially hydrolyzes a peptide from the end that has the free carboxyl group.

catalysis The increase in the speed of a reaction in the presence of a substance called a catalyst.

catalyst A substance that increases the speed of a chemical reaction.

catalytic site Position within an enzyme that provides the catalytic function.

cation Positively charged atomic particle that results from the loss of one or more electrons.

cellulose A polysaccharide of glucose with β-1,4 linkages.

cephalin A phosphatidylethanolamine.

ceramide Amide of fatty acid and sphingosine.

cerebroside Glycosphingolipid, containing only glucose or galactose, found in the brain.

chain reaction A repeated series of reactions in which a reactive intermediate formed in one step reacts in a subsequent step that in turn generates a reactant for the previous step.

chair–chair interconversion A process described as a flipping of one chair conformation into another in which the equatorial and axial positions are interchanged.

chair conformation The most stable conformation of cyclohexane.

chemical bond Attractive force that holds atoms together in compounds.

chemical equilibrium Condition in which the rate of the forward reaction equals the rate of the reverse reaction.

chemical reaction The conversion of reactants into products.

chemical shift The difference, in ppm, between the resonance of a nucleus and that of a reference nucleus such as the hydrogen atoms of tetramethylsilane.

chirality The property of an object that cannot be superimposed on its mirror image.

chiral molecule A molecule that cannot be superimposed on its mirror image.

chlorohydrin Halohydrin in which chlorine is the halogen atom.

chromosomes Units contained in somatic cells that possess genetic information.

cis On the same side of a ring or double bond.

cis isomer An isomer that has two groups of atoms oriented on the same side of a structural feature such as a cycloalkane ring.

citric acid cycle A series of reactions that oxidize an acetyl group to carbon dioxide and water and save stored energy in NADH, $FADH_2$, and ATP.

Claisen condensation reaction Reaction of two ester molecules to give a β-keto ester.

Clemmensen reduction Reduction of a carbonyl group of an aldehyde or ketone using zinc amalgam and hydrochloric acid.

coenzyme A cofactor that is an organic molecule.

coenzyme A A thiol ester that transfers acyl groups in acetyl CoA.

cofactor A nonprotein material that is an essential part of some enzymes.

collagen Protein component of connective tissue.

combustion A rapid chemical reaction of a substance with oxygen.

common names Historically derived names of compounds that are unrelated to composition; also known as trivial names.

competitive inhibitor Compound similar to a substrate that binds to the active site of an enzyme.

complementary shapes Two structures that fit together to form a unit.

complex lipid Lipid that can be hydrolyzed by base.

compounds Pure substances composed of elements joined together by forces called bonds.

concerted reaction A reaction with all bonds broken and formed simultaneously in a single step.

condensation polymer A polymer made by reacting monomers to give a polymer and some small molecule such as water.

condensation reaction Reaction combining two molecules and forming water as a second product.

condensed structural formula A simplified structural formula in which some of the bonds are not shown but implied.

configuration The spatial arrangement of atoms.

configurational isomers Isomers with atoms bonded in the same order but with different orientations in space.

conformational analysis The description of the conformations of a molecule and their associated energy.

conformations Structures of a compound that result from the rotation about single bonds.

conformers Different spatial arrangements of atoms in space as a result of rotation about single bonds.

conjugate acid The acid formed when a base gains a proton.

conjugate addition Another term for 1,4-addition reaction.

conjugate base The base formed when an acid loses a proton.

conjugated double bonds A series of double bonds separated by one single bond.

connectivity Order of connection of atoms in a molecule.

conrotatory Description of rotation of bonded atoms in the same sense in a stereochemical pathway.

constitutional isomers Isomers that differ in the bonding sequence or order of atoms; also called structural isomers.

constructive overlap The overlap of lobes of orbitals having the same sign.

coordinate covalent bond The bond between two atoms formed by the contribution of a pair of electrons from just one of the atoms.

corticosteroids Steroids produced by the adrenal cortex; include glucocorticoids and minerallocorticoids.

coupled reactions Reactions that occur together. One is energy releasing, and the other is energy consuming.

coupling constant The distance between adjacent components of a multiplet given in Hertz.

covalent bond A bond formed by the sharing of a pair of electrons between two atoms.

covalent compound Compound of discrete molecules joined by covalent bonds.

cumulated diene Diene with a C=C=C unit.

curved arrow formalism A method of keeping track of electrons in a description of a reaction mechanism.

cyano group The —C≡N functional group of a nitrile.

cyanohydrin The addition product of HCN and a carbonyl compound having a cyano group and a hydroxyl group on the same carbon atom.

cyclic compound A structure containing a ring of atoms.

cycloaddition The addition of two alkenes or polyenes to give a cyclic product having two fewer multiple bonds.

cycloalkane A hydrocarbon that contains a ring of carbon atoms bonded by single covalent bonds.

cyclohexadienyl cation Intermediate formed in electrophilic aromatic substitution.

D isomer Compound with a configuration related to D-glyceraldehyde.

deactivating group A substituent on an aromatic ring that decreases the reactivity of the ring toward electrophilic reagents.

deamination The loss of an amino group from a molecule such as an amino acid.

Debye unit Unit used to express dipole moments.

decarboxylation The loss of carbon dioxide from a carboxyl group as in carboxylic acid.

decoupling An experimental method to eliminate the coupling between nuclei.

degenerate orbitals Orbitals that have identical energy.

degree of substitution A count of the number of alkyl groups bonded to an atom such as carbon.

degree of unsaturation A measure of the degree of reduction of hydrogen atoms in a molecule due to rings or multiple bonds.

dehalogenation The elimination of a halogen molecule from a compound, usually from adjacent carbon atoms.

dehydration The removal of H and OH from adjacent atoms in a molecule, usually in an acid-catalyzed reaction.

dehydrogenation The elimination of a hydrogen molecule from a compound, usually from adjacent carbon atoms.

dehydrogenation reaction Reaction in which the reactant loses hydrogen.

dehydrohalogenation The elimination of hydrogen and halogen atoms, usually from adjacent carbon atoms.

delocalized Bonding electrons associated with more than two atoms.

delocalized orbital A molecular orbital resulting from combination of atomic orbitals to encompass more than two atoms.

demercuration The removal of mercury or mercury-containing groups from a molecule such as the product of an oxymercuration reaction.

denaturation The loss or destruction of the native conformation of a protein.

deoxyribonucleic acid (DNA) A polynucleotide containing deoxyribose, phosphate, and a mixture of adenine, thymine, guanine, and cytosine.

deoxyribose Aldopentose in which the —OH group attached to the C-2 atom of ribose is replaced by hydrogen.

deoxy sugar A carbohydrate with a hydrogen atom replacing a hydroxyl group.

deshielded Effect on a molecule causing the spectrum to shift to lower field.

destructive overlap The overlap of lobes of orbitals of opposite signs.

detergent Synthetic compound with polar and nonpolar groups that can form micelles.

dextrorotatory Capable of rotating the plane of polarized light in a clockwise direction.

diastereomers Stereoisomers that are not mirror images of each other. *See also* enantiomers.

diastereotopic atoms Nuclei that, when replaced, would give diastereomeric materials.

1,3-diaxial repulsion The steric hindrance between two axial hydrogen atoms or other groups of atoms located in a 1,3 relationship in a cyclohexane compound.

diazo coupling The reaction of an aryldiazonium ion with an aromatic compound in an electrophilic substitution reaction.

diazonium ion The $R—N_2^+$ ion formed in reaction of a primary amine with nitrous acid.

dicarboxylic acid Compound with two carboxylic acid groups such as succinic acid.

Dieckman reaction An intramolecular Claisen condensation.

dielectric constant A measure of the ability of a substance to separate oppositely charged ions.

Diels–Alder reaction The cycloaddition reaction of a diene and an alkene to give a six-membered ring.

diene An unsaturated compound with two carbon–carbon double bonds.

dienophile A reactant containing a double bond that reacts with a diene in the Diels–Alder reaction.

dihedral angle The angle between two groups in a Newman projection formula.

dimer A compound formed from two smaller compounds called monomers.

dipeptide Two amino acids combined by a peptide (amide) linkage.

dipole A pair of opposite charges of equal magnitude at a distance from each other.

dipole–dipole attractive forces Intermolecular attractive forces between the partial positive and partial negative sites of polar molecules.

dipole moment Product of the two opposite charges located at sites within a structure and the distance separating them.

disaccharide A sugar (carbohydrate) formed by two monosaccharides joined by an acetal or ketal bond.

displacement reaction Reaction in which an atom or group of atoms replaces an atom or group of atoms in a reactant.

disrotatory Description of the rotation of bonded groups of atoms in the opposite sense in a stereochemical pathway.

disulfide A group represented by R—S—S—R.

double bond The bond formed by the sharing of two pairs of electrons between two atoms.

E1 reaction A multistep elimination reaction in which the leaving group departs in the slow ionization step.

E2 reaction A bimolecular concerted elimination reaction that usually occurs via a coplanar transition state.

eclipsed conformation A conformation with a 0° dihedral angle between two groups in a Newman projection formula.

elastomer A polymer that has elasticity.

electrocyclic reaction A pericyclic reaction that forms a σ bond between ends of a π system.

electron A subatomic particle with a mass of 9.109×10^{-28} g and a charge of -1.06×10^{-19} coulomb (represented by a relative charge of -1).

electron configuration A description of the arrangement of the electrons in the atom by shells, subshells, and orbitals.

electron density The probability of finding electrons in a region of space.

electron-dot structure Structures using dashes for covalent bonds and pairs of dots for lone pair electrons.

electron-dot symbol A symbol giving the number of valence electrons as dots located around the elemental symbol.

electronegativity Number that indicates the electron-attracting tendency of an atom.

electron shell A name for principal enery levels designated by integers 1 to n.

electron spin A property of the electron; may be either clockwise or counterclockwise.

electrophile An electron pair acceptor in a chemical reaction.

electrophilic addition Mechanism of addition reaction of an electrophile to a site containing a multiple bond.

electrophilic aromatic substitution Substitution reaction of a hydrogen atom on an aromatic ring by an electrophilic intermediate usually generated using a Lewis acid.

electrophilicity The reactivity of an electrophile.

element Pure substance that cannot be decomposed into any simpler substance(s) by ordinary chemical reactions.

elimination The loss of two atoms or groups of atoms, usually from adjacent atoms and giving a π bond.

elimination–addition mechanism Two-stage mechanism of a nucleophilic aromatic substitution reaction.

enantiomeric excess The excess of one enantiomer over another in a mixture.

enantiomers Stereoisomers that are mirror images of each other. *See also* diastereomers.

enantiotopic Property of two atoms in a molecule whose environment allows formation of enantiomers by replacement of either atom.

endergonic Energy-absorbing process yielding products of higher free energy than reactants; $\Delta G^\circ > 0$.

endothermic reaction A process requiring heat energy from the surroundings.

enediol rearrangement A base-catalyzed rearrangement interconverting α-hydroxy carbonyl compound and interchanging the hydroxyl and carbonyl functional groups.

energy of activation The minimum energy required in a molecular collision to initiate a reaction between reactants.

enol An alcohol with the —OH group bonded to one of two double-bonded carbon atoms.

enolate ion The resonance-stabilized conjugate base formed by deprotonation of the α carbon atom.

enolizable hydrogen The acidic hydrogen atom at the α carbon atom that is lost or gained in keto–enol tautomerization.

enthalpy A quantity symbolized by H°; ΔH° is the energy difference between two states or substances.

entropy A quantity symbolized by S°; ΔS° is a measure of the change in the degree of disorder in a system.

envelope conformation One of the conformations of cyclopentane.

enzyme A biochemical catalyst that is predominantly protein.

epimers Diastereomers that differ in configuration at one chiral center.

epoxidation A reaction, using an oxidizing agent, that forms a three-membered ring containing an oxygen atom.

epoxide A three-membered ring containing one oxygen atom.

equatorial position A bond that is directed out from the average plane of the cyclohexane ring.

equilibrium A state in which opposing processes are in balance.

equilibrium constant A numerical quantity reflecting the relationship between the concentrations of reactants and products at equilibrium.

essential fatty acids Unsaturated fatty acids that cannot be synthesized by the body and must be obtained in the diet.

ester A compound containing an —OR or —OAr group bonded to a carbonyl group in place of the —OH group of a carboxylic acid.

esterase A hydrolase that catalyzes the hydrolysis of esters.

esterification Ester formation as in the reaction of an alcohol and a carboxylic acid.

estrogens Female sex hormones; examples are estrone and estradiol.

ether Compound with C—O—C structural unit.

exergonic reaction An energy-releasing reaction that yields products of lower free energy than the reactants.

exhaustive methylation Reaction of an amine with a methyl halide to form a quaternary ammonium ion.

exothermic reaction A process that releases heat energy to the surroundings.

***E,Z* notation** A system to assign double bond configuration based on priority of substituents.

fats Esters of glycerol and long-chain saturated carboxylic acids.

fat-soluble vitamins Nonpolar vitamins such as vitamins A, D, and E.

fatty acid A long-chain carboxylic acid containing an even number of carbon atoms.

fatty acid biosynthesis A series of reactions occurring in the cytoplasm of the cell that convert two-carbon-atom acetyl units into fatty acids.

Fehling's solution An alkaline solution of cupric ion as a complex ion used as a test reagent for aldehydes.

Fischer esterification The formation of an ester from a carboxylic acid and an alcohol in the presence of an acid catalyst.

Fischer projection A method of representing chiral molecules in two dimensions with a carbon chain arranged along a line and substituent bonds directed perpendicular to the axis.

flavin adenine dinucleotide (FAD) Reducing agent that accepts two hydrogen atoms in biochemical reactions.

formal charge A charge calculated for an atom in a molecule as represented by a particular Lewis structure.

free energy change A quantity symbolized by ΔG° that measures the spontaneity of a chemical reaction.

free radical Reactive species containing one unpaired electron.

frequency The number of wave cycles of light per second.

Friedel–Crafts acylation Formation of an acyl aromatic compound using an acyl derivative and a Lewis acid as with an acyl chloride and aluminum trichloride.

Friedel–Crafts alkylation Formation of an alkyl aromatic compound using an alkyl derivative and a Lewis acid as with an alkyl halide and an aluminum trihalide.

frontier molecular orbital The highest occupied molecular orbital used to describe pericyclic reactions.

fructose Ketohexose found in fruits.

functional group An atom or group of atoms in a molecule.

furan A five-membered ring containing one oxygen atom and two carbon–carbon double bonds.

fused-ring compound A compound in which two (or more) rings are joined through two (or more) adjacent carbon atoms.

Gabriel synthesis The steps forming a primary amine by alkylation of a phthalimide ion followed by hydrolysis.

galactose An aldohexose that is a component of lactose.

galactosemia A genetic disease that prevents the affected individual from converting galactose into glucose.

ganglioside A glycosphingolipid containing a higher saccharide as the sugar unit.

gauche conformation A conformation with a 60° dihedral angle in the Newman projection formula.

geometric isomers Isomers that have the same sequence of atoms, but different orientations in space. *See also* cis isomer; trans isomer.

geminal Location of two atoms on the same carbon atom.

geminal dihalide A dihalide with both halogen atoms bonded to the same carbon atom.

geminal diol The hydrate of an aldehyde or ketone.

glucocorticosteroids Steroids produced by the adrenal cortex and involved in the control of glucose levels in the body.

glucose Aldohexose that is a component of starch, cellulose, lactose, and sucrose.

glucoside A glycoside of glucose.

glycogen A storage form of glucose in animals.

glycol A diol that has hydroxyl groups on adjacent carbon atoms.

glycolipid A covalent molecule containing both a sugar and a lipid unit.

glycolysis The conversion of glucose into pyruvic acid.

glycoside An acetal or ketal of a carbohydrate.

glycosidic linkage Acetal or ketal formed between the anomeric carbon atom and a hydroxyl group of a second monosaccharide.

glycosphingolipid A substance consisting of sphingosine, fatty acids, and a carbohydrate.

Grignard reagent A compound containing a bond to a —MgX group where X is chlorine, bromine, or iodine.

haloform reaction Conversion of a methyl group of a methyl ketone into CHX_3 and forming a carboxylate salt by reaction with halogen under basic conditions.

halogenation The reaction of an alkane with a halogen to replace one or more hydrogen atoms by halogen atoms.

halogens The elements of Group VIIA.

halohydrin An alcohol with a halogen located on the adjacent carbon atom.

halonium ion A positively charged, three-membered ring containing a halogen atom.

Hammond postulate Reactive species represented on a reaction coordinate diagram that are similar in energy are similar in structure. The transition state structure may resemble the structure of either reactant or product, whichever it is closer to in energy.

heat of combustion The heat released by one mole of a compound when burned to form carbon dioxide and water.

heat of hydrogenation The energy difference between related unsaturated and saturated compounds as determined by a hydrogenation reaction.

heat of reaction The energy difference between the products and the reactants.

Hell–Volhard–Zelinsky reaction Reaction of a carboxylic acid with bromine and PBr_3 to give an α-bromo acyl bromide.

hemiacetal A compound formed by the reaction of 1 mole each of an aldehyde and an alcohol and having one hydroxyl and one alkoxy group on the former carbonyl carbon atom.

hemiketal A compound formed by the reaction of 1 mole each of a ketone and an alcohol.

heteroatom Any atom in a molecule other than carbon or hydrogen; usually nitrogen, oxygen, or sulfur.

heterocyclic compound A compound having one or more atoms other than carbon in a ring.

heterogeneous catalysis A reaction with the catalyst in a separate phase from the substrate.

heterolytic cleavage Breaking a bond so that each atom retains one of the two bonding electrons.

Hofmann elimination Elimination reaction of a quaternary ammonium ion to give the less substituted alkene.

Hofmann product The less substituted alkene product of an elimination reaction.

Hofmann rearrangement Reaction converting an amide into a primary amine with the loss of one carbon atom.

HOMO The highest occupied molecular orbital of a conjugated system.

homogeneous catalysis A reaction with the catalyst in the same phase as the reactants.

homologous series A series of compounds that differ from adjacent members by a repeating unit.

homologs Compounds that differ only by one or more $—CH_2—$ units.

homolytic cleavage Bond cleavage giving species each retaining one electron.

hormones Chemical messengers that are produced by endocrine glands. Some hormones are proteins.

Hückel's rule A cyclic compound is aromatic if it has a continuous series of overlapping atomic orbitals containing $4n + 2\ \pi$ electrons.

Hund's rule Electrons tend to avoid the same orbital so that electrons of equal energy locate singly in different orbitals before pairing occurs.

Hunsdiecker reaction Decarboxylation reaction replacing the carboxyl group with a halogen atom.

hybridization Combination of two or more atomic orbitals to form orbitals for bonding.

hybrid orbitals The result of mixing of two or more orbitals such as *s* and *p* to form directional orbitals suitable for bonding.

hydrate A geminal diol formed by addition of water to a carbonyl group.

hydration Addition of water to a molecule.

hydrazone Compound formed by the addition–elimination reaction of a carbonyl group with a hydrazine derivative.

hydride reagents A compound with hydrogen with a formal negative charge such as $NaBH_4$ or $LiAlH_4$ used as reducing agents. Also simple hydrides such as NaH used as bases.

hydride shift The movement of a hydrogen atom with its bonding pair of electrons from one atom to another—usually adjacent to one another.

hydroboration An addition reaction of a compound containing a boron–hydrogen bond to an unsaturated compound.

hydrocarbon A compound containing only carbon and hydrogen.

hydrogenation Reaction converting a multiple bond into a single bond by reaction with hydrogen.

hydrogen bond An intermolecular attraction between an electropositive hydrogen atom and a nonbonded electron pair of an electronegative atom of a neighboring molecule.

hydrolysis Heterolytic cleavage of a bond with water.

hydronium ion The principal form in which protons are found in aqueous solution, the ion H_3O^+.

hydrophilic Water-attracting. A term used to describe the surface of lipid bilayers and micelles.

hydrophobic Water-repelling. A term used to describe the interactions in the interior of lipid bilayers and micelles.

hydrophobic bonding A term describing the London forces between nonpolar hydrocarbon chains.

hydroxylation An addition reaction placing hydroxyl groups on adjacent carbon atoms of an unsaturated compound.

hydroxyl group A group represented by —OH.

imine A compound with a carbon–nitrogen double bond.

induced dipole A separation of charge within a molecule caused by a temporary dipole in the vicinity.

inductive effect Either electron donation or withdrawal from a site through sigma bonds.

inhibitors Compounds that destroy or deactivate enzymes.

initiation step First step in a free radical mechanism.

integral proteins Proteins that extend from the surface into the interior of a membrane.

integration The measurement of a peak's area, which is proportional to the number of atoms giving rise to the signal.

intermediate A species formed from a reactant in a chemical reaction that exists for a short time before reacting further.

intermolecular forces Forces of attraction between separate molecules.

inversion of configuration The formation of a product with opposite configuration from the reactant.

ion An electrically charged atom or molecular particle in which the number of electrons is not equal to the number of protons.

ionic bond The bond resulting from the transfer of electrons from a metal to a nonmetal.

ionic compound A neutral collection of oppositely charged ions.

irreversible reaction A reaction that does not proceed appreciably in the reverse direction.

isoionic point The pH at which there is no net charge on an amino acid or protein.

isolated diene Diene in which two double bonds are separated by at least one sp^3-hybridized carbon atom.

isomerism The existence of two different compounds with the same molecular formula.

isomers Substances having the same molecular formula but different structures.

isotope effect The change in the rate of a chemical reaction resulting from isotopic substitution as in the case of deuterium for hydrogen.

IUPAC Acronym for the International Union of Pure and Applied Chemistry.

IUPAC rules Set of rules for naming compounds.

Jones oxidation The oxidation of alcohols using chromic acid in acetone as solvent.

Kekulé structure A structure with alternating single and double bonds used to represent aromatic compounds.

ketal A compound formed from the reaction of 1 mole of a ketone and 2 moles of an alcohol, $R_2C(OR)_2$.

ketone A carbonyl compound whose carbonyl carbon atom is bonded to two alkyl or aryl groups or an alkyl group and an aryl group.

ketose A carbohydrate with a ketone functional group.

kinetically controlled reaction The products are controlled by the relative rates of two competing reactions.

kinetics The study of the rates of chemical reactions.

Knoevenagel reaction Condensation of a β-dicarbonyl compound with an aldehyde or ketone.

Kolbe reaction Conversion of a phenolate into an ortho-hydroxy aromatic carboxylic acid using a high pressure of carbon dioxide.

lactam A cyclic amide

lactase A hydrolase that catalyzes the hydrolysis of lactose.

lactone A cyclic ester.

lactose Disaccharide containing galactose and glucose.

leaving group The charged or uncharged atom or group of atoms that departs in a substitution or elimination reaction.

Le Châtelier's principle If a stress is applied to a system at equilibrium, the system will adjust to reduce the stress.

lecithin A phosphatidylcholine.

levorotatory Capable of rotating the plane of polarized light in a counterclockwise direction.

Lewis octet rule A rule referring to the eight electrons in the valence shell of an atom or ion in a compound.

Lewis structure Chemical formula showing valence electrons as dashes for bonds and dots for lone pair (nonbonding) electrons.

Lindlar's catalyst A heterogeneous catalyst containing palladium that forms cis alkenes from alkynes in a hydrogenation reaction.

linear combination of atomic orbitals (LCAO) The addition of wave functions of orbitals of two or more atoms to give wave functions of more complex molecular orbitals.

linear molecule A molecule in which all the atoms are arranged along a common axis.

lipid bilayer Two layers of lipid molecules arranged to form a membrane.

lipids A class of biomolecules that includes fats.

lock-and-key theory A model that pictures an enzyme as conformationally rigid.

London attractive forces Intermolecular forces from the attraction of temporary dipoles in adjacent molecules.

London forces Intermolecular forces involving temporary and induced dipoles.

lone pair electrons Valence-shell electrons associated with an atom but not involved in bonding.

LUMO The lowest unoccupied molecular orbital.

malonic ester synthesis Formation of substituted acetic acids by alkylation of malonate esters followed by hydrolysis and decarboxylation.

maltose A disaccharide containing two units of glucose.

Markovnikov's rule Rule predicting the product of addition to a double bond.

mass number A number equal to the sum of the number of protons and neutrons in the nucleus of the atom.

MCPBA An abbreviation for meta-chloroperoxybenzoic acid, a reagent used in epoxidation reactions.

mechanism A description of the pathway by which bonds break and form in a chemical reaction.

mercaptan A compound containing the sulfhydryl group, —SH.

meso compound A compound with chiral centers that is symmetrical and is not optically active.

meta Prefix specifying the 1,3 relation of substituents on a benzene ring.

metabolites Intermediate and final compounds in metabolism.

meta director A deactivating substituent on an aromatic ring that deactivates the ortho and para positions and thus favors attack of electrophiles at the meta position.

methide shift Movement of a methyl group and its bonding electron pair from one atom to another, usually an adjacent atom.

methine The C—H unit resulting when three of the other bonds are to carbon atoms.

methylene group The $—CH_2—$ unit resulting when carbon is bonded to two other atoms.

methyl group The $—CH_3$ unit.

micelle An aggregate of molecules or ions assembled so that hydrophobic portions are in the interior and hydrophilic portions are on the surface.

Michael addition The conjugate addition (1,4) of a nucleophile to an α,β-unsaturated carbonyl compound.

microscopic reversibility The principle connecting forward and reverse reactions with common intermediates and transition states.

miscible Term describing liquids that can dissolve in each other in all proportions.

molecular dipole moment A measure of the polarity of a molecule that derives from the vector sum of the bond dipole moments.

molecular formula A representation of a molecule indicating the number and type of each atom present in the molecule.

molecular orbital A region of space about two or more atoms where pairs of electrons are shared.

molecule A combination of atoms in discrete units.

monomer Small molecule that combines with similar small molecules to give a polymer.

monoprotic acid An acid that can transfer only one proton.

monosaccharide A simple carbohydrate that cannot be further hydrolyzed.

multiple bond Bond with more than one pair of electrons shared.

multiplet The number of peaks when an NMR absorption is split.

mutarotation The change in optical rotation due to equilibrium between anomeric forms.

NAD^+ (nicotinamide adenine dinucleotide) An oxidized coenzyme used in catabolic reactions.

NADPH (nicotinamide adenine dinucleotide phosphate) A reduced coenzyme used in biosynthesis.

neutral amino acid An amino acid containing only one amino group and one carboxyl group.

Newman projection formula A representation of a molecule looking along the axis between two carbon atoms.

nicotinamide adenine dinucleotide A biological reducing agent represented as NAD.

nitration Replacement of a hydrogen ion of an aromatic molecule by a nitro ($—NO_2$) group.

nitrile A functional group described by $—C{\equiv}N$.

nitronium ion The intermediate (NO_2^+) involved in aromatic nitration.

***N*-nitrosoamine** A compound with an $N—N{=}O$ group formed by reaction of secondary amines with nitrous acid.

nodal plane A planar region of space with zero electron density.

node A region in an orbital with zero electron density.

nonbonding electrons Valence-shell electrons associated with an atom but not involved in bonding.

nonbonding molecular orbital Molecular orbitals that have the same energy as the isolated atomic orbitals.

nonpolar bond Covalent bond in which electrons are shared equally.

nonpolar molecule Molecule in which any polarity of bonds cancels out.

nonspontaneous reaction A reaction requiring continuous addition of energy to occur.

normal hydrocarbon A hydrocarbon molecule without branches.

nuclear magnetic resonance A spectroscopic method that measures the absorption of energy by nuclei in the presence of a magnetic field.

nucleophile An atom or groups of atoms that is an electron pair donor in a chemical reaction.

nucleophilic acyl substitution Substitution reaction at the carbonyl carbon atom replacing a leaving group by a nucleophile.

nucleophilic addition Addition reaction initiated by the attack of a nucleophile at an electrophilic center such as the carbonyl carbon atom.

nucleophilic aromatic substitution Replacement of a negatively charged leaving group such as a halide ion on an aromatic ring by a nucleophile.

nucleophilicity Measure of the reactivity of a nucleophile in a substitution reaction.

nucleophilic substitution The replacement of a leaving group by a nucleophile resulting in a substituted product.

nylon A polyamide made from a diamine and a dicarboxylic acid.

octane number A rating scale of the burning efficiency of hydrocarbons.

octet rule Rule stating that atoms tend to have eight outer-shell electrons about them in compounds.

oil A triglyceride containing a high percentage of unsaturated fatty acids.

olefin An older name for an alkene.

open chain sugar Noncyclic form of a monosaccharide.

optical activity The ability of a substance to rotate plane-polarized light.

optical isomers Compounds that are nonsuperimposable mirror images of each other.

optical purity The specific rotation expressed as a fraction of the specific rotation of a single enantiomer.

optical rotation The amount and direction of rotation of plane-polarized light caused by a chiral compound.

orbital A region in space about the nucleus of an atom or about atoms of a molecule where no more than two electrons may be found.

orbital overlap The interpenetration of one atomic orbital by another to form a molecular orbital.

organolithium reagent An organic compound with a polar covalent or ionic bond to lithium.

ortho Prefix specifying the 1,2 relationship of substituents on a benzene ring.

ortho,para director A substituent on an aromatic ring that activates the ortho and para positions toward attack by an electrophile.

oxetane A four-membered heterocyclic compound containing one oxygen atom.

oxidation Loss of electrons. Often described as loss of hydrogen or gain of oxygen in an organic molecule.

oxidation number A positive or negative integer assigned to describe an element as a free atom, an ion, or as part of a polyatomic ion or molecule.

oxidation–reduction reaction A reaction in which the oxidation numbers of two or more atoms are changed. Also referred to as redox reaction.

oxidative cleavage The cleavage of a carbon–carbon multiple bond in an oxidation reaction.

oxidizing agent The substance that gains electrons and is reduced in a redox reaction.

oxime A compound with a C=N—OH group formed by reaction of a carbonyl compound with hydroxylamine.

oxonium ion Trivalent oxygen species with a positive charge on the oxygen atom.

oxymercuration An addition reaction of a mercuric salt to an alkene along with a nucleophile derived from either the salt or solvent.

ozonolysis The reaction of ozone with an unsaturated compound such as an alkene or alkyne.

P_i A representation of inorganic phosphate ions in biochemical reactions.

paired electrons Two electrons of opposite spin in the same orbital.

para Prefix specifying the 1,4 relationship of substituents on a benzene ring.

pepsin An enzyme that cleaves peptides at the nitrogen end of the aromatic amino acid groups.

peptidase A hydrolase that catalyzes the hydrolysis of peptide bonds.

peptide bond The amide bond in a polypeptide or protein.

pericyclic reaction Reactions that occur with the concerted reorganization of bonds via electrons through a cyclic transition state.

period A horizontal row in the periodic table.

periodic table An arrangement of elements, with elements of similar properties grouped together.

peripheral proteins Proteins attached by ionic forces to the surface of a bilayer.

peroxyacid A carboxylic acid with an O—O—H group in place of an O—H group.

perspective formulas Structural formulas written in two dimensions that impart some three-dimensional aspects to the representation.

phenol A compound that has the hydroxyl group bonded to a carbon atom of an aromatic ring.

phenyl Substituent derived by removal of a hydrogen atom from benzene and abbreviated as C_6H_5—.

phosphoglycerides Molecules consisting of one unit each of glycerol, phosphate, and alcohol and two units of fatty acids.

photochemical reaction Chemical reaction that occurs via an excited state intermediate formed by absorption of light energy.

pi (π) bond A bond formed by the side by side overlap of two *p* orbitals.

pinacol rearrangement The loss of water from a vicinal diol to give a ketone and resulting in migration of a carbon group to an adjacent atom.

pK_a A measure of the acidity of an acid, equal to $-\log K_a$.

pK_b A measure of the basicity of a base, equal to $-\log K_b$.

plane of symmetry A plane that bisects a molecule into two mirror images.

plane-polarized light Light consisting of waves vibrating in a single plane.

polar covalent bond A bond formed by sharing electrons between two atoms of unequal electronegativity.

polarimeter An instrument used to measure the optical activity of molecules.

polarizability The ease with which an electron cloud can be distorted by nearby charges.

polarizable electrons Electrons in bonds that can be displaced toward a positive site.

polar molecule Molecule in which the bond polarities do not cancel.

polyamide A polymer of units joined by amide bonds.

polycyclic hydrocarbon Hydrocarbon with at least two carbon atoms shared in common with two or more rings.

polymer Large molecule made up of repeating units called monomers.

polymerization Process forming a polymer from monomers.

polynuclear aromatic compound Two or more fused aromatic rings as in naphthalene.

polypeptides Molecules consisting of α-amino acids linked by peptide (amide) bonds.

polysaccharides Polymers consisting of many monosaccharides linked by glycosidic bonds.

primary alcohol A carbon compound with a hydroxyl group bonded to a primary carbon atom.

primary amine An amine with a single hydrocarbon group in place of one hydrogen atom of ammonia.

primary carbon atom A carbon atom that is directly bonded to only one other carbon atom.

primary structure The sequence of amino acids in a polypeptide or protein.

products The substances produced in a chemical reaction.

progesterone A female sex hormone responsible for maintaining pregnancy.

propagation steps Repeating consecutive steps in a free radical reaction.

prostaglandins Biological derivatives of arachidonic acid that occur in low concentrations in body tissue and have a wide range of physiological activities.

protecting group A temporarily formed group that transforms a functional group into a less reactive functional group so that reactions can transform other unprotected functional groups.

protein A polymer of amino acids joined by peptide bonds.

protic solvent A solvent with easily exchangeable protons.

pyran A six-membered ring containing one oxygen atom and two carbon–carbon double bonds.

pyranose Cyclic form of a sugar containing six atoms in the ring.

pyridinium chlorochromate An oxidizing agent, represented as PCC that is made from CrO_3, pyridine, and HCl.

pyrimidine bases Cytosine, thymine, and uracil; components of nucleic acids.

quaternary ammonium ion An ammonium ion having four hydrocarbon groups bonded to nitrogen and bearing a positive charge.

quaternary carbon atom Carbon bonded to four other carbon atoms.

quaternary structure The manner in which protein subunits (chains) are assembled to give the whole protein.

racemic mixture An equimolar mixture of enantiomers.

racemization A process in which a chiral substance is converted into a racemic mixture of products.

radical A species with an unpaired electron.

Raney nickel A finely divided form of nickel used as a hydrogenation catalyst.

rate-determining step The slowest step in a sequence of reactions. This step has the highest activation energy.

rate equation A mathematical relationship giving the order of the reactants in a rate law.

reactants The substances that enter into a chemical reaction.

reaction coordinate diagram A plot of potential energy on the vertical axis that corresponds to the energy associated with molecular changes that occur in a chemical reaction.

reaction mechanism Description of the sequence of steps of bond formation and cleavage in a chemical reaction.

reagent A compound or mixture of compounds used to carry out a chemical test.

rearrangement reaction Intramolecular migration of an atom or group of atoms from one site to another.

reducing agent A substance that loses electrons and is oxidized in a redox reaction.

reducing sugar A carbohydrate that causes the reduction of Benedict's solution (or Tollens's reagent).

reductase An enzyme that catalyzes a reduction reaction.

reduction The gain of electrons by a substance.

reductive amination Synthesis of an amine by reduction of an imine formed by reaction of a carbonyl compound with an amine.

Reformatskii reaction Reaction of an aldehyde or ketone with an α-halo ester using zinc.

regioselective reaction A reaction that gives predominately one of several possible compounds with a specific orientation of substituted or added groups.

regiospecific reaction A reaction that gives a single compound with a specific orientation of substituted or added groups.

resolution The separation of a racemic mixture into its enantiomeric constituents.

resonance energy The calculated stabilization energy resulting from the delocalization of electrons relative to a reference localized structure.

resonance structure Two or more plausible Lewis structures used when no single structure can accurately represent the molecule.

retention of configuration Formation of a product with the same configuration as the reactant.

retrosynthetic analysis A reverse thought process starting from products and going to reactants to develop a synthesis.

reversible reaction Reaction that proceeds in both forward and reverse directions.

ribose A pentose present in ribonucleic acids.

ring strain The strain associated with a ring compound that is composed of both angle strain and torsional strain.

Rosenmund reduction The reduction of an acid halide to an aldehyde using a deactivated transition metal catalyst.

Sandmeyer reaction Replacement of a diazonium ion of an aryl compound by a nucleophile by means of a cuprous salt.

saponification The hydrolysis of an ester bond by a strong base.

saturated fat Fat consisting mainly of saturated fatty acids.

saturated hydrocarbon A hydrocarbon that has only carbon–carbon single bonds.

Saytzeff elimination An elimination reaction that gives the more highly substituted alkene.

***s* character** The fraction or percent that the *s* orbital contributes to a hybridized orbital.

***s-cis* conformation** A conformation about a single bond in a conjugated system that resembles the cis orientation of geometric isomers.

secondary alcohol A hydrocarbon compound with a hydroxyl group bonded to a secondary carbon atom.

secondary amine An amine with two hydrocarbon groups in place of two hydrogen atoms of ammonia.

secondary carbon atom A carbon atom bonded to two other carbon atoms.

secondary structure The spatial arrangement of amino acid residues that are close to each other in the polypeptide chain.

semicarbazone A compound formed by the addition–elimination reaction of a carbonyl compound and semicarbazide.

sequence rule Procedures to rank substituents in Cahn–Ingold–Prelog system.

sex hormones Steroids produced predominantly by the gonads (ovaries in females and testes in males).

shell A description of the electrons in a space about the nucleus. The shells are designated by integers.

shielded The result that atoms have on a nucleus causing the absorption to occur at a higher field.

side chain A group of atoms appended to a main chain as in hydrocarbons or peptides.

sigma bond A cylindrically symmetrical bond with its electron density oriented along the internuclear axis.

sigmatropic rearrangement Migration of a σ bond from one end of a conjugated system to the other end.

Simmons–Smith reaction The formation of a cyclopropane compound from an alkene using a carbenoid species containing zinc.

simple lipids Lipids that cannot be hydrolyzed by a base.

single bond A shared pair of electrons between atoms.

skew conformation Any conformation that does not have groups at either 0° or 60° dihedral angles.

soap Salt of long-chain carboxylic acids.

space-filling models Models representing relative volumes of atoms in a molecule.

specificity The selectivity of enzymes for the individual substrates and reactions that they catalyze.

specific rotation A standard method of compiling the optical activity of chiral substance.

sphingophospholipids Lipids that consist of one unit each of sphingosine, an amide of a fatty acid, phosphate, and choline.

***sp* hybrid orbital** One of two orbitals produced by mixing one *s* and one *p* orbital.

***sp*² hybrid orbital** One of three orbitals produced by mixing one *s* and two *p* orbitals.

***sp*³ hybrid orbital** One of four orbitals produced by mixing one *s* and three *p* orbitals.

spin decoupling An experimental technique removing the effect of spin-spin splitting on the NMR spectrum.

spin-spin splitting The interaction of the spins of two or more nuclei usually connected by a small number of bonds.

spirocyclic compound A bicyclic compound that shares only one common atom between two rings.

spontaneous reaction Reaction that occurs without an outside source of energy.

staggered conformation Any conformation with 60° dihedral angles.

starch A polymer of glucose containing α linkages between glucose units.

stereochemistry The description of the three-dimensional arrangement of atoms in molecules.

stereogenic center An atom with four nonequivalent atoms or groups of atoms bonded to it.

stereoisomers Isomers with the same structure but different configurations.

stereoselective reaction A reaction in which stereoisomeric reactants give a predominance of stereoisomeric products.

stereospecific reaction A reaction in which stereoisomeric reactants give stereoisomeric products.

steric hindrance Interactions that result when two groups are close enough so that their electrons repel each other as given by the van der Waals radius.

steric strain Van der Waals strain.

steroids Lipids containing a characteristic system of four fused rings of carbon atoms.

straight chain A sequence of carbon atoms bonded to each other without intervening atoms or side chains.

***s-trans* conformation** A conformation about a single bond in a conjugated system that resembles the trans orientation of geometric isomers.

structural formula Formula representing the spatial arrangement of atoms and bonds using lines to represent bonds.

structural isomers Isomers that differ in the bonding sequence of their atoms; also called constitutional isomers.

structure The arrangement of the components of a substance.

subshell A part of a shell characterized by a shape according to type. The subshells are labeled *s*, *p*, *d*, and *f*.

substituent An atom or group of atoms attached to a skeleton of carbon atoms.

substitution reaction Reaction in which one atom or group of atoms replaces another atom or group of atoms in a molecule.

substrate A reactant in an enzyme-catalyzed reaction.

sucrose A disaccaride containing glucose and fructose.

sulfa drug Antibacterial drug derived from sulfanilamide.

sulfhydryl group A group represented by —SH.

sulfide Compound with C—S—C structural unit.

sulfonation Replacement of a hydrogen atom of an aromatic ring by a sulfonic acid group ($-SO_3H$)

superimposition The simultaneous blending of all atoms in a model with atoms in another model to show identity.

symmetry-allowed Concerted reactions that can occur because the process involves the appropriate overlap of orbitals of like sign.

symmetry-forbidden Reactions that cannot occur by a concerted process because the symmetry of the interacting orbitals would lead to destructive interference.

syn The addition or elimination of groups on the same face of a molecule.

syn coplanar Groups having 0° dihedral angle.

systematic name IUPAC name containing information about the composition of a substance.

tautomerism Isomerism of keto and enol forms by migration of a hydrogen atom from the α-carbon atom to the carbonyl oxygen atom.

tautomers Isomers that differ by the shift of a hydrogen atom from one site to another.

temporary dipole A separation of charge produced momentarily in an otherwise nonpolar substance

terminal alkyne Alkyne of th type R—C≡C—H.

termination The conclusion of synthesis of the protein chain.

terpene A class of compounds that can be dissected into units derived from isoprene.

tertiary alcohol A hydrocarbon compound with a hydroxyl group bonded to a tertiary carbon atom.

tertiary amine An amine with hydrocarbon groups in place of all three hydrogen atoms of ammonia.

tertiary carbon atom A carbon atom bonded to three other carbon atoms.

tertiary structure The spatial arrangement of amino acid residues that are far apart in the polypeptide chain.

testosterone A male sex hormone.

tetrahedral intermediate Intermediate formed by nucleophilic addition to a carbonyl carbon atom.

tetrahedral molecule A molecule that has an atom located in the center of a tetrahedron and four atoms bonded to the central atom located at the corners of the tetrahedron.

thermodynamic control Reactions that give product distributions controlled by their relative stabilities which are the result of an equilibrium process.

thermodynamics The science of the energy changes accompanying physical and chemical changes.

thioesters Esters of thiols and carboxylic acids containing a carbonyl carbon–sulfur single bond.

thiol A compound containing a sulfhydryl group (—S—H) bonded to a carbon atom.

tissue lipids Lipid materials in cell membranes.

Tollens's reagent An alkaline solution of $[Ag(NH_3)_2]^+$ that is used as a test for aldehydes.

torsional energy The energy associated with bonding electrons of two groups on adjacent atoms.

tosylate ester An ester of toluenesulfonic acid and an alcohol; also known as a tosylate.

trans On the opposite sides of either a ring or double bond.

transamination An interconversion process between keto compounds and amino compounds.

trans diaxial An anti coplanar arrangement of atoms at adjacent carbon atoms—usually in cyclohexane compounds.

transesterification Substitution of one alkoxyl group of an ester by another under either acid- or base-catalyzed conditions.

trans isomer An isomer that has two groups of atoms oriented on opposite sides of a structural feature such as a cycloalkane ring.

transition state The state of highest energy between reactants and products shown as a maximum on a reaction coordinate diagram.

transmembrane proteins Proteins that extend across the membrane.

triacylglycerols A newer name for triglycerides.

tricarboxylic acid (TCA) cycle The citric acid cycle.

triglycerides Esters of glycerol and fatty acids.

trigonal planar molecule A molecule with three atoms arranged around a central atom, with all atoms in a common plane and all bond angles at 120°.

trigonal pyramidal molecule A molecule with the central atom bonded to three other atoms so that a three-sided pyramid is formed. The three atoms bonded to the central atom are in a common plane.

triple bond A bond formed by the sharing of three pairs of electrons between two atoms.

triprotic acid An acid that can transfer three protons.

unsaturated hydrocarbon A hydrocarbon that has double and/or triple bonds.

unshared electron pair A pair of valence-shell electrons associated with an atom but not involved in bonding.

urethane An ester of a carbamic acid.

valence The number of bonds normally formed by an atom in a neutral molecule.

valence-shell electron-pair repulsion (VSEPR) theory A theory relating the shape of molecules to the distribution of electron pairs about a central atom.

valence-shell electrons Electrons of the *s* and *p* subshells in the highest occupied energy level.

van der Waals radius A measure of the size of an atom or group of atoms in a molecule.

van der Waals strain Steric strain resulting from close approach of two atoms or groups of atoms bonded at two sites in a molecule.

vicinal Location of two substituents on adjacent carbon atoms.

vicinal dihalide A dihalide with halogen atoms on adjacent carbon atoms.

vinyl group The $CH_2{=}CH{-}$ group; also known as the ethenyl group.

vinyl halide A halogen-containing compound with halogen bonded to the sp^2-hybridized carbon atom.

wave function A mathematical description of an orbital. The square of the wave function gives the electron density.

wavelength The distance between corresponding points on a wave.

wavenumber The number of wavelengths per unit of distance.

wax An ester of a fatty acid and a long-chain alcohol.

Williamson ether synthesis The reaction of an alkoxide ion and a primary alkyl halide or alkyl tosylate.

Wittig reaction Formation of an alkene by reaction of a carbonyl compound with a phosphorus ylide.

Wolff–Kishner reduction Deoxygenation of an aldehyde or ketone converting a carbonyl group to a methylene group using hydrazine and a strong base.

Woodward–Fieser rules A set of rules giving additive structural components that predict the λ_{max} of the ultraviolet absorption of an unsaturated compound.

Woodward–Hoffmann rules A set of rules that determine whether a reaction is symmetry-allowed or symmetry-forbidden.

zwitterion An electrically neutral ion resulting from transfer of a proton from an acidic to a basic site in a molecule.

zymogen An inactive storage form of an enzyme.

Appendix G: Answers to In-Text Problems

The in-text problems are problems that are within each chapter. This appendix gives answers to those problems for which solutions are not provided. The answers and solutions to end-of-chapter exercises are provided in a separate study guide.

Chapter 1

1.1 Six of the sixteen electrons of sulfur, five of fifteen electrons of phosphorus; S $1s^2 2s^2 2p^6 3s^2 3p^4$, P $1s^2 2s^2 2p^6 3s^2 3p^3$

1.2 Sulfur, which is higher in Group VIA.

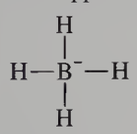
1.4 $1s^2 2s^2 2p^6$; $Mg(OH)_2$, $MgSO_4$

1.5 −1 for permanganate; −2 for dichromate

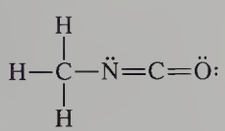
1.7 Three nonpolar covalent C—H bonds to one carbon atom; two nonpolar covalent C—H bonds and a polar covalent C—Cl bond to the other carbon atom.

1.8 The structures are similar except for the oxygen atom bonded to sulfur in dimethyl sulfoxide. It is a coordinate covalent bond with both electrons supplied by sulfur.

1.9



1.11

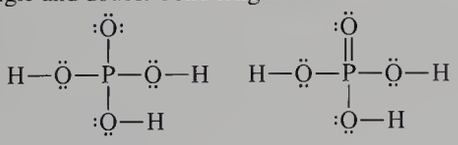


1.12 −1 for oxygen, +1 for sulfur

1.13 0 for carbon, +1 for oxygen; +1 for the ion

1.15 There is an equivalent resonance structure interchanging the N—O and N=O bonds, and the bond length is intermediate between the single and double bond lengths.

1.16



1.18 120° for C—N=C; 180° for N=C=S

1.19 −0.39

1.20 sp^3–sp^2 ; 120°

1.21 Bonds involving an *sp*-hybridized carbon atom are always shorter than bonds involving only sp^3-hybridized carbon atoms.

1.22 Both have a double bond that consists of a σ and a π bond, and the shapes of the molecules are similar. The lone pair electrons are in an sp^2 orbital at a 120° angle to the C=N bond.

1.23 Both have a triple bond that consists of a σ and two π bonds, and the shapes of the molecules are similar. The lone pair electrons are in an *sp* orbital at a 180° angle to the C≡N bond.

1.24 Both carbon and oxygen are sp^2 hybridized.

Chapter 2

2.2 CH_2=CH—CH_3 from one mole of hydrogen; CH_3—CH_2—CH_3 from two moles of hydrogen.

2.4 ketone

2.5 carbon–carbon double bond, ester

2.6 There are two equivalent contributing resonance forms with one C—O and one C=O bond. The bond length is between those of C—O and C=O bonds.

2.8 amide

2.9 The atomic radius of nitrogen is less than that of carbon.

2.10 It is similar to an ester. 120°

2.11

CH_3—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3; $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$; $CH_3(CH_2)_9CH_3$

2.12 (a) $NH_2(CH_2)_4NH_2$ (b) $(CH_3)_3COCH_3$ (c) $CH_3CH_2S(CH_2)_2CH_3$

2.13 a carbon–carbon double bond and a ketone

2.15 five ether groups and one ketone

2.16 $C_{10}H_9NO_2$ $C_{12}H_{16}N_4O$ $C_{14}H_{20}O_4$

2.17 They are isomers differing in the locations of the hydrogen, fluorine, and chlorine atoms on the leftmost two carbon atoms.

2.18 They are isomers differing in the locations of a hydroxyl and a carbonyl group.

2.19 The dipole moment is between 0 and 2.7 D, the moments of propane and ethanal. Because the shapes are similar, the boiling point should be between −42 and 20 °C.

2.20 About 102 °C, which is 33 degrees higher than hexane.

2.21 $CHCl_3$ is more polar. CCl_4 is nonpolar. The boiling points reflect differences in molecular weight, not polarity.

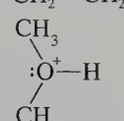
2.22 Ethylene glycol can also form intermolecular hydrogen bonds even while intramolecularly hydrogen bonded.

2.24 The polymer and the oil associate by London forces because the structures are similar.

2.25 It can lose or gain a proton. CH_3O^- ; $CH_3OH_2^+$

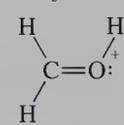
2.26 CH_2=CH_2 is a Lewis base; H^+ is a Lewis acid.

2.27



109° Oxygen has the formal positive charge.

2.28



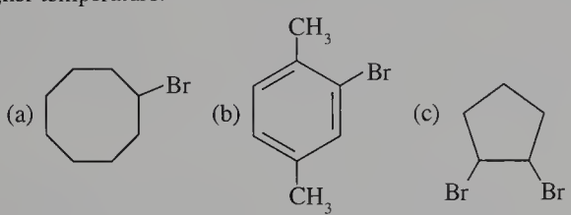
120°

2.29 oxidation reaction; oxidizing agent
2.30 There is no net oxidation or reduction.
2.32 elimination reaction; dehydrochlorination reaction
2.33 No, because a bond is broken by reaction with water. Yes, because a molecule of water is incorporated in the product.
2.34 Yes, because a bond is formed joining atoms in two reactants. Simultaneous formation of a second smaller molecule is not required.
2.35 (a) elimination reaction (b) rearrangement reaction (c) addition reaction
2.36 hydrolysis reaction requiring water

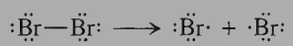
Chapter 3

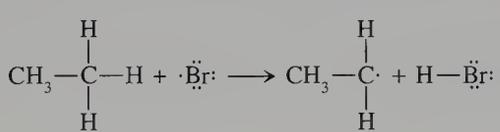
3.1 $$K = \frac{[CH_3OH]\,[Cl^-]}{[OH^-]\,[CH_3Cl]}$$

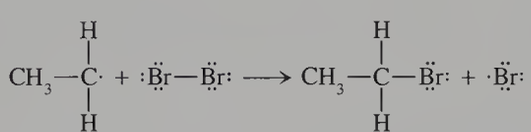
The equilibrium is strongly to the right and is quantitative.
3.3 83% product; 17% reactant
3.4 increase concentration of CH_3OH; remove H_2O product
3.5 1×10^{-7}; 50%
3.6 triethylamine; 10.49 and 11.01; diethylammonium ion
3.7 on the left; $K = 10^{-11}$
3.9 CH_3SH
3.10 The electron-withdrawing fluorine atoms stabilize the conjugate base of 2,2,2-trifluoroethanol.
3.11 Resonance forms can be written that locate the negative charge on either of the two oxygen atoms, stabilizing the conjugate base.
3.13 2.7×10^7
3.14 2-bromopropane
3.15 (a) –35 kJ (b) –95 kJ
3.16 zero
3.17 The ring compound is more highly ordered than the open chain compound.
3.19 –45.9 kJ ; –17.4 kJ ; the negative ΔS°_{rxn} disfavors the reaction at the higher temperature.
3.20



3.21 The electron-withdrawing chlorine atoms stabilize the charge on carbon in the conjugate base.
3.22 The conjugate base of ethanal is resonance-stabilized; the second resonance form has the negative charge of the conjugate base of ethanal placed on the oxygen atom.
3.23 Yes, because a primary carbocation is converted to a secondary carbocation.
3.24



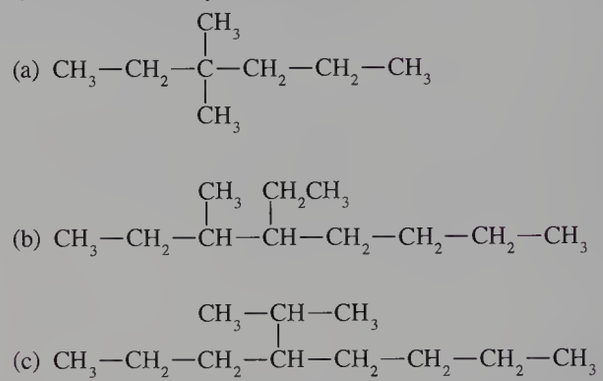




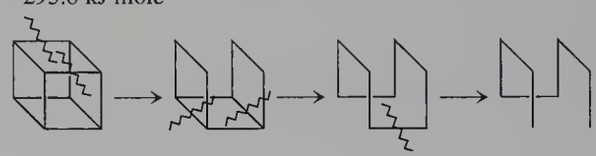
3.25 The reaction with CH_3Br is faster, indicating that the bromide ion is the better leaving group.
3.26 first order in each, second order overall; rate = $k\,[CH_3CH_2Br]\,[CN^-]$
3.27 the slower reaction, that of CH_3Cl
3.28 three transition states; two intermediates

Chapter 4

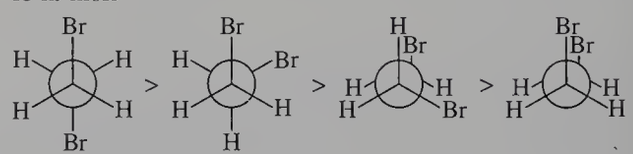
4.1 $C_{29}H_{60}$
4.4 Four carbon atoms bearing oxygen atoms are primary. The central carbon atom is quaternary.
4.5 2,6,10,14-tetramethylhexadecane
4.7



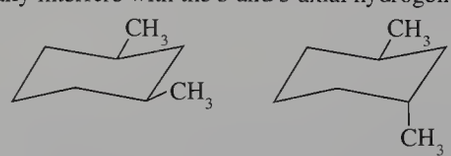
4.8 2-methylpropyl
4.9 2,2-dimethylpropyl
4.10 1,5-dimethylhexyl
4.11 It is more stable. The number of branches accounts for this stability.
4.12 2.7 kJ mole^{-1}
4.14 –295.6 kJ mole^{-1}
4.16



4.17 $C_{10}H_{16}$; $C_{10}H_{17}N$; three each
4.18 yes, cis and trans isomers of the alkyl groups bonded to the three-membered ring
4.19 (a) isobutylcyclopentane (b) 1-cyclobutyl-3-methylpentane (c) *cis*-1-bromo-5-methylcyclodecane
4.20 (–155.2 kJ mole^{-1} + 111 kJ mole^{-1}) = –44 kJ mole^{-1}
4.21 15 kJ mole^{-1}
4.22

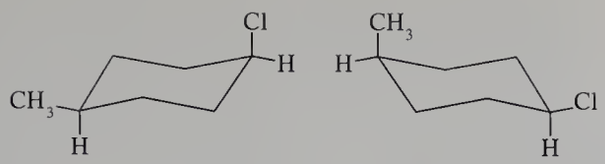


order of decreasing stability: anti > gauche > H/Br eclipsed > Br/Br eclipsed
4.23 larger than OH but smaller than CH_3 ; about 6 kJ mole^{-1}
4.24 86% equatorial at 0 °C
4.25 The linear group does not have any branching atoms that can sterically interfere with the 3 and 5 axial hydrogen atoms.
4.26



The cis compound is more stable by 7.6 kJ mole^{-1}.

4.27



The conformation with the equatorial methyl group is more stable by 4.8 kJ mole^{-1} and is 89% of the conformational mixture.

4.28 less ring strain in two six-membered rings compared to one five-membered and one seven-membered ring

4.29 3β position is equatorial and is less hindered; 4α will react faster because it is also equatorial.

Chapter 5

5.1

$CH_3CHCH_2CH_2\cdot$ 422 kJ mole^{-1} $CH_3CH\dot{C}HCH_3$ 410 kJ mole^{-1}

$CH_3\dot{C}CH_2CH_3$ 401 kJ mole^{-1} $CH_3CHCH\dot{C}H_2$ 422 kJ mole^{-1}

5.3 $CH_3CH_2CH_2CH_2CH_2\cdot$ 422 kJ mole^{-1} $CH_3\dot{C}HCH_2CH_2CH_3$ 410 kJ mole^{-1} $CH_3CH_2\dot{C}HCH_2CH_3$ 410 kJ mole^{-1}

5.5 The two bridgehead C—H bonds are equivalent. All six of the CH_2 units in the three two-membered bridges are equivalent.

5.7 −3 kJ mole^{-1}

5.9 9405 kJ mole^{-1}

5.10 one monochlorinated, two dichlorinated, two trichlorinated

5.11 six dichlorinated butanes, three dichlorinated 2-methylpropanes

5.12 There are four nonequivalent carbon atoms. However, substitution at either C-2 or C-3 can give cis and trans isomers.

5.14 (a) 31% tertiary, 69% secondary (b) 47% tertiary, 53% secondary

5.15 1-bromo-1-ethylcyclohexane

Chapter 6

6.1 The carbon atom in vinyl chloride is sp^2 hybridized and forms shorter and stronger bonds than the sp^3-hybridized carbon atom of chloroethane. The C—Cl bond length should be about 2% shorter, or 175 pm.

6.3 The rightmost double bond is monosubstituted; the other two double bonds are trisubstituted.

6.4 (a) both trisubstituted; conjugated double bonds
(b) disubstituted and tetrasubstituted; conjugated double bonds
(c) disubstituted and tetrasubstituted
(d) disubstituted and trisubstituted

6.6 The same as oxygen. There is no effect on the degree of unsaturation calculation.

6.7 (a) 3 (b) 3 (c) 4 (d) 4

6.8 Only at the double bond nearest the hydroxyl group.

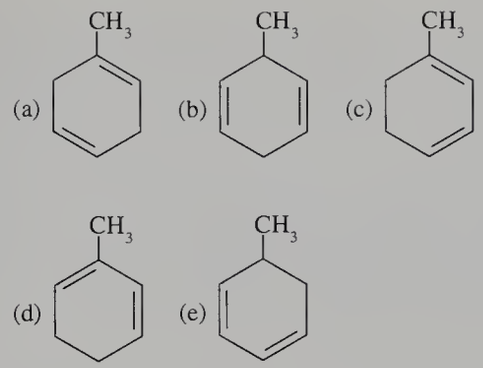
6.9 From right to left the bonds are cis, cis, and trans. Eight isomers.

6.10 $-\overset{\overset{CH_3}{|}}{C}=N-OH < -\overset{\overset{O}{\|}}{C}-H < -\overset{\overset{O}{\|}}{C}-OH < -CH_2Cl$

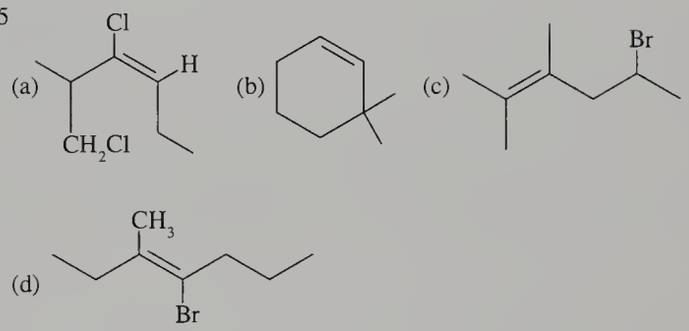
6.12 (a) *Z* (b) *E* (c) *Z*

6.13 (*Z*)-2,3-dibromo-2-hexene

6.14



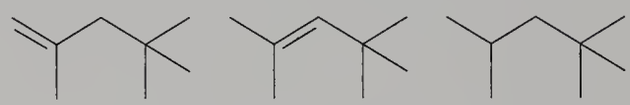
6.15



6.17 The carbonyl group of carboxylic acids and esters is not easily reduced.

6.18 $(CH_3)_2C=CHCHCH_2CHCH_2CH_3$ (CH$_3$ and CH$_3$ branches)

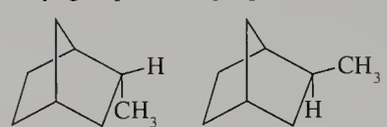
6.19 The isomers differ only in the position of the double bond, which when hydrogenated gives the same saturated product.



6.20 The unsaturation number is 6. There are no rings.

6.21 Approach of hydrogen from the "top" to give the equatorial methyl group is more hindered than the alternate approach to give the axial methyl group. The major product is the cis isomer.

6.22



major minor

6.23 Hydrogen will add from "below" the A/B ring and give an axial C—H bond at C-5.

6.24 The products are the same in the combustion reaction regardless of the hydrocarbon skeleton. Hydrogenation of alkenes with different hydrocarbon skeletons does not give the same saturated product.

6.25 −14 kJ mole^{-1}

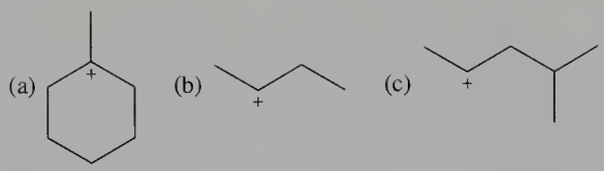
Chapter 7

7.1 −112 kJ mole^{-1}

7.2 H_2O, syn

7.3 (a) 2-chloro-2-methylbutane
(b) 2-chlorobutane
(c) 2-chloropentane and 3-chloropentane

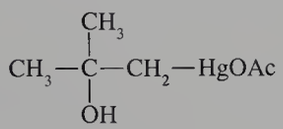
7.5



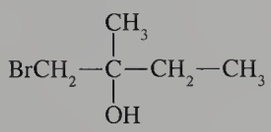
7.6 II > I > III

7.7 1-Butene is less stable than 2-butene and is of higher energy. Thus it is closer in energy to the transition state.

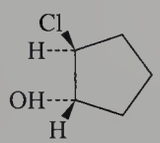
7.10 $^{+}HgOAc$ is the electrophile.



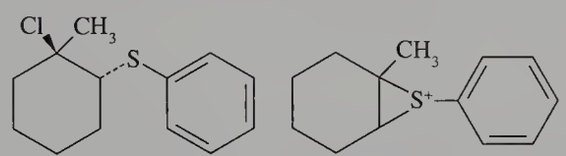
7.11



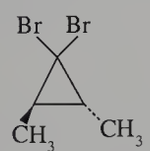
7.12 Anti addition of chlorine and hydroxyl group gives the trans isomer.



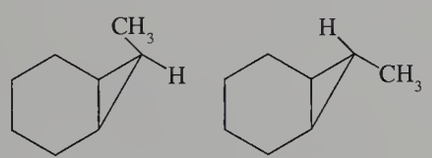
7.13



7.14 The mechanism should be the same as for $CHCl_3$.

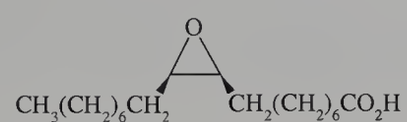


7.15 The ethylidene can approach so that the methyl group is over the cyclohexene ring or directed away from it.



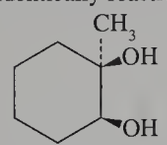
major minor

7.16



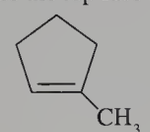
7.18 Any of the three trisubstituted double bonds can react. If all were identically reactive, there would be 33% of the desired product.

7.19

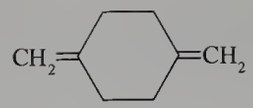


7.21 Approach of the reagent occurs from the "bottom" of the ring because the top face is sterically hindered by the axial methyl group.

7.22



7.23



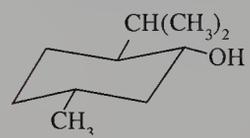
7.25 No, because either the *E* or *Z* isomer of 3-methyl-3-hexene would give these products.

Chapter 8

8.2 All are secondary.

8.4 *cis*-1-fluoro-4-isopropylcyclohexane

8.6



8.9 Displacement of Br^- by OH^- to give $BrCH_2CH_2CH_2CH_2CH_2OH$ followed by loss of a proton to give an alkoxide that intramolecularly displaces the second bromide ion.

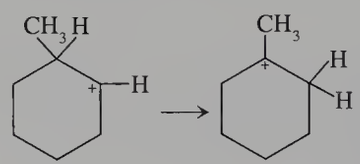
8.10 There is a *tert*-butyl group bonded to the primary carbon atom of 2,2-dimethyl-1-bromopropane that sterically hinders attack at the back side by the nucleophile.

8.11 The second reaction with 1-bromopropane because the site for attack by the nucleophile is primary.

8.13 Attack by a nucleophile from the back side for an S_N2 mechanism is impossible. The strain energy developed to form a planar carbocation as required for an S_N1 mechanism is too large.

8.15 S_N2 for I; S_N1 for II and III

8.16 Hydride shift from C-1 to C-2 converting a secondary carbocation to a tertiary carbocation.



8.18 1-butene, (*E*)-2-butene, (*Z*)-2-butene; 1,3-butadiene

8.19 1-octene

8.20 They are obtained by addition of chlorine to an alkene, which is the desired product.

8.22 (*E*)- and (*Z*)-2-pentene

8.23 2-methyl-1-butene, 2-methyl-2-butene; 1-pentene, (*E*)- and (*Z*)-2-pentene

8.24 Four can be formed. 2,3-Dimethyl-2-pentene is major product. 2-Ethyl-3-methyl-1-butene is minor product. The other two products are (*E*)- and (*Z*)-3,4-dimethyl-2-pentene.

8.25 There is a methyl group located trans to the bromine rather than a hydrogen atom required for the elimination reaction. Elimination of hydrogen can thus only occur at the C-6 carbon of the reactant.

8.26 (a) 1-methylcyclohexene (b) 3-ethyl-2-pentene (c) isopropylidenecyclohexane

8.28 3-methyl-1-butene and 2-methyl-2-butene without rearrangement; 2-methyl-1-butene from rearrangement

8.29 A methide shift gives a secondary carbocation that yields 2-methyl-1-butene (minor product) and 2-methyl-2-butene (major product).

Chapter 9

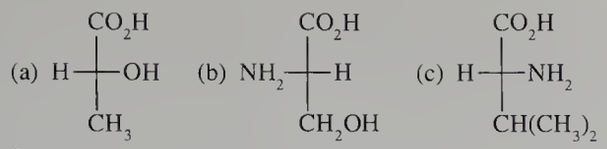
9.1 Only (c). (a) has two equivalent butyl groups. (b) has two equivalent bromine atoms.

9.3 Yes, the carbon atom bonded to the benzene ring is a stereogenic center.

9.4 −109; testosterone

9.5 36.7

9.7

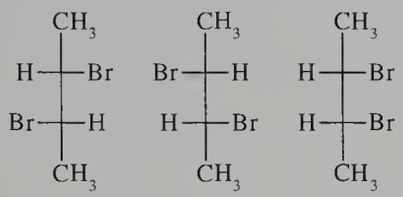


9.8 *S*

9.10 No, the sign of the rotation is unrelated to the configuration. The relative configurations are the same because reaction does not occur at a stereogenic center. The configuration is (*R*).

9.12 (2*R*,3*R*)-2-bromo-3-chlorobutane; (2*R*,3*S*)-3-bromo-2-butanol

9.13

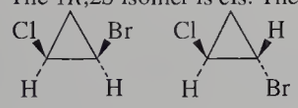


enantiomers meso

The enantiomers have opposite optical rotations. The meso compound is optically inactive.

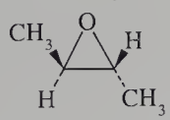
9.15 (2*R*,3*R*,4*R*); (2*R*,3*R*,4*S*); (2*R*,3*S*,4*R*); (2*S*,3*R*,4*R*); (2*R*,3*S*,4*S*): (2*S*,3*R*,4*S*); (2*S*,3*S*,4*R*); (2*S*,3*S*,4*S*)

9.17 The 1*R*,2*S* isomer is cis. The structures are diastereomers.



1*R*,2*S* 1*S*,2*S*

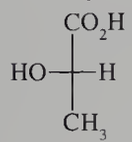
9.18 2*S*,3*S*



9.19 (*R*)-2-bromo-1-chlorobutane has no new stereogenic centers. However, the priority of the methyl group compared to CH_2Cl changes the assignment of configuration.

9.21 No rotation because a racemic mixture is formed.

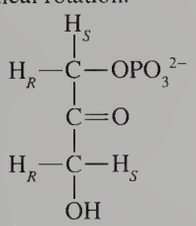
9.22 The enzyme is chiral and the reaction is stereospecific.



9.23 A meso compound having cis methyl groups. The configuration is 2*R*,3*S*.

9.24 Unequal amounts of (2*S*,3*R*)-2-bromo-3-chlorobutane and (2*S*,3*S*)-2-bromo-3-chlorobutane, which are diastereomers. There is a net optical rotation.

9.26



9.27 si

Chapter 10

10.1 Trimethylborane has an electron-deficient boron atom. There are no nonbonded electrons to serve as the site of nucleophilicity.

10.2 The amide ion is the better nucleophile and stronger base.

10.3 diethyl selenide

10.4 The hydrocarbon groups of quinuclidine are tied back and do not sterically hinder the site of nucleophilicity.

10.5 (*R*)-2-butanol and (*S*)-2-butanol

10.7 60.5%; partial racemization of product via an S_N1 mechanism

10.8 3-Bromocyclohexene reacts via an S_N1 mechanism in which a resonance-stabilized carbocation is formed.

10.9 Formamide and methanol are both protic solvents, and hydrogen bonding decreases the nucleophilicity of the chloride ion. Dimethylformamide is aprotic.

10.11 Both terminal nitrogen atoms have a negative charge.

10.12 The higher concentration of base gives the E2 product.

10.13 The sterically hindered *tert*-butoxide ion is a poorer nucleophile and elimination is favored by default.

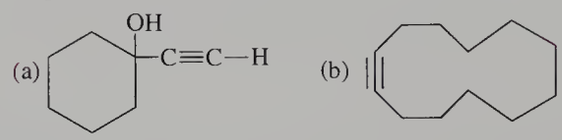
Chapter 11

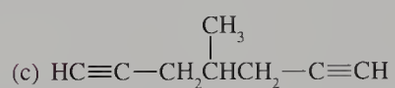
11.1 142 pm

11.2 2-butyne; 2×10^3 assuming that $\Delta S°_{rxn} = 0$

11.4 $CH_2{=}CHCH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH_3$

11.5

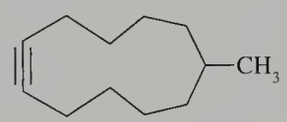




11.6 Equilibrium lies to the right. $K = 10^{25}$.

11.7 Both compounds are less saturated and will produce fewer moles of water. The lower heat capacity of the product mixture results in a hotter flame.

11.9



11.10 2-Butyne because the multiple bond has more alkyl substituents.

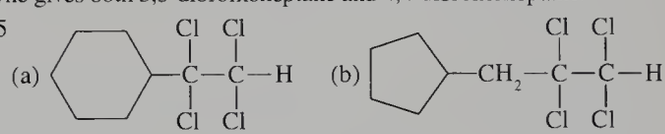
11.11 Reduction of 11-tetradecyn-1-ol using sodium and liquid ammonia.

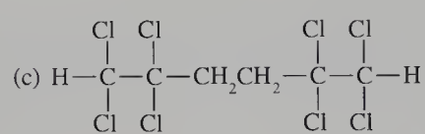
11.12 Reduction of 9-tricosyne using the Lindlar catalyst.

11.13 $CH_3CH_2CH_2CH_2CH{=}CHBr$ $CH_3CH_2CH_2CH_2\dot{C}{=}CHBr$

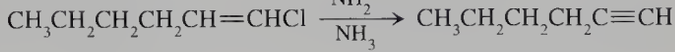
11.14 Both *sp*-hybridized carbon atoms in 3-hexyne are equivalent, and addition of HBr gives the same unsaturated bromo compound, regardless of the direction of addition. Subsequent addition of HBr occurs by Markovnikov's rule to give 3,3-dibromohexane. Addition of HBr to 3-heptyne gives both 3,3-dibromoheptane and 4,4-dibromoheptane.

11.15

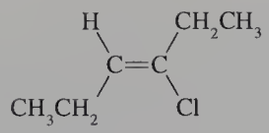




11.17



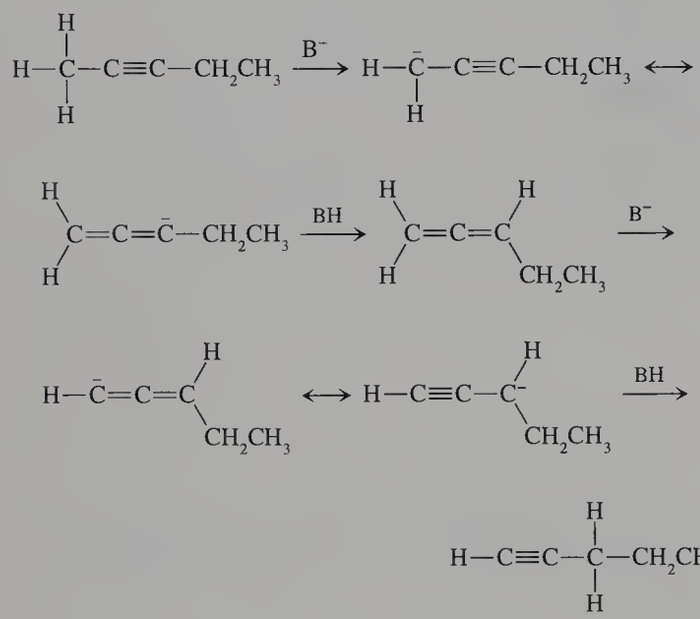
Both 1-hexyne and 2-hexyne can form as well as 1,2-hexadiene.

11.18 

11.19 The second ionization constant of an acid is always smaller than the first ionization constant. It is more difficult to remove a proton from a negatively charged substance.

11.20 $CH_3—C{\equiv}C^- + (CH_3)_2CHCH_2Br$

11.21 The terminal alkyne will form because its alkynide salt results from reaction with the strong base.

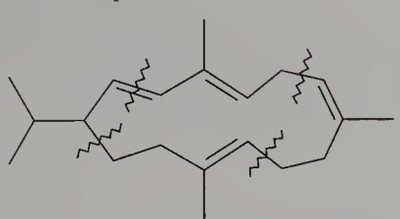


11.22 2-Pentyne, the more stable alkyne, is formed rather than 1-pentyne.

Chapter 12

12.1 The two double bonds on the right are conjugated. The other double bonds are isolated.

12.2 It is a diterpene.

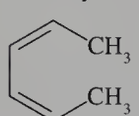


12.3 230 kJ mole^{-1} for 2*E*,5*E*-heptadiene, which is twice that of a disubstituted alkene; 215 kJ mole^{-1} for 2*E*,4*E*-heptadiene, which is disubstituted but is also conjugated

12.5 II < III < V < I < IV

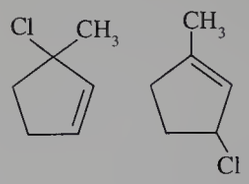
12.6 Three; π_1 is symmetric and has no nodal plane; π_2 is antisymmetric and has one nodal plane; π_3 is symmetric and has two nodal planes.

12.8 The equilibrium constant is smaller because the s-cis conformation is sterically hindered.

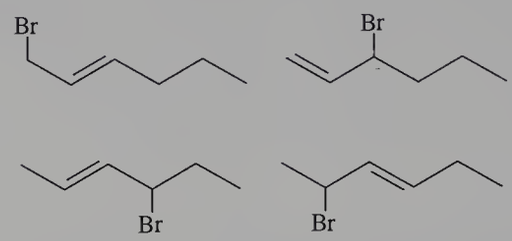


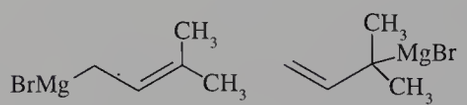
12.9 The equilibrium constant is smaller because the s-cis conformation has eclipsed alkyl groups that cause greater steric hindrance with increased size.

12.11 The more stable trisubstituted alkene is favored.



minor major

12.12 

12.14 

major minor

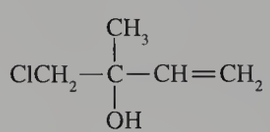
The more stable structure has the more substituted double bond. The partial negative charge on the carbon atom is more stable on a primary carbon atom compared to a tertiary carbon atom.

12.15 Two; the C-1, C-3, and C-5 atoms have radical character.

12.17 II because one terminal carbon atom of the allyl cation is disubstituted.

12.18 The carbocation is resonance stabilized. 3,4-dibromo-1-butene and 1,4-dibromo-2-butene

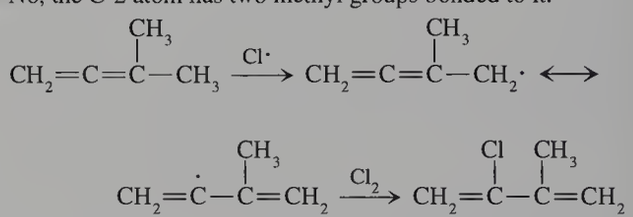
12.19 1,2-addition; electrophile is Cl^+.



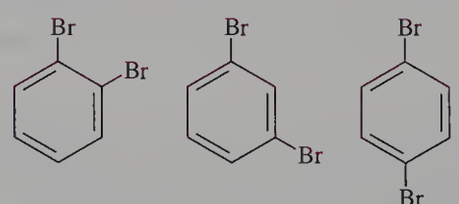
12.20 45% product from 1,4-addition; 1% product from free radical substitution of vinyl C—H bond; 54% product from allylic free radical substitution

12.21 The same as in ethene, 107 pm.

12.22 No, the C-2 atom has two methyl groups bonded to it.

12.23 

Chapter 13

13.1 

There is an additional 1,2 compound if the double bonds are localized.

13.3 See Figure 12.2. Value for two terminal double bonds and a disubstituted double bond is (2 × 126 + 115) kJ mole^{-1}. Thus resonance energy is 30 kJ mole^{-1}.

13.4 Yes, $n = 4$.

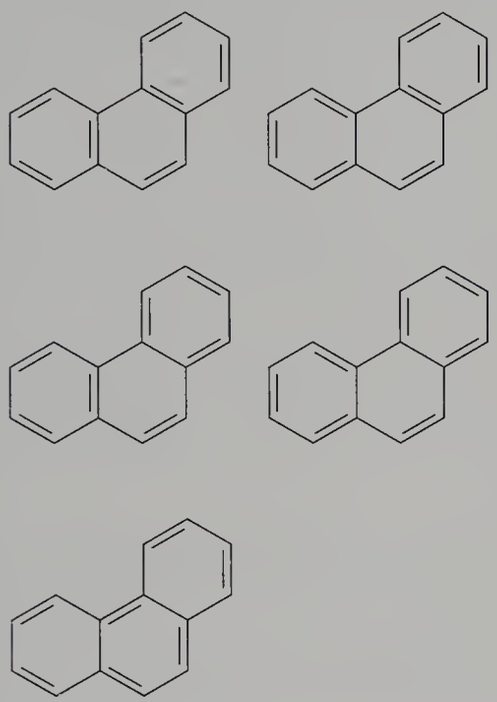
13.5 

13.6 No, there are only 4 π electrons.

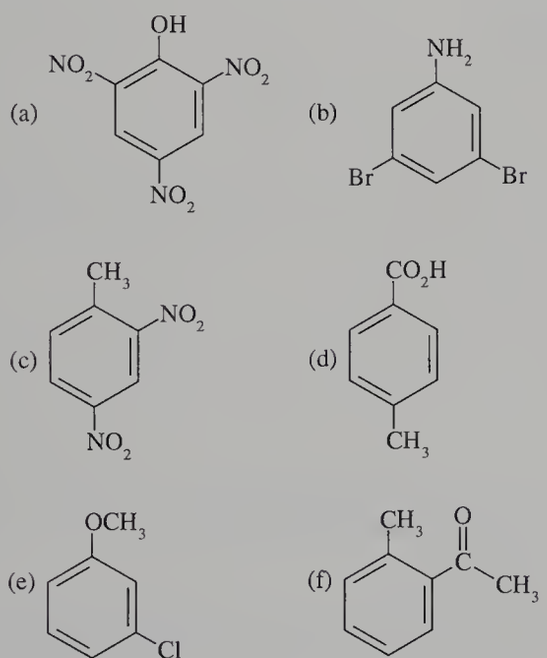
13.7 There are four electrons; two electrons are paired and two are present as unpaired electrons in degenerate orbitals.

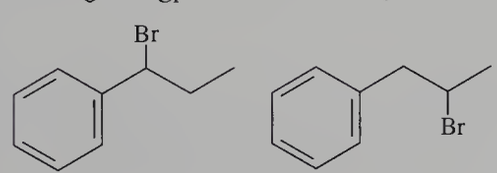
13.9 Eighteen electrons and the compound is aromatic, with $n = 4$.

13.10 268 kJ mole^{-1}

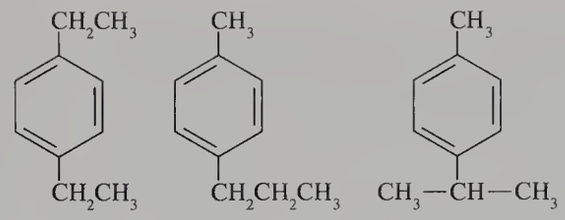
13.12 

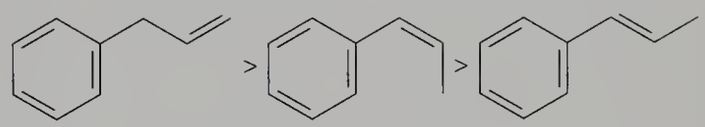
Four of the five resonance forms have a double bond between C-9 and C-10.

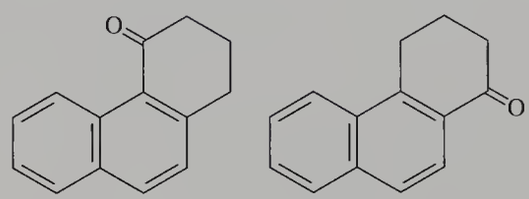
13.15 

13.16 

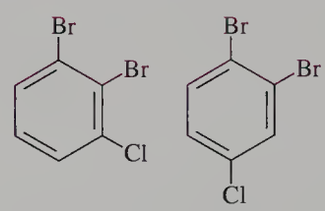
peroxides absent peroxides present

13.18 

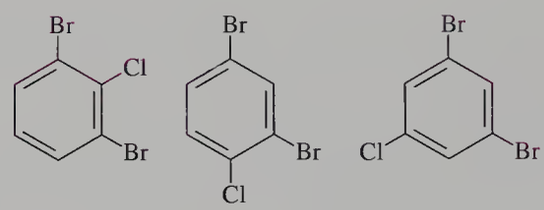
13.19 

13.20 

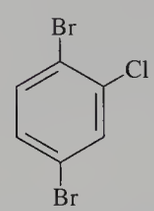
Chapter 14

14.1 

from *o*-dibromobenzene

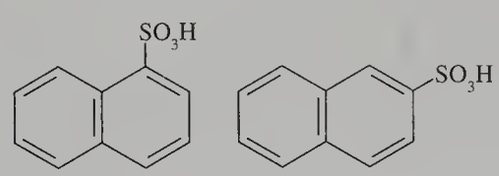


from *m*-dibromobenzene



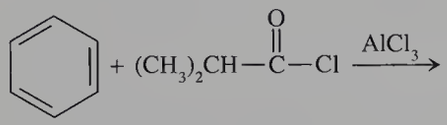
from *p*-dibromobenzene

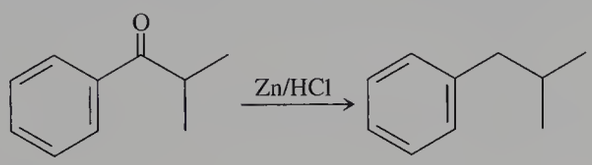
14.3 Isomer II is more stable. Isomer I is the product of kinetic control. Isomer I is less stable than isomer II because the sulfonic acid group is sterically hindered by the adjacent aromatic ring.



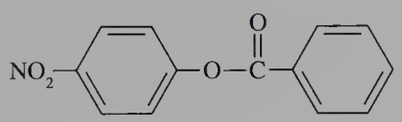
isomer I isomer II

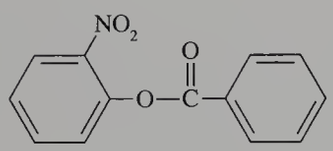
14.5 *sec*-Butylbenzene as a result of hydride shift from the C-2 atom of the butyl to give a secondary carbocation.
14.6 Protonation of 2-methylpropene gives the *tert*-butyl carbocation, which is the electrophile.
14.7 Friedel–Crafts acylation followed by Clemmensen reduction.



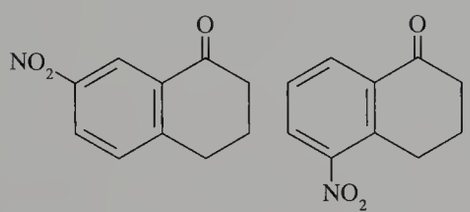


14.10

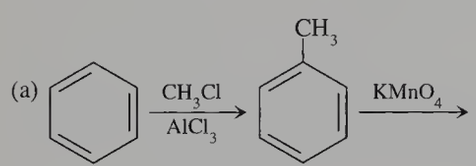


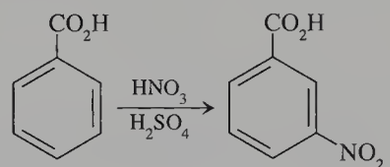


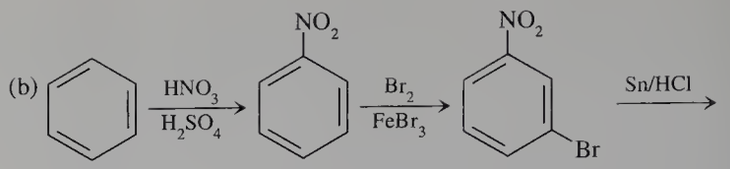
14.11

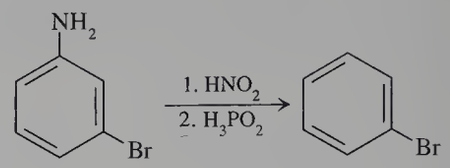


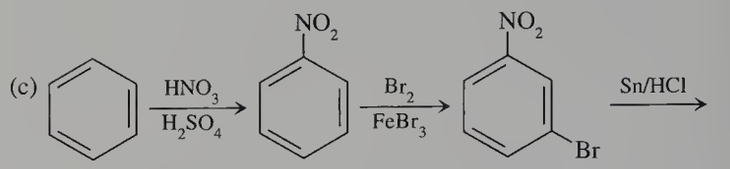
14.12 The oxygen atom is part of an ether and is an activating group.
14.14 The boron atom is electron deficient and withdraws electrons from the aromatic ring.
14.15 The lone pair electrons of nitrogen in the nitroso group can be donated by resonance to the aromatic ring.
14.16 Methyl group is weakly activating, and chloro is weakly deactivating. Thus the two groups have only small effects on the rate of reaction. The methyl group directs the electrophile to two possible positions ortho and para to it. The chloro group directs the electrophile to the other two possible positions. Thus four isomers result.
14.17 The *tert*-butyl group sterically hinders attack at the ortho position more than does the isopropyl group.
14.18 (b) alone gives the desired isomer. In (a) the product is 5-chloro-2-ethyl-1-nitrobenzene. The compound in (c) is too deactivated for a Friedel–Crafts reaction.
14.20

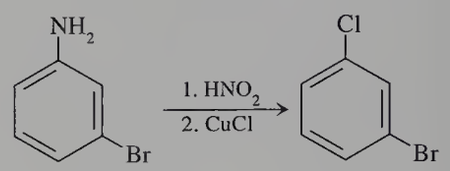








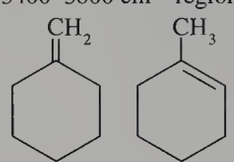




14.21 The 2-position is deactivated by the $—CO_2H$ group, so substitution occurs at the alternate position that is normally favored in thiophene.
14.22 The pyridine ring is deactivated. The two positions in the substituted rings are favored as in the case of naphthalene.

Chapter 15

15.1 (a) 217 + 39 + 3(5) + 5 = 276
(b) 217 + 39 + 30 + 3(5) + 5 = 306
(c) 217 + 3(5) + 5 = 237
15.2 Azulene has a λ_{max} in the visible region, whereas naphthalene does not.
15.5 Compound I has an intense broad O—H stretching absorption in the 3400–3600 cm^{-1} region.
15.6



I II

Compound I has an absorption in the 895–885 cm^{-1} region; compound II has an absorption in the 840–790 cm^{-1} region.
15.8 318 Hz; 5.30 δ
15.9 (a) 2 (b) 4 (c) 3
15.11 Tin is below silicon in the periodic table and is less electronegative. Thus tin deshields the protons of the methyl group less than does silicon.
15.12 C-1 hydrogen atoms at 3.72 ppm; C-2 hydrogen atoms at 2.15 ppm; C-3 hydrogen atom at 4.27 ppm; C-4 hydrogen atoms at 1.60 ppm
15.13 All three hydrogen atoms should have resonances below those of benzene due to the electronegative nitrogen atom. The equivalent C-2 and C-6 hydrogen atoms should be at lowest field.

15.14 (a) Ratio of C-1 methylene hydrogen atoms to two equivalent methyl groups is 1:3. (b) Ratio of C-1 methylene hydrogen atoms to three equivalent methyl groups is 2:9. (c) Ratio of equivalent C-3 and C-4 methylene hydrogen atoms to vinyl hydrogen atoms is 1:1

15.15 All contain the same number of NMR absorptions—four. Compound II has a very low field resonance of intensity 1. The remaining compounds have two low field absorptions. Those due to hydrogen atoms on carbon bearing chlorine are at lower field than those due to hydrogen atoms on carbon bearing bromine. From low field to high field the intensities are: I (2:1), III (2:2), IV(2:1). Thus only compounds II and III can be distinguished by number and intensity of absorptions.

15.17 (a) high field doublet of intensity 6 and low field heptet of intensity 1; (b) high field doublet of intensity 3 and low field quartet of intensity 1; (c) singlet of intensity 3 due to C-1 hydrogen atoms, quartet of intensity 2 and triplet of intensity 3; (d) two doublets each of intensity I

15.18 The largest difference in chemical shift is only 70 Hz. If the coupling constant for these trans hydrogen atoms is larger than 7 Hz, the spectrum will not be first order.

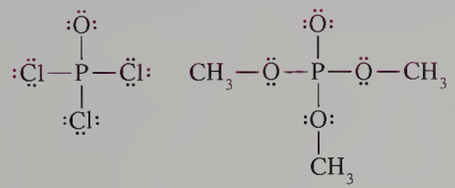
15.20 Each spectrum consists of two doublets. The coupling constants decrease in the order the compounds were listed.

15.21 In general, neglecting symmetry, ethers have two low field resonances, whereas alcohols have only one.

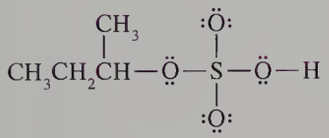
15.22 4-Heptanol has only four ^{13}C resonances compared to seven for 3-heptanol.

Chapter 16

16.1



16.2



The product has the *S* configuration.

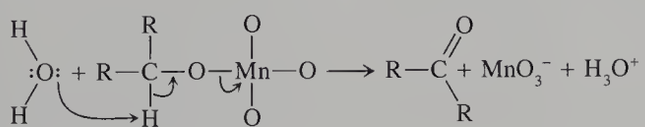
16.3 Use water containing ^{18}O. Attack at silicon will give alcohol without the isotope. Attack at carbon will give alcohol containing the isotope.

16.5 A hydride shift from C-2 to C-3 occurs as the transition state develops some carbocation character.

16.7 only 2-butanol

16.8 $R_2CHOH + H^+ \longrightarrow R_2CHOH_2^+$

$R_2CHOH_2^+ + MnO_4^- \longrightarrow R_2CHOMnO_3$



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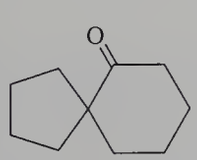

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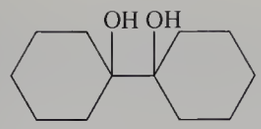
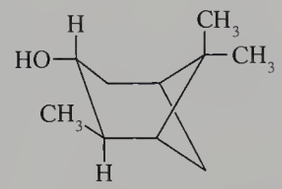


16.13 The cis isomer, which has an axial chlorine atom. Attack is easier from the equatorial position.

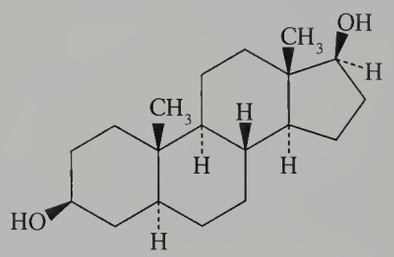
16.14 anti addition

16.16 3,3-dimethyl-2-butanol; no, a rearrangement occurs to give 2,3-dimethyl-2-butanol.

16.17 Syn addition occurs from the "bottom", the side away from the methyl groups.



16.18



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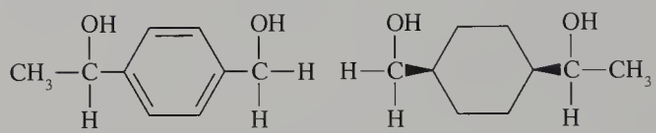
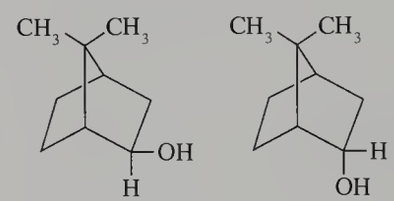
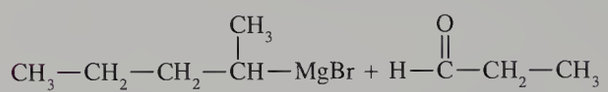


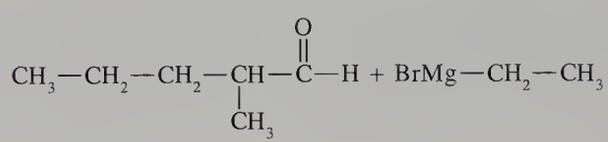
16.20



major minor

16.21





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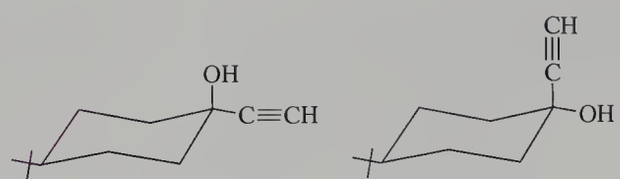


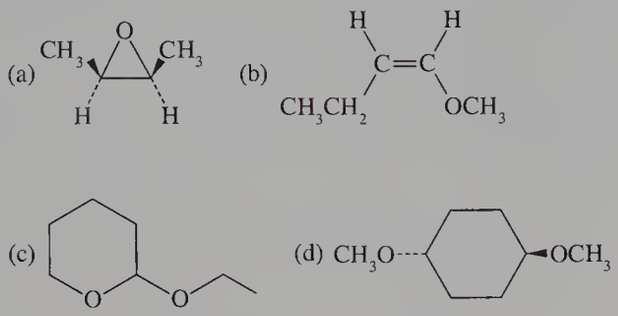
major minor

Chapter 17

17.1 (a) ethoxycyclopentane (b) *trans*-1,3-dimethoxycyclohexane (c) *cis*-1,3-diethoxycyclopentane

17.2 (a), (c), and (d)

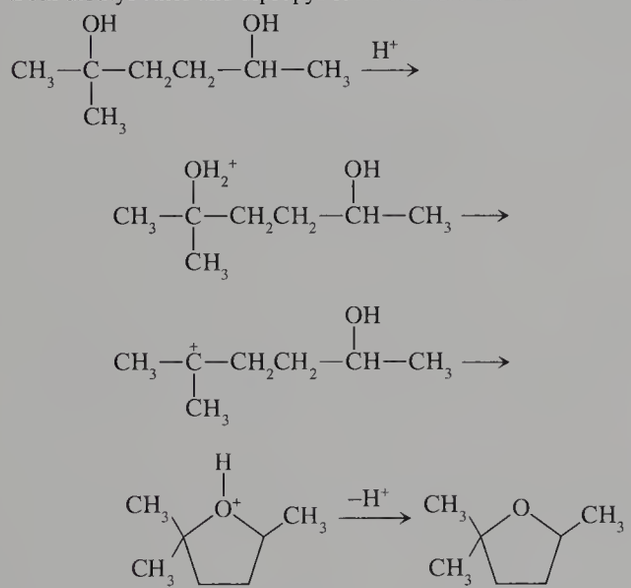
17.3



17.4 Both have a higher ratio of oxygen to carbon atoms than simple ethers. As a result, hydrogen bonding with water is more extensive.

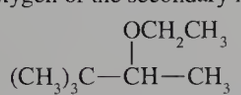
17.6 Both dibutyl ether and dipropyl ether can also form.

17.7



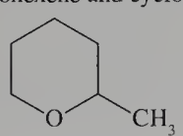
The oxygen of the secondary hydroxyl group is retained.

17.8



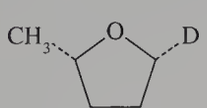
17.9 (a) cyclohexene in ethanol (b) 1-butene in 1-propanol (c) cyclohexene and cyclohexanol

17.10



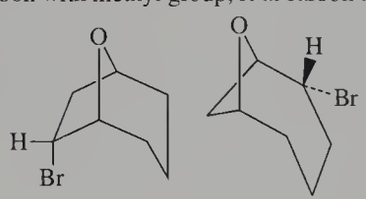
17.12 (a) phenoxide and 1-bromopropane (b) *tert*-butoxide and benzyl bromide (c) methoxide and 1,4-dibromobutane

17.13 Reactant has 1*S*,4*S* configuration.



S at carbon with methyl group; *R* at carbon atom with deuterium

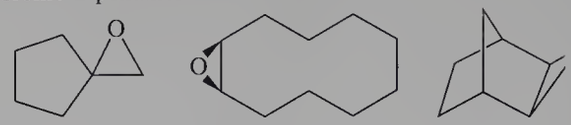
17.14



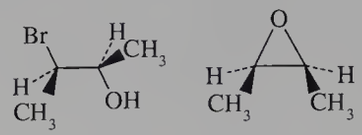
major minor

17.15 I CH_3I and *o*-dihydroxybenzene
II bromomethylcyclohexane and cyclohexanol
III 5-bromo-2-pentanol

17.18

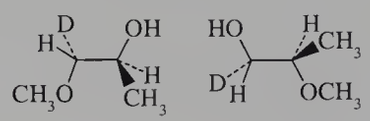


17.19



17.21 (a) $HO-CH_2CH_2-C\equiv N$ (b) (*R*)-2-pentanol (c) 2-methyl-4-hexyn-2-ol

17.23 2*S*,3*S* for reactant



2*S*,3*R* 2*S*,3*R*

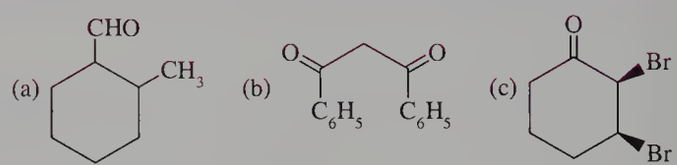
17.24 $CH_3CH_2-S-CH_2CH_2-OH$; the intermediate alkoxide ($CH_3CH_2-S-CH_2CH_2-O^-$) initially formed is sufficiently basic to remove a proton from the thiol and form the nucleophilic ethanethiolate.

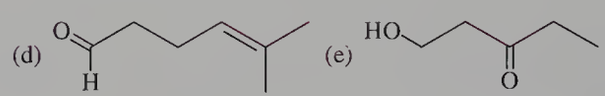
17.25 ethyl vinyl ether

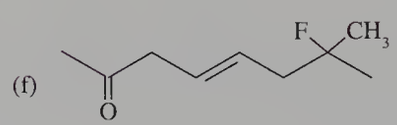
17.26 (a) 2-butanol (b) 2-methyl-1-propanol (c) 2-methyl-2-propanol

Chapter 18

18.3

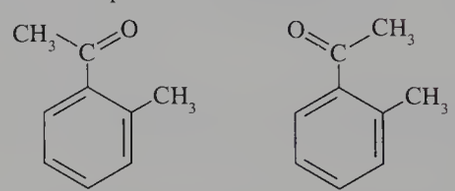






18.4 (a) 2,3-dimethyl-2-cyclohexenone
(b) 2-oxocyclopentanecarbaldehyde
(c) 2-methyl-1,3-cyclohexanedione
(d) 2-fluoroacetophenone

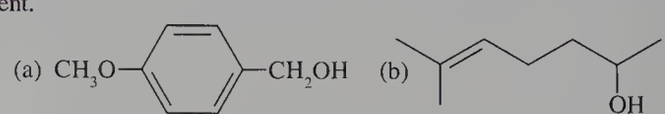
18.6



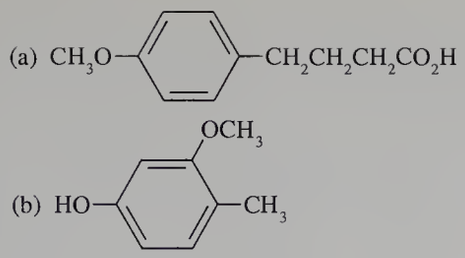
most stable

18.7 Only 2-butanone can be, because it is not oxidized by Tollens's reagent.

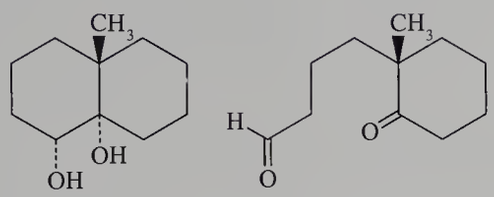
18.8



18.9

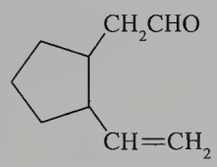


18.11

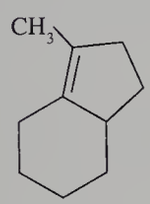


18.12 Friedel–Crafts acylation of benzene with *p*-nitrobenzoyl chloride.

18.13



18.14



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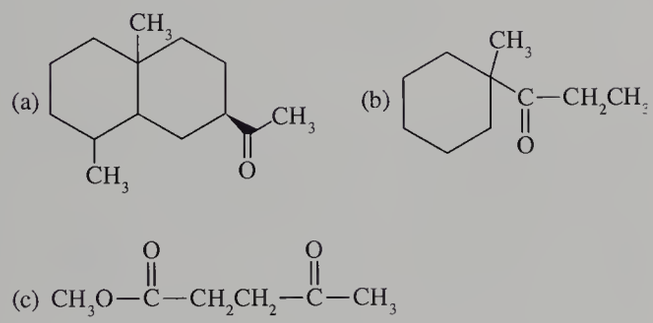
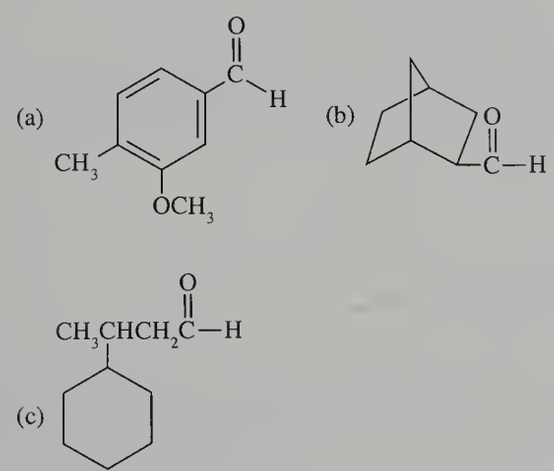


18.16



18.17 (a) 2-Ethylcyclobutanone has a carbonyl stretching vibration at 1780 cm^{-1} compared to 1745 cm^{-1} for 2-methylcyclopentanone. (b) The conjugated 2-cyclohexenone has a carbonyl stretching vibration at 1670 cm^{-1}, whereas the unconjugated ketone has a carbonyl stretching vibration at 1715 cm^{-1}. (c) 4-Methoxybenzaldehyde has a carbonyl stretching vibration at lower wavenumber. (d) 2-Methylcyclohexanone has a carbonyl stretching vibration at somewhat lower wavenumber.

18.18 The alkyl group is inductively electron donating and stabilizes the dipolar resonance form.

18.19 (a) 2-butanone (b) butanal

18.20 3-methyl-2-butanone

Chapter 19

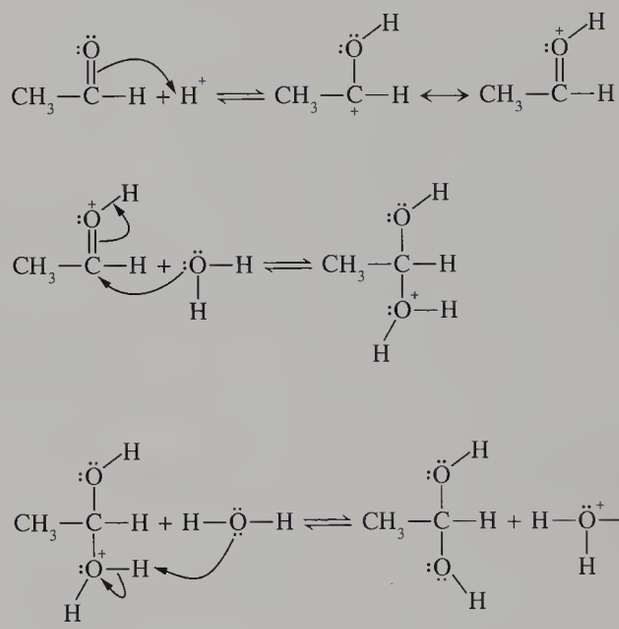
19.1 −1 kJ $mole^{-1}$

19.2 −255 kJ $mole^{-1}$ based on difference between propanone and propanal

19.3 Resonance stabilization of carbonyl group by *p*-methoxy group disfavors addition reaction.

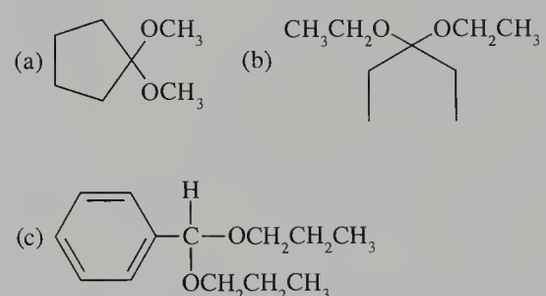
19.5 Steric effect of methyl groups of ketone destabilizes addition product.

19.7



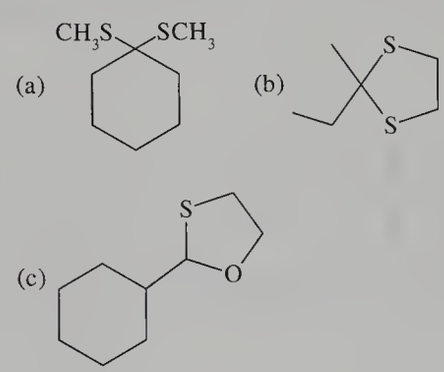
19.8 ketal

19.9

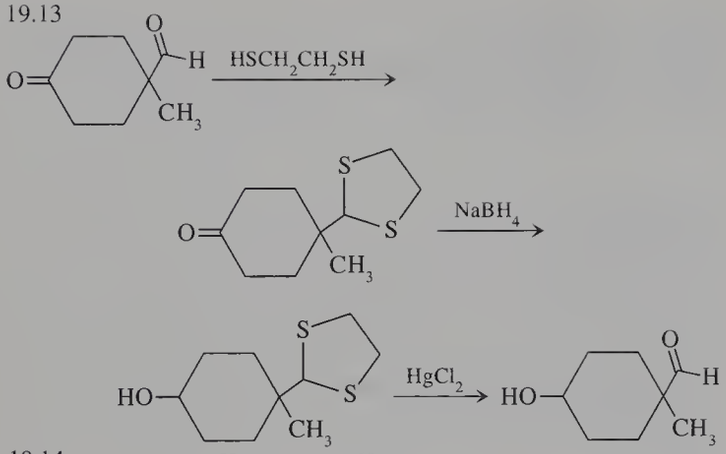


19.11 The acidic hydrogen of the hydroxyl group would destroy the Grignard as it forms. Prepare the THP derivative of the alcohol, and then prepare the Grignard to react with benzaldehyde.

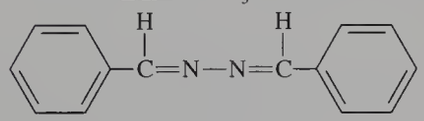
19.12



19.13



19.14



19.16 (a) cyclooctanone and ylide from methyl bromide
(b) benzophenone and ylide from ethyl bromide
(c) propanone and ylide from 1-bromopropane
(d) cyclohexanone and ylide from ethyl bromide

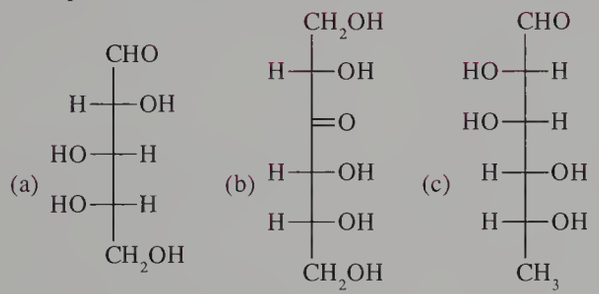
19.17 2-methylpropanal and ylide from 1-bromobutane or butanal and ylide from 2-methyl-1-bromopropane; either reaction will give a mixture of *E* and *Z* isomers

19.18 React dimethyl sulfide with bromomethane to form a trimethylsulfonium salt and then react with a strong base to remove a proton from one methyl group.

Chapter 20

20.1 a ketopentose

20.2



20.4 Formation of an enediol with a double bond between C-2 and C-3 leads to an epimeric mixture.

20.8 Yes, via the isomeric aldose, ribose, which is formed by an enediol intermediate.

20.9 (a) 2-deoxyribose and methanol (b) allose and benzyl alcohol (c) talose and isopropyl alcohol

20.11 formaldehyde, formic acid, and 1,3-propanedial; two moles of periodate

20.12 lyxose and xylulose

20.13 allose and altrose; allose will give an optically inactive aldaric acid

Chapter 21

21.1 The sp^2-hybridized carbon atom makes the C–O bond shorter. In addition, there is an additional small shortening as a result of resonance donation of lone pair electrons to the carbonyl carbon atom to give a double bond.

21.3 (*R*)-3,5-dihydroxy-3-methylpentanoic acid

21.4 toluene < benzaldehyde < benzyl alcohol < benzoic acid in both cases

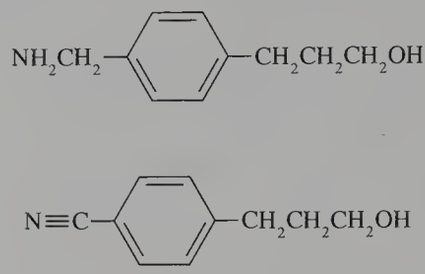
21.6 Electron-withdrawing by resonance is possible for the *p*-nitro group but not for the *m*-nitro group.

21.7 The carbon atom of the carbonyl group has a partial positive charge that withdraws electrons from the carboxyl group.

21.8 6.3×10^{-4}; 1.6×10^{2}

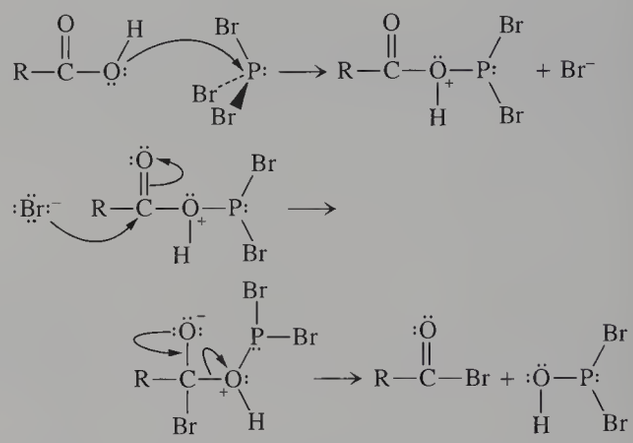
21.10 (a) haloform reaction with iodine and hydroxide ion
(b) Jones reagent (c) Jones reagent

21.11



21.12 Decarboxylation can occur by loss of either an axial or an equatorial carboxyl group. The products are a mixture of *cis*- and *trans*-4-methylcyclohexanecarboxylic acids.

21.14



21.15 Maleic acid is the cis isomer, which can form a cyclic anhydride. Fumaric acid, with trans carboxyl groups, can only form intermolecular anhydride bonds, yielding a polymer.

21.16 Fischer esterification of 2-methyl-2-(*p*-chlorophenoxy)propanoic acid with ethanol

21.17 The equilibrium constant for esterification of phenol is unfavorable.

21.18 The carbonyl stretching vibration of I occurs at lower wavenumber than 1710 cm^{-1} because of conjugation.

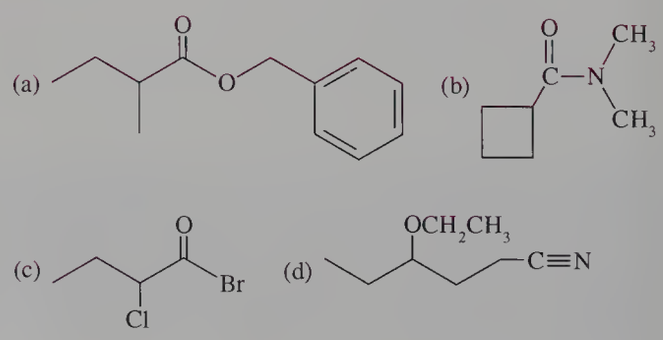
21.19 2-methylpropanoic acid

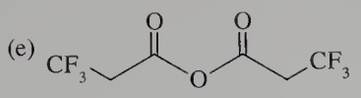
21.20 In proton NMR, hexanedioic acid has two triplets at high field, whereas the isomer has a quartet and a doublet. In ^{13}C NMR, hexanedioic acid has two triplets at high field, whereas the isomer has a quartet and a doublet.

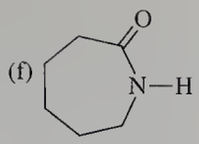
21.21 *p*-methylbenzoic acid

Chapter 22

22.3



(e) 

(f) 

22.4 11-hydroxy-8-dodecenoic acid lactone

22.5 The compound on the left because it has a carboxylic acid group

22.6 Donation of lone pair electrons of the ester to the carbonyl carbon atom decreases the polarity of the carbonyl group.

22.7 It is not resonance stabilized. Two equivalent resonance forms can be written for the conjugate acid of ethanoic acid.

22.8 (a) the acyl chloride (b) the acyl chloride

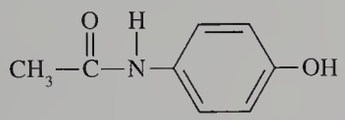
22.11 The amide group cannot be stabilized by resonance donation of electrons of the nitrogen atom because the double bond at a bridgehead atom in this resonance form is too strained. Hydrolysis relieves ring strain.

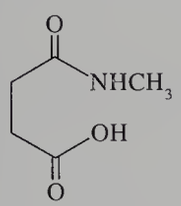
22.12 acetate ion and *p*-ethoxyaniline

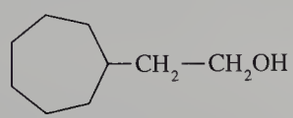
22.13 $CH_3(CH_2)_{14}CO_2(CH_2)_{15}CH_3$

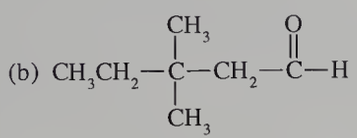
22.15 Tertiary alcohols would dehydrate under acid conditions.

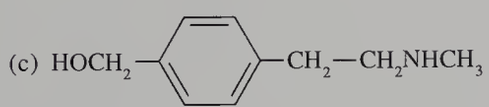
22.17 Transesterification exchanges the methanol with the diol. At high temperatures the methanol is vaporized and removed from the equilibrium mixture.

22.18 

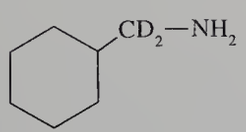
22.19 

22.20 (a) 

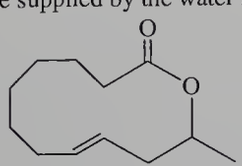
(b) 

(c) 

(d) $H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$

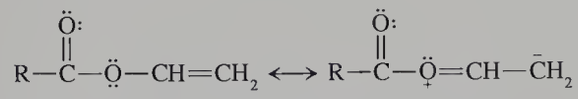
22.21 

Hydride reagents (or deuteride reagents) supply atoms to the carbonyl carbon atom. The hydrogen atoms eventually bonded to the nitrogen atom are supplied by the water in workup.

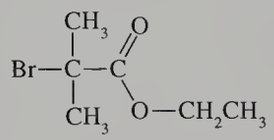
22.22 

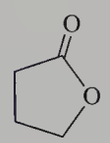
22.23 Add two moles of a Grignard reagent to an ester of methanoic acid such as ethyl methanoate.

22.25 The vinyl group withdraws electrons from the oxygen atom. Thus, the oxygen atom cannot as readily supply electrons to stabilize the dipolar resonance form.



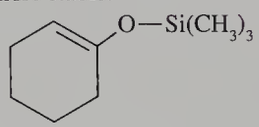
22.26 The lone pair electrons of the oxygen atom can be supplied to the carbonyl carbon atom and thus stabilize the dipolar resonance form.

22.27 

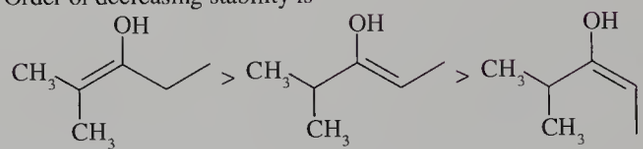
22.28 

Chapter 23

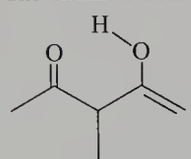
23.2 The high bond energy of the Si—O bond makes the enol derivative more stable.



23.4 Order of decreasing stability is



23.5 The alternate enol has a less substituted double bond.

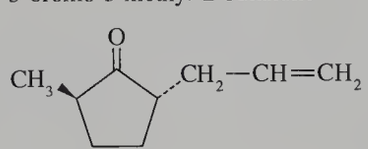


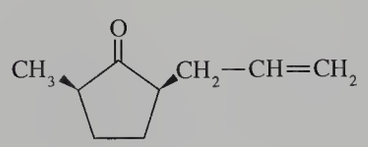
23.6 Both (b) and (c) may enolize. Only (c) produces a racemic mixture.

23.7 2-Methylcyclohexanone can incorporate three deuterium atoms; 3-methylcyclohexanone can incorporate four.

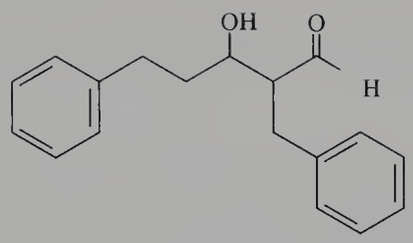
23.8 only (b)

23.10 3-bromo-3-methyl-2-butanone

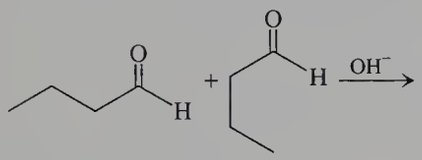
23.12 

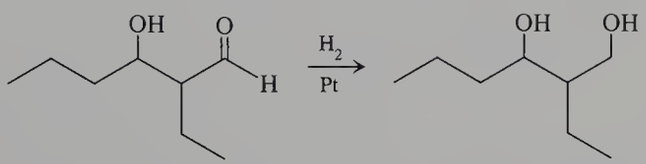


23.13

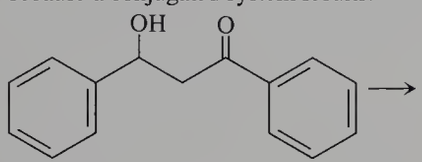


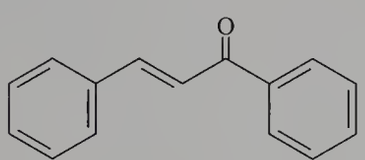
23.15 The starting material is butanal. The aldol product of butanal is reduced to form the diol.



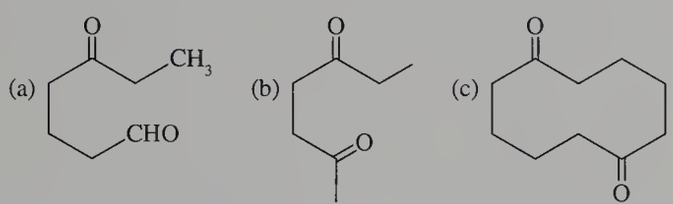


23.16 Formation of a mixed aldol followed by dehydration, which occurs because a conjugated system results.

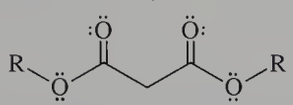




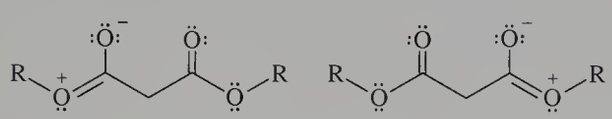
23.18



23.19



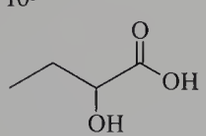
most stable form



equivalent forms

23.21 10^3

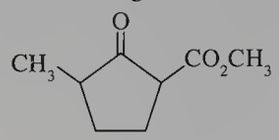
23.22



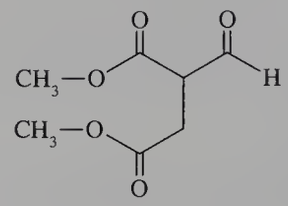
23.24 Pentanenitrile and LDA followed by addition of 2-bromopropane will largely give elimination product. 3-Methylbutanenitrile and LDA followed by addition of 1-bromopropane will give a better yield.

23.25 (c) and (d) cannot undergo a Claisen condensation because neither has two α hydrogen atoms.

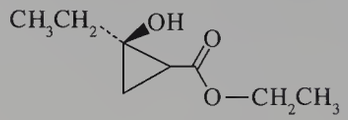
23.28 The α carbon atom on the left does not have two hydrogen atoms, so the condensation reaction using this site to attack the alternate carbonyl carbon atom is reversible. Only the carbanion derived from the α carbon atom on the right can attack the carbonyl carbon atom on the left to give the following product.



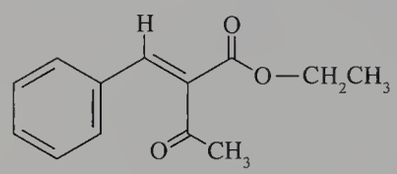
23.29



23.30

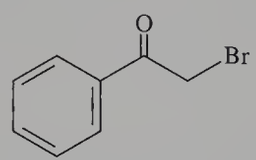


23.31



23.33 React ethyl 2-bromoacetate with acetophenone, then heat with aqueous acid.

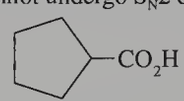
23.35



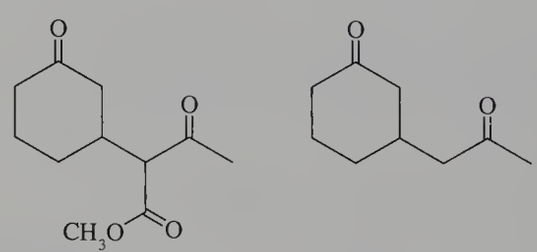
23.36 Alkylate ethyl acetoacetate with 1-bromopropane. Then alkylate the product with 3-bromo-1-propene. Hydrolyze the dialkylated product and decarboxylate the dicarboxylic acid.

23.38 The required alkyl halide, 2-bromo-2-methylbutane, is tertiary and cannot undergo S_N2 displacement.

23.39



23.40

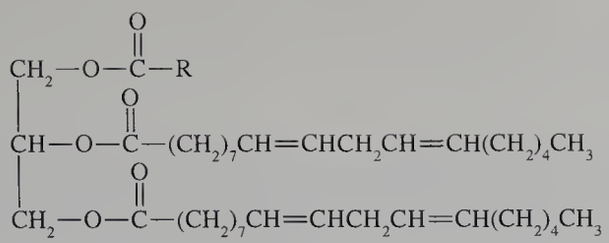


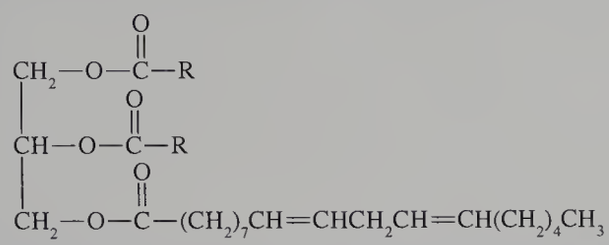
Chapter 24

24.1 Palmitic acid melts 64° higher. The cis double bond of palmitoleic acid decreases London forces.

24.2 The alcohol of the ester is saturated. The carboxylic acid of the ester has 5 double bonds.

24.3 On average, about one and one-half moles of linoleic acid residues per mole of oil must be present.





24.4 a glycerophospholipid of ethanolamine, with palmitic and oleic acid residues

24.5 seven moles, six cycles

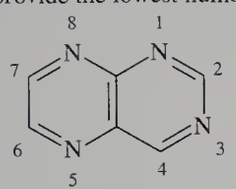
Chapter 25

25.1 The small restricted C—N—C bond angle is severely strained in the transition state where the ideal bond angle is 120°.

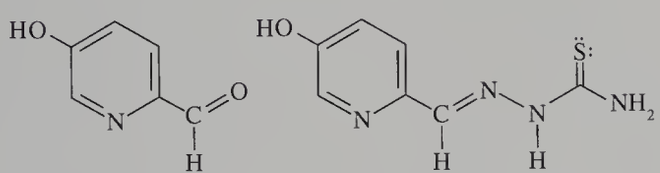
25.2 The atomic radius of nitrogen is smaller than that of carbon. The N—H bond length of methyleneimine should be about 6 pm shorter than the C—H bond length of ethylene, or about 101 pm.

25.4 tertiary amine

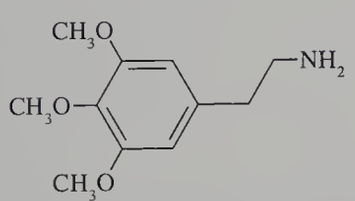
25.5 The two nitrogen atoms in a 1,3 relationship in the ring on the right provide the lowest numbers for the name.



25.6



25.7



25.8 6-bromo-3-chloroindole

25.10 The π electrons move toward nitrogen in resonance forms placing a negative charge on nitrogen and decreasing the electron density on the carbon atoms of the pyridine ring.

25.11 5×10^{-4}; 2×10^{-11}; 10.7

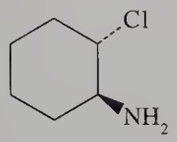
25.12 approximately 3–4, similar to triethylamine and trimethylamine

25.13 (a) Displacement of halide from a 1-halo-2,2-dimethylpropane is sterically hindered. (b) Displacement of halide from the secondary alkyl halide cannot compete with elimination reactions. (c) Aromatic rings do not undergo S_N2 displacement reactions. (d) Attack at the back side of the required bridgehead halogen compound is impossible.

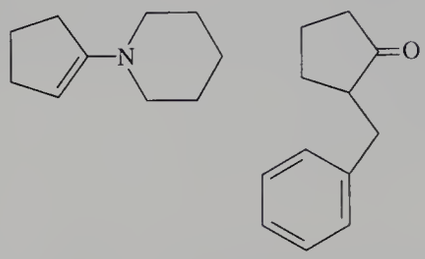
25.15 Reductive amination of 2-phenylethanal using ammonia; reduction of 2-phenylethyl azide with lithium aluminum hydride; reduction of 2-phenylethanamide with lithium aluminum hydride

25.17 Nitrate to give 2,4-dinitrotoluene and then reduce using Sn/HCl.

25.18



25.19



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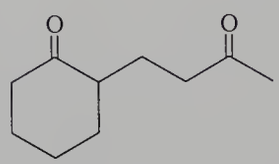
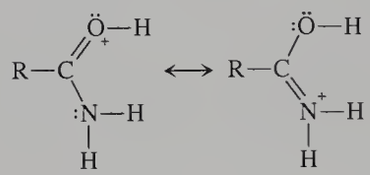
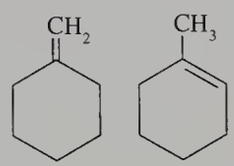


25.22 Protonation on nitrogen gives an ammonium ion with no contributing resonance forms. In fact, loss of resonance associated with the amide results. Protonation on oxygen gives a resonance-stabilized structure.



25.23



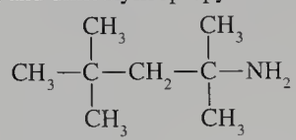
major minor

25.24 They are more acidic as a result of resonance stabilization of the negative charge developed as the C—H bond breaks.

25.25 Elimination would occur preferentially at the β carbon atom of the ethyl group to give ethylene.

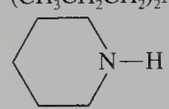
25.26 The tertiary amines diethylmethylamine, dimethylpropylamine, and dimethylisopropylamine

25.27



25.28 $(CH_3CH_2CH_2)_2NH$

25.29

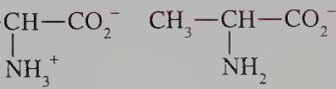


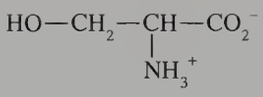
Chapter 26

26.2

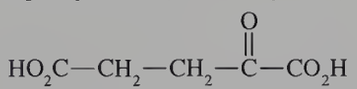
26.3 tryptophan

26.4



26.5 

26.7 2-phenylethanal, sodium cyanide, and ammonium chloride

26.8 

26.10 threonine is N-terminal, arginine is C-terminal; Thr-Lys-Pro-Arg; threonyllysylprolylarginine

26.11 Ala-Gly-Gly; Gly-Ala-Gly; Gly-Gly-Ala

26.12 Tyr, Gly-Gly-Phe, and Leu

26.13 The N-terminal amino acid is tyrosine.

Chapter 27

27.1 negative end toward aromatic ring; 1.6 D

27.3 See Section 25.5. Approximately 4 for secondary amine; greater than 8.75 for substituted pyridine because of electron withdrawal of chlorine, which decreases basicity.

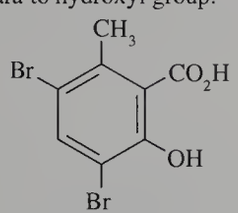
27.4 The nitrogen atom of pyridine ring is more basic. The pyridine ring decreases the basicity of the amino group as a result of electron withdrawal. The nitrogen atom of the amino-substituted pyridine ring has a larger electron density than in pyridine itself because of electron donation by the amino group.

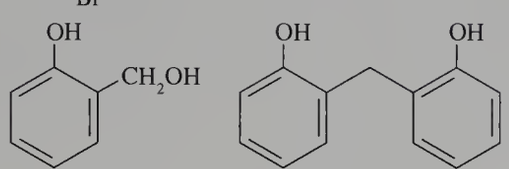
27.5 Compound I is 3,4-dichlorobenzoic acid; compound II is *p*-chloroacetophenone.

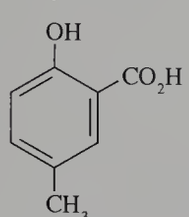
27.7 3-methylaniline and 4-methylaniline in approximately equal amounts resulting from addition of ammonia to either carbon atom of the triple bond in the benzyne intermediate.

27.8 Form phenoxide by adding sodium hydroxide to 2,4,5-trichlorophenol. React phenoxide with ethyl ester of bromoacetic acid. Hydrolyze ester.

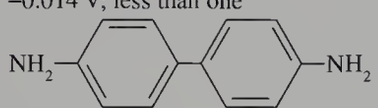
27.9 Ring atom bearing carboxyl group. Bromination occurs ortho and para to hydroxyl group.



27.10 

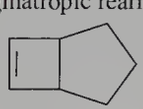
27.11 

27.12 –0.014 V; less than one

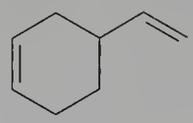
27.13 

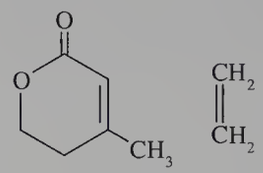
Chapter 28

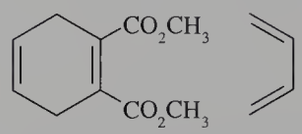
28.1 (a) cycloaddition (b) electrocyclic reaction (c) sigmatropic rearrangement (d) cycloaddition

28.3 

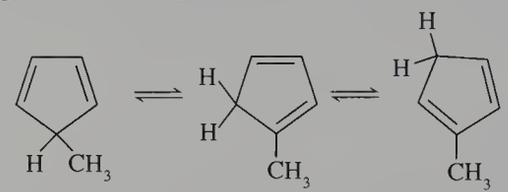
28.4 forbidden because the indicated product is the result of conrotatory motion

28.6 

28.7 

28.8 

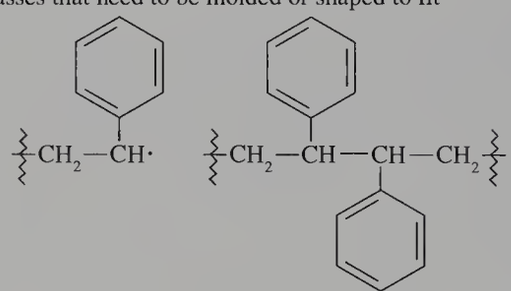
28.10 a series of [1,5] sigmatropic shifts that effectively transfer a hydrogen atom to an adjacent carbon atom

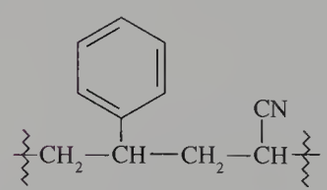


Chapter 29

29.1 the para isomer, because the linear polymer chains should pack efficiently and consequently have extensive intermolecular attractive forces

29.3 thermosetting plastics for handles; thermoplastics for frames of eyeglasses that need to be molded or shaped to fit

29.5 

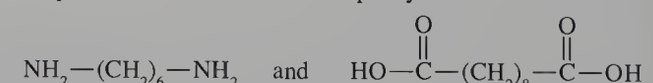
29.6 

29.8 $HO_2C—CH_2—CH_2—CO_2H$

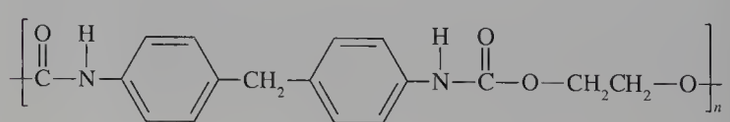
29.9 There would be some competing dehydrobromination reaction of the bromo compound by the alkoxide.

29.10 A hydrolysis reaction of the ester can occur.

29.11 Reaction with diphenyl carbonate would be more favorable because alkyl esters are more stable than phenyl esters.

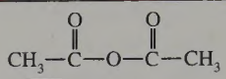
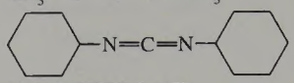
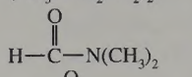
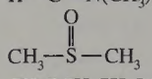
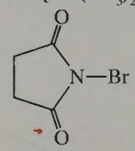
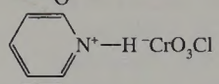
29.12 

29.13 Ketones do not undergo addition reactions as favorably as do aldehydes, and reactions with formaldehyde are especially favorable.

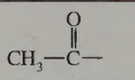
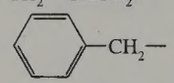
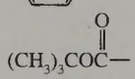
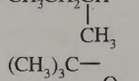
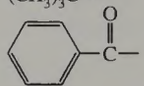
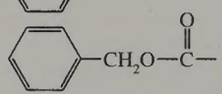
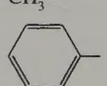
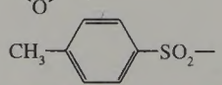
29.14 

Index

Chemical Abbreviations for Reagents and Solvents

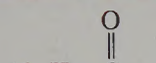
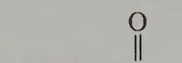
Abbreviation	*Meaning*	*Structure*
Ac_2O	acetic anhydride	
DCC	dicyclohexylcarbodiimide	
DIBAL	diisobutylaluminum hydride	$[(CH_3)_2CHCH_2]_2AlH$
diglyme	bis(2-methoxyethyl) ether	$(CH_3OCH_2CH_2)_2O$
DMF	dimethylformamide	
DMSO	dimethyl sulfoxide	
glyme	1,2-dimethoxyethane	$CH_3OCH_2CH_2OCH_3$
LAH	lithium aluminum hydride	$LiAlH_4$
LDA	lithium diisopropylamide	$LiN[CH(CH_3)_2]_2$
NBS	*N*-bromosuccinimide	
PCC	pyridinium chlorochromate	
THF	tetrahydrofuran	
TMS	tetramethylsilane	$(CH_3)_4Si$

Abbreviations and Structures of Common Groups*

Abbreviation	*Meaning*	*Structure*
Ac	acetyl	
	allyl	$CH_2{=}CHCH_2{-}$
	benzyl	
Boc	*tert*-butylcarbonyl	
n-Bu	butyl	$CH_3CH_2CH_2CH_2{-}$
i-Bu	isobutyl	$(CH_3)_2CHCH_2{-}$
s-Bu	*sec*-butyl	
t-Bu	*tert*-butyl	$(CH_3)_3C{-}$
Bz	benzoyl	
Cbz	benzyloxycarbonyl	
Et	ethyl	$CH_3CH_2{-}$
Me	methyl	$CH_3{-}$
Ph	phenyl	
Pr	propyl	$CH_3CH_2CH_2{-}$
i-Pr	isopropyl	$(CH_3)_2CH{-}$
THP	tetrahydropyranyl	
Ts	tosyl	

*The majority of these abbreviations are not used in this text but are given as references for other publications.

Cahn–Ingold–Prelog Priorities of Groups

1 H—
2 D—
3 CH_3—
4 CH_3CH_2—
5 $(CH_3)_2CHCH_2$—
6 $(CH_3)_3CCH_2$—
7 $(CH_3)_2CH$—
8 CH_2=CH—
9 $(CH_3)_3C$—
10 HC≡C—
11 $HOCH_2$—
12 
13 
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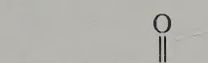
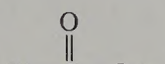
15 
16 HS—CH_2—
17 H_2N—
18 HO—
19 CH_3O—
20 CH_3CH_2O—
21 
22 
23 F—
24 HS—
25 Cl—
26 Br—
27 I—

Average Bond Energies (kJ mole^{-1})

	H	*C*	*N*	*O*	*F*	*Si*	*S*	*Cl*	*Br*	*I*
H	435	414	389	464	586	318	347	431	366	297
C		347	305	359	485	301	272	339	284	217
N			163	222	272			192		
O				196	188	451		217	201	234
F					159	564				
Si						222		380	309	234
S							251	255	217	
Cl								242		
Br									192	
I										150

Bond Dissociation Energies (kJ mole^{-1})

	H	*F*	*Cl*	*Br*	*I*	*OH*	NH_2	CH_3
methyl	439	451	349	293	234	383	355	376
ethyl	422	447	341	289	222	380	355	359
propyl	422	447	341	289	222			
isopropyl	410	443	339	284				
tert-butyl	401		330	264	209			
phenyl	460	527	406	339	272	464	427	423
benzyl	356		301	236	194			314
allyl	364		286	228	171			301
vinyl	452		368	334				426

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