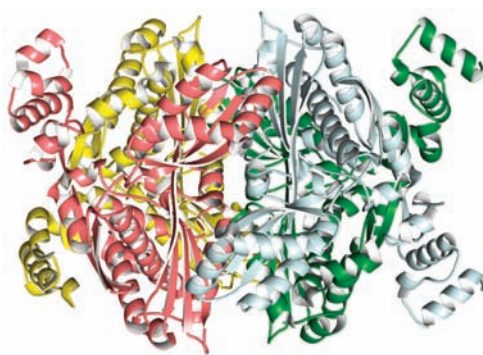


# 1



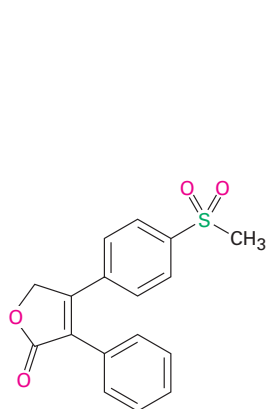
The enzyme HMG-CoA reductase, shown here as a so-called ribbon model, catalyzes a crucial step in the body's synthesis of cholesterol. Understanding how this enzyme functions has led to the development of drugs credited with saving millions of lives.

## Structure and Bonding

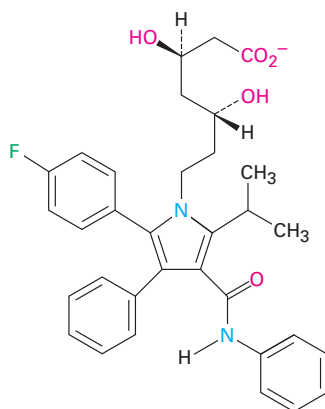
- 1.1 Atomic Structure: The Nucleus
- 1.2 Atomic Structure: Orbitals
- 1.3 Atomic Structure: Electron Configurations
- 1.4 Development of Chemical Bonding Theory
- 1.5 Describing Chemical Bonds: Valence Bond Theory
- 1.6  $sp^3$  Hybrid Orbitals and the Structure of Methane
- 1.7  $sp^3$  Hybrid Orbitals and the Structure of Ethane
- 1.8  $sp^2$  Hybrid Orbitals and the Structure of Ethylene
- 1.9  $sp$  Hybrid Orbitals and the Structure of Acetylene
- 1.10 Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur
- 1.11 Describing Chemical Bonds: Molecular Orbital Theory
- 1.12 Drawing Chemical Structures

A Deeper Look—Organic Foods: Risk versus Benefit

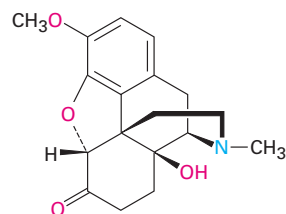
What is organic chemistry, and why should you study it? The answers to these questions are all around you. Every living organism is made of organic chemicals. The proteins that make up your hair, skin, and muscles; the DNA that controls your genetic heritage; the foods that nourish you; and the medicines that heal you are all organic chemicals. Anyone with a curiosity about life and living things, and anyone who wants to be a part of the remarkable advances now occurring in medicine and the biological sciences, must first understand organic chemistry. Look at the following drawings for instance, which show the chemical structures of some molecules whose names might be familiar to you. Although the drawings may appear unintelligible at this point, don't worry. Before long, they'll make perfectly good sense, and you'll soon be drawing similar structures for any substance you're interested in.



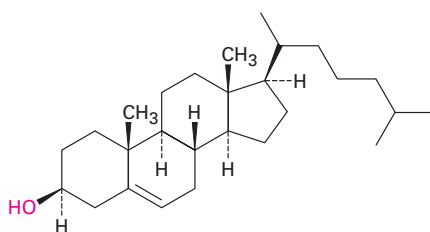
Rofecoxib  
(Vioxx)



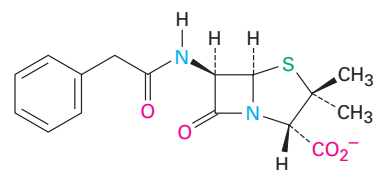
Atorvastatin  
(Lipitor)



Oxycodone  
(OxyContin)



Cholesterol

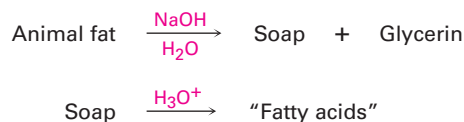


Benzylpenicillin

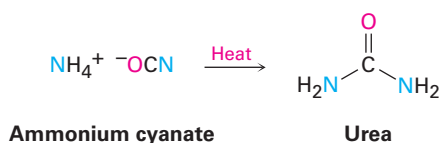
**OWL** Sign in to OWL for Organic Chemistry at [www.cengage.com/owl](http://www.cengage.com/owl) to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

The foundations of organic chemistry date from the mid-1700s, when chemistry was evolving from an alchemist's art into a modern science. Little was known about chemistry at that time, and the behavior of the "organic" substances isolated from plants and animals seemed different from that of the "inorganic" substances found in minerals. Organic compounds were generally low-melting solids and were usually more difficult to isolate, purify, and work with than high-melting inorganic compounds.

To many chemists, the simplest explanation for the difference in behavior between organic and inorganic compounds was that organic compounds contained a peculiar "vital force" as a result of their origin in living sources. Because of this vital force, chemists believed, organic compounds could not be prepared and manipulated in the laboratory as could inorganic compounds. As early as 1816, however, this vitalistic theory received a heavy blow when Michel Chevreul found that soap, prepared by the reaction of alkali with animal fat, could be separated into several pure organic compounds, which he termed *fatty acids*. For the first time, one organic substance (fat) was converted into others (fatty acids plus glycerin) without the intervention of an outside vital force.



Little more than a decade later, the vitalistic theory suffered still further when Friedrich Wöhler discovered in 1828 that it was possible to convert the "inorganic" salt ammonium cyanate into the "organic" substance urea, which had previously been found in human urine.



By the mid-1800s, the weight of evidence was clearly against the vitalistic theory and it was clear that there was no fundamental difference between organic and inorganic compounds. The same fundamental principles explain the behaviors of all substances, regardless of origin or complexity. The only distinguishing characteristic of organic chemicals is that all contain the element carbon.

**Organic chemistry**, then, is the study of carbon compounds. But why is carbon special? Why, of the more than 50 million presently known chemical compounds, do most of them contain carbon? The answers to these questions come from carbon's electronic structure and its consequent position in the periodic table (**Figure 1.1**). As a group 4A element, carbon can share four valence electrons and form four strong covalent bonds. Furthermore, carbon atoms can bond to one another, forming long chains and rings. Carbon, alone of all elements, is able to form an immense diversity of compounds, from the simple methane, with one carbon atom, to the staggeringly complex DNA, which can have more than *100 million* carbons.

**Figure 1.1** The position of carbon in the periodic table. Other elements commonly found in organic compounds are shown in the colors typically used to represent them.

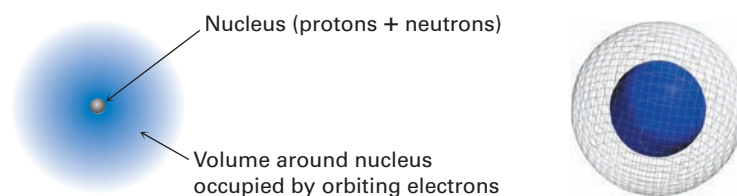
Group 1A												3A 4A 5A 6A 7A					8A
H	2A											B	C	N	O	F	Ne
Li	Be											Al	Si	P	S	Cl	Ar
Na	Mg											Ga	Ge	As	Se	Br	Kr
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	In	Sn	Sb	Te	I	Xe
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	Tl	Pb	Bi	Po	At	Rn
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg						
Fr	Ra	Ac															

Not all carbon compounds are derived from living organisms of course. Modern chemists have developed a remarkably sophisticated ability to design and synthesize new organic compounds in the laboratory—medicines, dyes, polymers, and a host of other substances. Organic chemistry touches the lives of everyone; its study can be a fascinating undertaking.

**Why This Chapter?** We'll ease into the study of organic chemistry by first reviewing some ideas about atoms, bonds, and molecular geometry that you may recall from your general chemistry course. Much of the material in this chapter and the next is likely to be familiar to you, but it's nevertheless a good idea to make sure you understand it before going on.

## 1.1 Atomic Structure: The Nucleus

As you probably know from your general chemistry course, an atom consists of a dense, positively charged nucleus surrounded at a relatively large distance by negatively charged electrons (**Figure 1.2**). The nucleus consists of subatomic particles called protons, which are positively charged, and neutrons, which are electrically neutral. Because an atom is neutral overall, the number of positive protons in the nucleus and the number of negative electrons surrounding the nucleus are the same.



**Figure 1.2** A schematic view of an atom. The dense, positively charged nucleus contains most of the atom's mass and is surrounded by negatively charged electrons. The three-dimensional view on the right shows calculated electron-density surfaces. Electron density increases steadily toward the nucleus and is 40 times greater at the blue solid surface than at the gray mesh surface.

Although extremely small—about  $10^{-14}$  to  $10^{-15}$  meter (m) in diameter—the nucleus nevertheless contains essentially all the mass of the atom. Electrons have negligible mass and circulate around the nucleus at a distance of approximately  $10^{-10}$  m. Thus, the diameter of a typical atom is about  $2 \times 10^{-10}$  m, or

200 picometers (pm), where  $1 \text{ pm} = 10^{-12} \text{ m}$ . To give you an idea of how small this is, a thin pencil line is about 3 million carbon atoms wide. Many organic chemists and biochemists, particularly in the United States, still use the unit *angstrom* ( $\text{\AA}$ ) to express atomic distances, where  $1 \text{ \AA} = 100 \text{ pm} = 10^{-10} \text{ m}$ , but we'll stay with the SI unit picometer in this book.

A specific atom is described by its atomic number ( $Z$ ), which gives the number of protons (or electrons) it contains, and its mass number ( $A$ ), which gives the total number of protons plus neutrons in its nucleus. All the atoms of a given element have the same atomic number—1 for hydrogen, 6 for carbon, 15 for phosphorus, and so on—but they can have different mass numbers depending on how many neutrons they contain. Atoms with the same atomic number but different mass numbers are called **isotopes**.

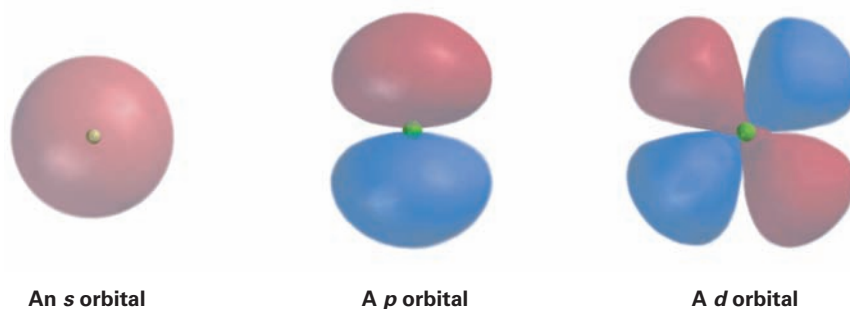
The weighted average mass in atomic mass units (amu) of an element's naturally occurring isotopes is called the element's atomic mass (or atomic weight)—1.008 amu for hydrogen, 12.011 amu for carbon, 30.974 amu for phosphorus, and so on. Atomic masses of the elements are given in the periodic table in the front of this book.

## 1.2 Atomic Structure: Orbitals

How are the electrons distributed in an atom? You might recall from your general chemistry course that, according to the quantum mechanical model, the behavior of a specific electron in an atom can be described by a mathematical expression called a *wave equation*—the same type of expression used to describe the motion of waves in a fluid. The solution to a wave equation is called a *wave function*, or **orbital**, and is denoted by the Greek letter psi ( $\psi$ ).

By plotting the square of the wave function,  $\psi^2$ , in three-dimensional space, an orbital describes the volume of space around a nucleus that an electron is most likely to occupy. You might therefore think of an orbital as looking like a photograph of the electron taken at a slow shutter speed. In such a photo, the orbital would appear as a blurry cloud, indicating the region of space where the electron has been. This electron cloud doesn't have a sharp boundary, but for practical purposes we can set the limits by saying that an orbital represents the space where an electron spends 90% to 95% of its time.

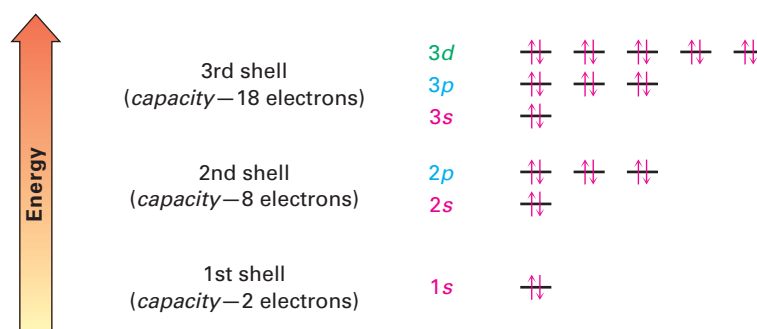
What do orbitals look like? There are four different kinds of orbitals, denoted  $s$ ,  $p$ ,  $d$ , and  $f$ , each with a different shape. Of the four, we'll be concerned primarily with  $s$  and  $p$  orbitals because these are the most common in organic and biological chemistry. An  $s$  orbital is spherical, with the nucleus at its center; a  $p$  orbital is dumbbell-shaped; and four of the five  $d$  orbitals are cloverleaf-shaped, as shown in **Figure 1.3**. The fifth  $d$  orbital is shaped like an elongated dumbbell with a doughnut around its middle.



**Figure 1.3** Representations of  $s$ ,  $p$ , and  $d$  orbitals. An  $s$  orbital is spherical, a  $p$  orbital is dumbbell-shaped, and four of the five  $d$  orbitals are cloverleaf-shaped. Different lobes of  $p$  and  $d$  orbitals are often drawn for convenience as teardrops, but their actual shape is more like that of a doorknob, as indicated.

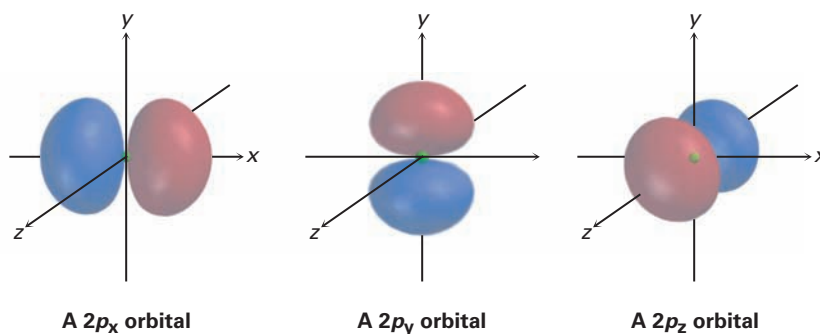
The orbitals in an atom are organized into different **electron shells**, centered around the nucleus and having successively larger size and energy. Different shells contain different numbers and kinds of orbitals, and each orbital within a shell can be occupied by two electrons. The first shell contains only a single  $s$  orbital, denoted  $1s$ , and thus holds only 2 electrons. The second shell contains one  $2s$  orbital and three  $2p$  orbitals and thus holds a total of 8 electrons. The third shell contains a  $3s$  orbital, three  $3p$  orbitals, and five  $3d$  orbitals, for a total capacity of 18 electrons. These orbital groupings and their energy levels are shown in **Figure 1.4**.

**Figure 1.4** The energy levels of electrons in an atom. The first shell holds a maximum of 2 electrons in one  $1s$  orbital; the second shell holds a maximum of 8 electrons in one  $2s$  and three  $2p$  orbitals; the third shell holds a maximum of 18 electrons in one  $3s$ , three  $3p$ , and five  $3d$  orbitals; and so on. The two electrons in each orbital are represented by up and down arrows,  $\uparrow\downarrow$ . Although not shown, the energy level of the  $4s$  orbital falls between  $3p$  and  $3d$ .



The three different  $p$  orbitals within a given shell are oriented in space along mutually perpendicular directions, denoted  $p_x$ ,  $p_y$ , and  $p_z$ . As shown in **Figure 1.5**, the two lobes of each  $p$  orbital are separated by a region of zero electron density called a **node**. Furthermore, the two orbital regions separated by the node have different algebraic signs,  $+$  and  $-$ , in the wave function, as represented by the different colors in Figure 1.5. We'll see in **Section 1.11** that these algebraic signs of different orbital lobes have important consequences with respect to chemical bonding and chemical reactivity.

**Figure 1.5** Shapes of the  $2p$  orbitals. Each of the three mutually perpendicular, dumbbell-shaped orbitals has **two lobes** separated by a node. The two lobes have different algebraic signs in the corresponding wave function, as indicated by the different colors.



## 1.3 Atomic Structure: Electron Configurations

The lowest-energy arrangement, or **ground-state electron configuration**, of an atom is a listing of the orbitals occupied by its electrons. We can predict this arrangement by following three rules.

### RULE 1

The lowest-energy orbitals fill up first, according to the order  $1s \rightarrow 2s \rightarrow 2p \rightarrow 3s \rightarrow 3p \rightarrow 4s \rightarrow 3d$ , a statement called the aufbau principle. Note that the  $4s$  orbital lies between the  $3p$  and  $3d$  orbitals in energy.

### RULE 2

Electrons act in some ways as if they were spinning around an axis, somewhat as the earth spins. This spin can have two orientations, denoted as up ( $\uparrow$ ) and down ( $\downarrow$ ). Only two electrons can occupy an orbital, and they must be of opposite spin, a statement called the Pauli exclusion principle.

### RULE 3

If two or more empty orbitals of equal energy are available, one electron occupies each with spins parallel until all orbitals are half-full, a statement called Hund's rule.

Some examples of how these rules apply are shown in Table 1.1. Hydrogen, for instance, has only one electron, which must occupy the lowest-energy orbital. Thus, hydrogen has a  $1s$  ground-state configuration. Carbon has six electrons and the ground-state configuration  $1s^2 2s^2 2p_x^1 2p_y^1$ , and so forth. Note that a superscript is used to represent the number of electrons in a particular orbital.

**Table 1.1** Ground-State Electron Configurations of Some Elements

Element	Atomic number	Configuration	Element	Atomic number	Configuration
Hydrogen	1	$1s \uparrow$	Phosphorus	15	$3p \uparrow \uparrow \uparrow$
Carbon	6	$2p \uparrow \uparrow \text{---}$			$3s \uparrow \downarrow$
		$2s \uparrow \downarrow$			$2p \uparrow \downarrow \uparrow \downarrow \uparrow \downarrow$
		$1s \uparrow \downarrow$			$2s \uparrow \downarrow$
					$1s \uparrow \downarrow$

### Problem 1.1

Give the ground-state electron configuration for each of the following elements:

- (a) Oxygen      (b) Nitrogen      (c) Sulfur

### Problem 1.2

How many electrons does each of the following elements have in its outermost electron shell?

- (a) Magnesium      (b) Cobalt      (c) Selenium

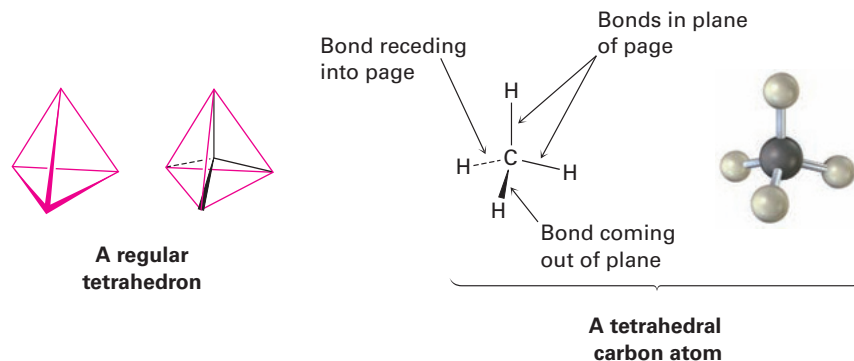
## 1.4 Development of Chemical Bonding Theory

By the mid-1800s, the new science of chemistry was developing rapidly and chemists had begun to probe the forces holding compounds together. In 1858, August Kekulé and Archibald Couper independently proposed that, in all organic compounds, carbon is *tetravalent*—it always forms four bonds when it joins other elements to form stable compounds. Furthermore, said Kekulé, carbon atoms can bond to one another to form extended chains of linked atoms. In 1865, Kekulé provided another major advance when he suggested that carbon chains can double back on themselves to form *rings* of atoms.

Although Kekulé and Couper were correct in describing the tetravalent nature of carbon, chemistry was still viewed in a two-dimensional way until 1874. In that year, Jacobus van't Hoff and Joseph Le Bel added a third dimension to our ideas about organic compounds when they proposed that the four bonds of carbon are not oriented randomly but have specific spatial directions. Van't Hoff went even further and suggested that the four atoms to which carbon is bonded sit at the corners of a regular tetrahedron, with carbon in the center.

A representation of a tetrahedral carbon atom is shown in **Figure 1.6**. Note the conventions used to show three-dimensionality: solid lines represent bonds in the plane of the page, the heavy wedged line represents a bond coming out of the page toward the viewer, and the dashed line represents a bond receding back behind the page, away from the viewer. These representations will be used throughout the text.

**Figure 1.6** A representation of a tetrahedral carbon atom. The solid lines represent bonds in the plane of the paper, the heavy wedged line represents a bond coming out of the plane of the page, and the dashed line represents a bond going back behind the plane of the page.



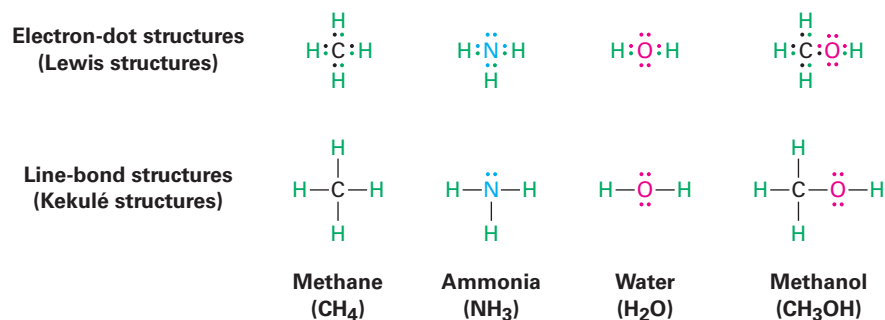
Why, though, do atoms bond together, and how can bonds be described electronically? The *why* question is relatively easy to answer: atoms bond together because the compound that results is more stable and lower in energy than the separate atoms. Energy—usually as heat—always flows out of the chemical system when a bond forms. Conversely, energy must be put into the chemical system to break a bond. Making bonds always releases energy, and breaking bonds always absorbs energy. The *how* question is more difficult. To answer it, we need to know more about the electronic properties of atoms.

We know through observation that eight electrons (an electron *octet*) in an atom's outermost shell, or **valence shell**, impart special stability to the noble-gas elements in group 8A of the periodic table: Ne (2 + 8); Ar (2 + 8 + 8); Kr (2 + 8 + 18 + 8). We also know that the chemistry of main-group elements is governed by their tendency to take on the electron configuration of the nearest

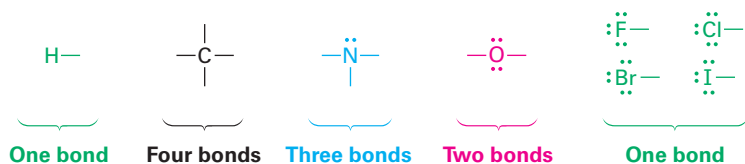
noble gas. The alkali metals in group 1A, for example, achieve a noble-gas configuration by losing the single  $s$  electron from their valence shell to form a cation, while the halogens in group 7A achieve a noble-gas configuration by gaining a  $p$  electron to fill their valence shell and form an anion. The resultant ions are held together in compounds like  $\text{Na}^+ \text{Cl}^-$  by an electrostatic attraction that we call an *ionic bond*.

But how do elements closer to the middle of the periodic table form bonds? Look at methane,  $\text{CH}_4$ , the main constituent of natural gas, for example. The bonding in methane is not ionic because it would take too much energy for carbon ( $1s^2 2s^2 2p^2$ ) either to gain or lose four electrons to achieve a noble-gas configuration. As a result, carbon bonds to other atoms, not by gaining or losing electrons, but by sharing them. Such a shared-electron bond, first proposed in 1916 by G. N. Lewis, is called a **covalent bond**. The neutral collection of atoms held together by covalent bonds is called a **molecule**.

A simple way of indicating the covalent bonds in molecules is to use what are called *Lewis structures*, or **electron-dot structures**, in which the valence-shell electrons of an atom are represented as dots. Thus, hydrogen has one dot representing its  $1s$  electron, carbon has four dots ( $2s^2 2p^2$ ), oxygen has six dots ( $2s^2 2p^4$ ), and so on. A stable molecule results whenever a noble-gas configuration is achieved for all the atoms—eight dots (an octet) for main-group atoms or two dots for hydrogen. Simpler still is the use of *Kekulé structures*, or **line-bond structures**, in which a two-electron covalent bond is indicated as a line drawn between atoms.

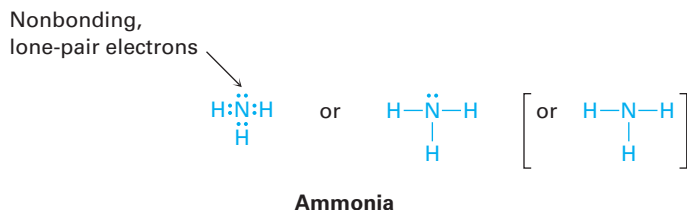


The number of covalent bonds an atom forms depends on how many additional valence electrons it needs to reach a noble-gas configuration. Hydrogen has one valence electron ( $1s$ ) and needs one more to reach the helium configuration ( $1s^2$ ), so it forms one bond. Carbon has four valence electrons ( $2s^2 2p^2$ ) and needs four more to reach the neon configuration ( $2s^2 2p^6$ ), so it forms four bonds. Nitrogen has five valence electrons ( $2s^2 2p^3$ ), needs three more, and forms three bonds; oxygen has six valence electrons ( $2s^2 2p^4$ ), needs two more, and forms two bonds; and the halogens have seven valence electrons, need one more, and form one bond.





Valence electrons that are not used for bonding are called **lone-pair electrons**, or *nonbonding electrons*. The nitrogen atom in ammonia,  $\text{NH}_3$ , for instance, shares six valence electrons in three covalent bonds and has its remaining two valence electrons in a nonbonding lone pair. As a time-saving shorthand, nonbonding electrons are often omitted when drawing line-bond structures, but you still have to keep them in mind since they're often crucial in chemical reactions.



### Worked Example 1.1

#### Predicting the Number of Bonds Formed by an Atom

How many hydrogen atoms does phosphorus bond to in forming phosphine,  $\text{PH}_3$ ?

##### Strategy

Identify the periodic group of phosphorus, and tell from that how many electrons (bonds) are needed to make an octet.

##### Solution

Phosphorus is in group 5A of the periodic table and has five valence electrons. It thus needs to share three more electrons to make an octet and therefore bonds to three hydrogen atoms, giving  $\text{PH}_3$ .

### Worked Example 1.2

#### Drawing Electron-Dot and Line-Bond Structures

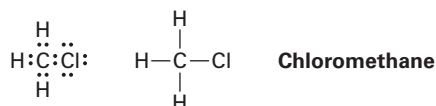
Draw both electron-dot and line-bond structures for chloromethane,  $\text{CH}_3\text{Cl}$ .

##### Strategy

Remember that a bond—that is, a pair of shared electrons—is represented as a line between atoms.

##### Solution

Hydrogen has one valence electron, carbon has four valence electrons, and chlorine has seven valence electrons. Thus, chloromethane is represented as

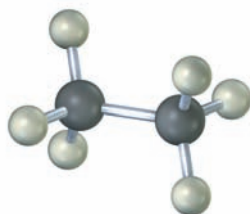


##### Problem 1.3

Draw a molecule of chloroform,  $\text{CHCl}_3$ , using solid, wedged, and dashed lines to show its tetrahedral geometry.

**Problem 1.4**

Convert the following representation of ethane,  $C_2H_6$ , into a conventional drawing that uses solid, wedged, and dashed lines to indicate tetrahedral geometry around each carbon (gray = C, ivory = H).



Ethane

**Problem 1.5**

What are likely formulas for the following substances?

- (a)  $CCl_?$     (b)  $AlH_?$     (c)  $CH_?Cl_2$     (d)  $SiF_?$     (e)  $CH_3NH_?$

**Problem 1.6**

Write line-bond structures for the following substances, showing all nonbonding electrons:

- (a)  $CHCl_3$ , chloroform    (b)  $H_2S$ , hydrogen sulfide  
(c)  $CH_3NH_2$ , methylamine    (d)  $CH_3Li$ , methyllithium

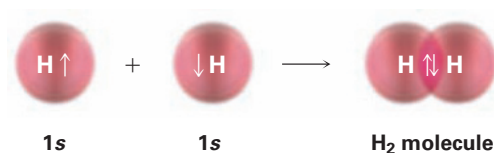
**Problem 1.7**

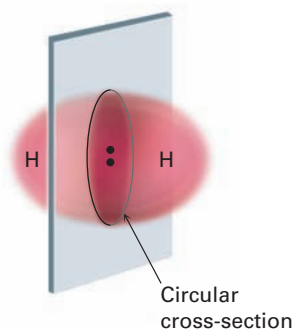
Why can't an organic molecule have the formula  $C_2H_7$ ?

## 1.5 Describing Chemical Bonds: Valence Bond Theory

How does electron sharing lead to bonding between atoms? Two models have been developed to describe covalent bonding: *valence bond theory* and *molecular orbital theory*. Each model has its strengths and weaknesses, and chemists tend to use them interchangeably depending on the circumstances. Valence bond theory is the more easily visualized of the two, so most of the descriptions we'll use in this book derive from that approach.

According to **valence bond theory**, a covalent bond forms when two atoms approach each other closely and a singly occupied orbital on one atom overlaps a singly occupied orbital on the other atom. The electrons are now paired in the overlapping orbitals and are attracted to the nuclei of both atoms, thus bonding the atoms together. In the  $H_2$  molecule, for instance, the H–H bond results from the overlap of two singly occupied hydrogen 1s orbitals.



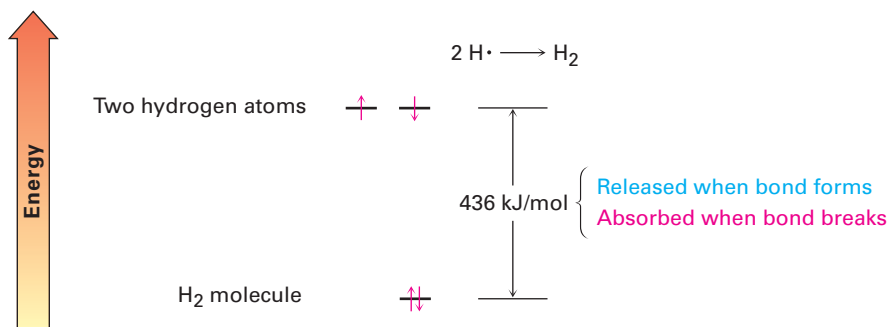


**Figure 1.7** The cylindrical symmetry of the H–H  $\sigma$  bond in an  $H_2$  molecule. The intersection of a plane cutting through the  $\sigma$  bond is a circle.

The overlapping orbitals in the  $H_2$  molecule have the elongated egg shape we might get by pressing two spheres together. If a plane were to pass through the middle of the bond, the intersection of the plane and the overlapping orbitals would be a circle. In other words, the H–H bond is cylindrically symmetrical, as shown in **Figure 1.7**. Such bonds, which are formed by the head-on overlap of two atomic orbitals along a line drawn between the nuclei, are called **sigma ( $\sigma$ ) bonds**.

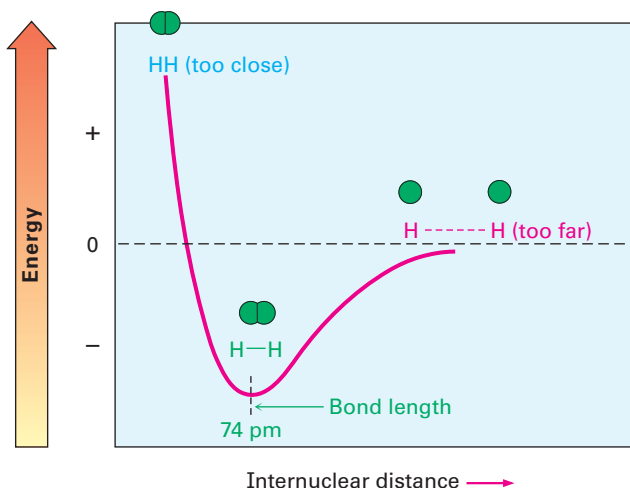
During the bond-forming reaction  $2 H\cdot \rightarrow H_2$ , 436 kJ/mol (104 kcal/mol) of energy is released. Because the product  $H_2$  molecule has 436 kJ/mol less energy than the starting 2  $H\cdot$  atoms, the product is more stable than the reactant and we say that the H–H bond has a **bond strength** of 436 kJ/mol. In other words, we would have to put 436 kJ/mol of energy *into* the H–H bond to break the  $H_2$  molecule apart into H atoms (**Figure 1.8**). [For convenience, we'll generally give energies in both kilocalories (kcal) and the SI unit kilojoules (kJ): 1 kJ = 0.2390 kcal; 1 kcal = 4.184 kJ.]

**Figure 1.8** Relative energy levels of two H atoms and the  $H_2$  molecule. The  $H_2$  molecule has 436 kJ/mol (104 kcal/mol) less energy than the two H atoms, so 436 kJ/mol of energy is **released** when the H–H bond **forms**. Conversely, 436 kJ/mol is **absorbed** when the H–H bond **breaks**.



How close are the two nuclei in the  $H_2$  molecule? If they are too close, they will repel each other because both are positively charged, yet if they're too far apart, they won't be able to share the bonding electrons. Thus, there is an optimum distance between nuclei that leads to maximum stability (**Figure 1.9**). Called the **bond length**, this distance is 74 pm in the  $H_2$  molecule. Every covalent bond has both a characteristic bond strength and bond length.

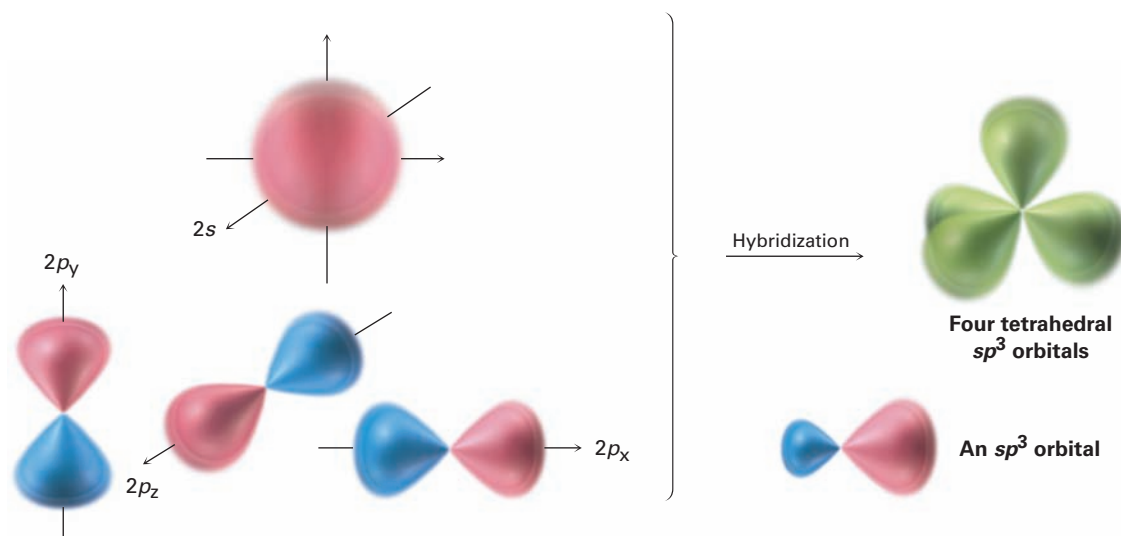
**Figure 1.9** A plot of energy versus internuclear distance for two H atoms. The distance between nuclei at the minimum energy point is the **bond length**.



## 1.6 $sp^3$ Hybrid Orbitals and the Structure of Methane

The bonding in the hydrogen molecule is fairly straightforward, but the situation is more complicated in organic molecules with tetravalent carbon atoms. Take methane,  $\text{CH}_4$ , for instance. As we've seen, carbon has four valence electrons ( $2s^2 2p^2$ ) and forms four bonds. Because carbon uses two kinds of orbitals for bonding,  $2s$  and  $2p$ , we might expect methane to have two kinds of C–H bonds. In fact, though, all four C–H bonds in methane are identical and are spatially oriented toward the corners of a regular tetrahedron (Figure 1.6). How can we explain this?

An answer was provided in 1931 by Linus Pauling, who showed mathematically how an  $s$  orbital and three  $p$  orbitals on an atom can combine, or *hybridize*, to form four equivalent atomic orbitals with tetrahedral orientation. Shown in **Figure 1.10**, these tetrahedrally oriented orbitals are called  **$sp^3$  hybrids**. Note that the superscript 3 in the name  $sp^3$  tells how many of each type of atomic orbital combine to form the hybrid, not how many electrons occupy it.



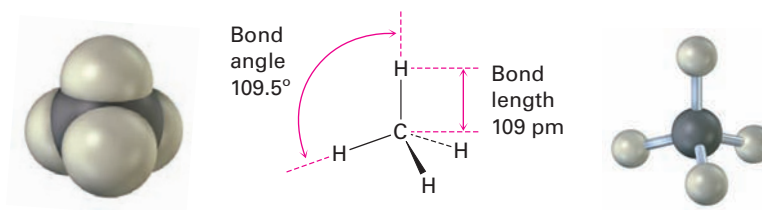
**Figure 1.10** Four  $sp^3$  hybrid orbitals, oriented to the corners of a regular tetrahedron, are formed by combination of an  $s$  orbital and three  $p$  orbitals (red/blue). The  $sp^3$  hybrids have two lobes and are unsymmetrical about the nucleus, giving them a directionality and allowing them to form strong bonds when they overlap an orbital from another atom.

The concept of hybridization explains how carbon forms four equivalent tetrahedral bonds but not why it does so. The shape of the hybrid orbital suggests the answer. When an  $s$  orbital hybridizes with three  $p$  orbitals, the resultant  $sp^3$  hybrid orbitals are unsymmetrical about the nucleus. One of the two lobes is larger than the other and can therefore overlap more effectively with an orbital from another atom to form a bond. As a result,  $sp^3$  hybrid orbitals form stronger bonds than do unhybridized  $s$  or  $p$  orbitals.

The asymmetry of  $sp^3$  orbitals arises because, as noted previously, the two lobes of a  $p$  orbital have different algebraic signs,  $+$  and  $-$ , in the wave function. Thus, when a  $p$  orbital hybridizes with an  $s$  orbital, the positive  $p$  lobe adds to the  $s$  orbital but the negative  $p$  lobe subtracts from the  $s$  orbital. The resultant hybrid orbital is therefore unsymmetrical about the nucleus and is strongly oriented in one direction.

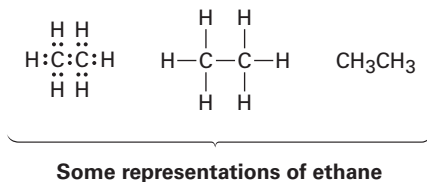
When each of the four identical  $sp^3$  hybrid orbitals of a carbon atom overlaps with the  $1s$  orbital of a hydrogen atom, four identical C–H bonds are formed and methane results. Each C–H bond in methane has a strength of 439 kJ/mol (105 kcal/mol) and a length of 109 pm. Because the four bonds have a specific geometry, we also can define a property called the **bond angle**. The angle formed by each H–C–H is  $109.5^\circ$ , the so-called tetrahedral angle. Methane thus has the structure shown in **Figure 1.11**.

**Figure 1.11** The structure of methane, showing its  $109.5^\circ$  bond angles.

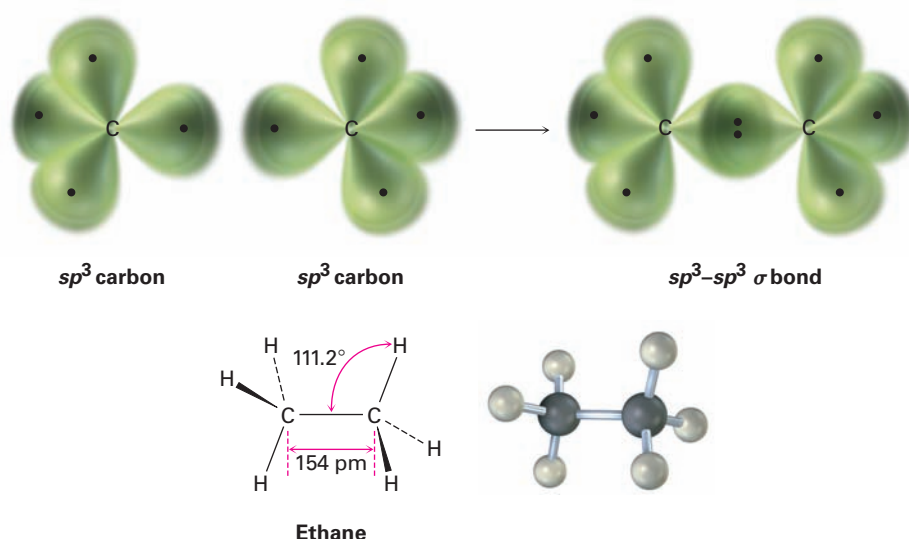


## 1.7 $sp^3$ Hybrid Orbitals and the Structure of Ethane

The same kind of orbital hybridization that accounts for the methane structure also accounts for the bonding together of carbon atoms into chains and rings to make possible many millions of organic compounds. Ethane,  $C_2H_6$ , is the simplest molecule containing a carbon–carbon bond.



We can picture the ethane molecule by imagining that the two carbon atoms bond to each other by  $\sigma$  overlap of an  $sp^3$  hybrid orbital from each (**Figure 1.12**). The remaining three  $sp^3$  hybrid orbitals on each carbon overlap with the  $1s$  orbitals of three hydrogens to form the six C–H bonds. The C–H bonds in ethane are similar to those in methane, although a bit weaker—421 kJ/mol (101 kcal/mol) for ethane versus 439 kJ/mol for methane. The C–C bond is 154 pm long and has a strength of 377 kJ/mol (90 kcal/mol). All the bond angles of ethane are near, although not exactly at, the tetrahedral value of  $109.5^\circ$ .



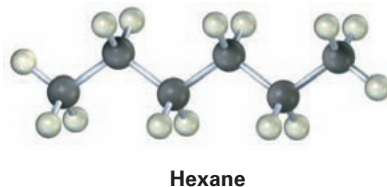
**Figure 1.12** The structure of ethane. The carbon-carbon bond is formed by  $\sigma$  overlap of  $sp^3$  hybrid orbitals. For clarity, the smaller lobes of the  $sp^3$  hybrid orbitals are not shown.

### Problem 1.8

Draw a line-bond structure for propane,  $\text{CH}_3\text{CH}_2\text{CH}_3$ . Predict the value of each bond angle, and indicate the overall shape of the molecule.

### Problem 1.9

Convert the following molecular model of hexane, a component of gasoline, into a line-bond structure (gray = C, ivory = H).



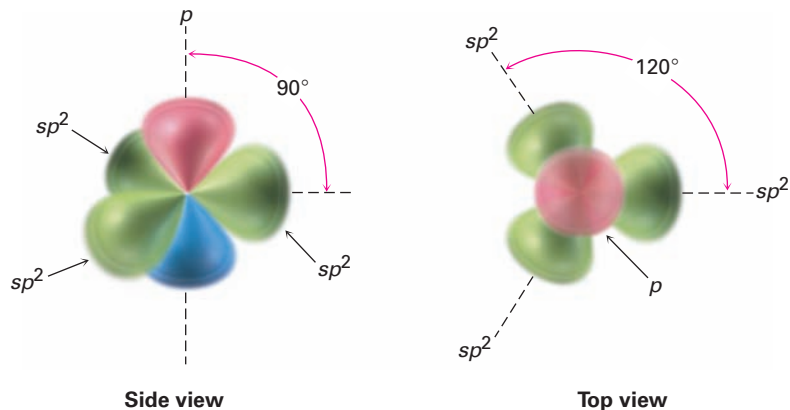
## 1.8 $sp^2$ Hybrid Orbitals and the Structure of Ethylene

The bonds we've seen in methane and ethane are called *single bonds* because they result from the sharing of one electron pair between bonded atoms. It was recognized nearly 150 years ago, however, that carbon atoms can also form *double bonds* by sharing *two* electron pairs between atoms or *triple bonds* by sharing *three* electron pairs. Ethylene, for instance, has the structure  $\text{H}_2\text{C}=\text{CH}_2$  and contains a carbon-carbon double bond, while acetylene has the structure  $\text{HC}\equiv\text{CH}$  and contains a carbon-carbon triple bond.

How are multiple bonds described by valence bond theory? When we discussed  $sp^3$  hybrid orbitals in **Section 1.6**, we said that the four valence-shell atomic orbitals of carbon combine to form four equivalent  $sp^3$  hybrids. Imagine instead that the  $2s$  orbital combines with only *two* of the three available

$2p$  orbitals. Three  $sp^2$  hybrid orbitals result, and one  $2p$  orbital remains unchanged. Like  $sp^3$  hybrids,  $sp^2$  hybrid orbitals are unsymmetrical about the nucleus and are strongly oriented in a specific direction so they can form strong bonds. The three  $sp^2$  orbitals lie in a plane at angles of  $120^\circ$  to one another, with the remaining  $p$  orbital perpendicular to the  $sp^2$  plane, as shown in **Figure 1.13**.

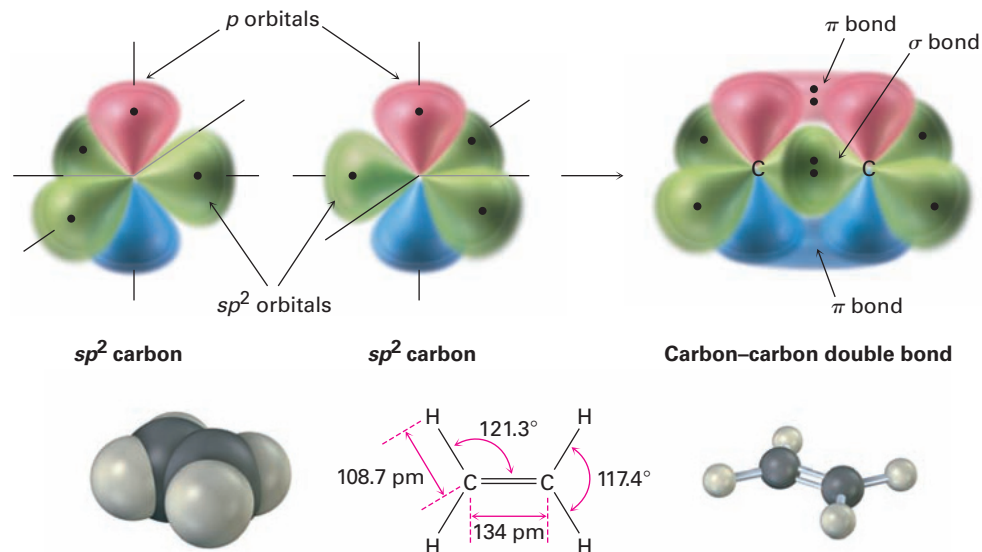
**Figure 1.13**  $sp^2$  Hybridization. The three equivalent  $sp^2$  hybrid orbitals lie in a plane at angles of  $120^\circ$  to one another, and a single unhybridized  $p$  orbital (red/blue) is perpendicular to the  $sp^2$  plane.



When two carbons with  $sp^2$  hybridization approach each other, they form a strong  $\sigma$  bond by  $sp^2$ - $sp^2$  head-on overlap. At the same time, the unhybridized  $p$  orbitals interact by sideways overlap to form what is called a pi ( $\pi$ ) bond. The combination of an  $sp^2$ - $sp^2$   $\sigma$  bond and a  $2p$ - $2p$   $\pi$  bond results in the sharing of four electrons and the formation of a carbon-carbon double bond (**Figure 1.14**). Note that the electrons in the  $\sigma$  bond occupy the region centered between nuclei, while the electrons in the  $\pi$  bond occupy regions above and below a line drawn between nuclei.

To complete the structure of ethylene, four hydrogen atoms form  $\sigma$  bonds with the remaining four  $sp^2$  orbitals. Ethylene thus has a planar structure, with H-C-H and H-C-C bond angles of approximately  $120^\circ$ . (The actual values are  $117.4^\circ$  for the H-C-H bond angle and  $121.3^\circ$  for the H-C-C bond angle.) Each C-H bond has a length of 108.7 pm and a strength of 464 kJ/mol (111 kcal/mol).

**Figure 1.14** The structure of ethylene. One part of the double bond in ethylene results from  $\sigma$  (head-on) overlap of  $sp^2$  orbitals, and the other part results from  $\pi$  (sideways) overlap of unhybridized  $p$  orbitals (red/blue). The  $\pi$  bond has regions of electron density above and below a line drawn between nuclei.



As you might expect, the carbon–carbon double bond in ethylene is both shorter and stronger than the single bond in ethane because it has four electrons bonding the nuclei together rather than two. Ethylene has a C=C bond length of 134 pm and a strength of 728 kJ/mol (174 kcal/mol) versus a C–C length of 154 pm and a strength of 377 kJ/mol for ethane. The carbon–carbon double bond is less than twice as strong as a single bond because the sideways overlap in the  $\pi$  part of the double bond is not as great as the head-on overlap in the  $\sigma$  part.

## Drawing Electron-Dot and Line-Bond Structures

### Worked Example 1.3

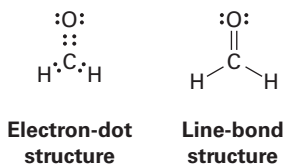
Commonly used in biology as a tissue preservative, formaldehyde,  $\text{CH}_2\text{O}$ , contains a carbon–oxygen double bond. Draw electron-dot and line-bond structures of formaldehyde, and indicate the hybridization of the carbon orbitals.

#### Strategy

We know that hydrogen forms one covalent bond, carbon forms four, and oxygen forms two. Trial and error, combined with intuition, is needed to fit the atoms together.

#### Solution

There is only one way that two hydrogens, one carbon, and one oxygen can combine:



Like the carbon atoms in ethylene, the carbon atom in formaldehyde is in a double bond and its orbitals are therefore  $sp^2$ -hybridized.

#### Problem 1.10

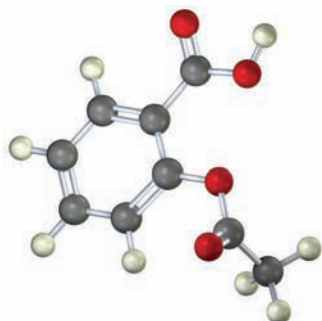
Draw a line-bond structure for propene,  $\text{CH}_3\text{CH}=\text{CH}_2$ . Indicate the hybridization of the orbitals on each carbon, and predict the value of each bond angle.

#### Problem 1.11

Draw a line-bond structure for 1,3-butadiene,  $\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}_2$ . Indicate the hybridization of the orbitals on each carbon, and predict the value of each bond angle.

#### Problem 1.12

Following is a molecular model of aspirin (acetylsalicylic acid). Identify the hybridization of the orbitals on each carbon atom in aspirin, and tell which atoms have lone pairs of electrons (gray = C, red = O, ivory = H).



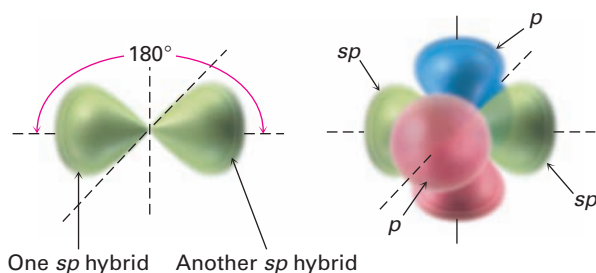
**Aspirin**  
(acetylsalicylic acid)



## 1.9 $sp$ Hybrid Orbitals and the Structure of Acetylene

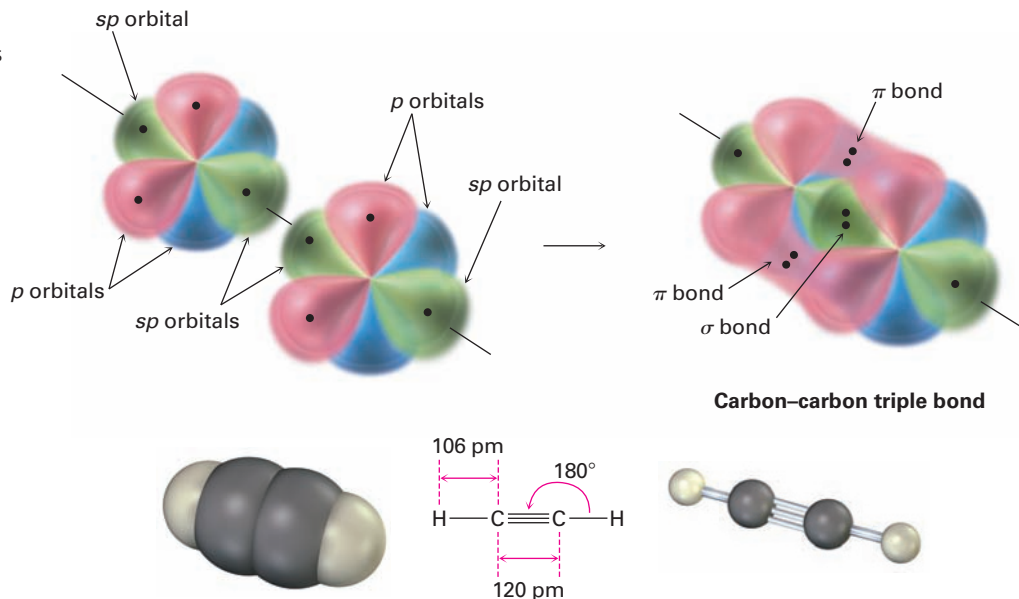
In addition to forming single and double bonds by sharing two and four electrons, respectively, carbon also can form a *triple bond* by sharing six electrons. To account for the triple bond in a molecule such as acetylene,  $\text{H}-\text{C}\equiv\text{C}-\text{H}$ , we need a third kind of hybrid orbital, an  $sp$  hybrid. Imagine that, instead of combining with two or three  $p$  orbitals, a carbon  $2s$  orbital hybridizes with only a single  $p$  orbital. Two  $sp$  hybrid orbitals result, and two  $p$  orbitals remain unchanged. The two  $sp$  orbitals are oriented  $180^\circ$  apart on the  $x$ -axis, while the remaining two  $p$  orbitals are perpendicular on the  $y$ -axis and the  $z$ -axis, as shown in **Figure 1.15**.

**Figure 1.15**  $sp$  Hybridization. The two  $sp$  hybrid orbitals are oriented  $180^\circ$  away from each other, perpendicular to the two remaining  $p$  orbitals (red/blue).



When two  $sp$  carbon atoms approach each other,  $sp$  hybrid orbitals on each carbon overlap head-on to form a strong  $sp$ - $sp$   $\sigma$  bond. At the same time, the  $p_z$  orbitals from each carbon form a  $p_z$ - $p_z$   $\pi$  bond by sideways overlap, and the  $p_y$  orbitals overlap similarly to form a  $p_y$ - $p_y$   $\pi$  bond. The net effect is the sharing of six electrons and formation of a carbon-carbon triple bond. The two remaining  $sp$  hybrid orbitals each form a  $\sigma$  bond with hydrogen to complete the acetylene molecule (**Figure 1.16**).

**Figure 1.16** The structure of acetylene. The two carbon atoms are joined by one  $sp$ - $sp$   $\sigma$  bond and two  $p$ - $p$   $\pi$  bonds.



As suggested by  $sp$  hybridization, acetylene is a linear molecule with H–C–C bond angles of  $180^\circ$ . The C–H bonds have a length of 106 pm and a strength of 558 kJ/mol (133 kcal/mol). The C–C bond length in acetylene is 120 pm, and its strength is about 965 kJ/mol (231 kcal/mol), making it the shortest and strongest of any carbon–carbon bond. A comparison of  $sp$ ,  $sp^2$ , and  $sp^3$  hybridization is given in Table 1.2.

**Table 1.2** Comparison of C–C and C–H Bonds in Methane, Ethane, Ethylene, and Acetylene

Molecule	Bond	Bond strength		Bond length (pm)
		(kJ/mol)	(kcal/mol)	
Methane, CH <sub>4</sub>	( $sp^3$ ) C–H	439	105	109
Ethane, CH <sub>3</sub> CH <sub>3</sub>	( $sp^3$ ) C–C ( $sp^3$ )	377	90	154
	( $sp^3$ ) C–H	421	101	109
Ethylene, H <sub>2</sub> C=CH <sub>2</sub>	( $sp^2$ ) C=C ( $sp^2$ )	728	174	134
	( $sp^2$ ) C–H	464	111	109
Acetylene, HC≡CH	( $sp$ ) C≡C ( $sp$ )	965	231	120
	( $sp$ ) C–H	558	133	106

### Problem 1.13

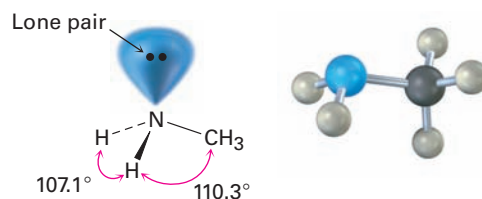
Draw a line-bond structure for propyne, CH<sub>3</sub>C≡CH. Indicate the hybridization of the orbitals on each carbon, and predict a value for each bond angle.

## 1.10 Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur

The valence-bond concept of orbital hybridization described in the previous four sections is not limited to carbon. Covalent bonds formed by other elements can also be described using hybrid orbitals. Look, for instance, at the nitrogen atom in methylamine (CH<sub>3</sub>NH<sub>2</sub>), an organic derivative of ammonia (NH<sub>3</sub>) and the substance responsible for the odor of rotting fish.

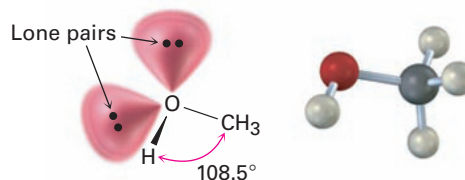
The experimentally measured H–N–H bond angle in methylamine is  $107.1^\circ$ , and the C–N–H bond angle is  $110.3^\circ$ , both of which are close to the  $109.5^\circ$  tetrahedral angle found in methane. We therefore assume that nitrogen forms four  $sp^3$ -hybridized orbitals, just as carbon does. One of the four  $sp^3$  orbitals is occupied by two nonbonding electrons, and the other three hybrid orbitals have one electron each. Overlap of these three half-filled nitrogen orbitals with half-filled orbitals from other atoms (C or H) gives methylamine. Note that the unshared lone pair of electrons in the fourth  $sp^3$  hybrid orbital of nitrogen occupies as much space as an N–H bond does and is very

important to the chemistry of methylamine and other nitrogen-containing organic molecules.



**Methylamine**

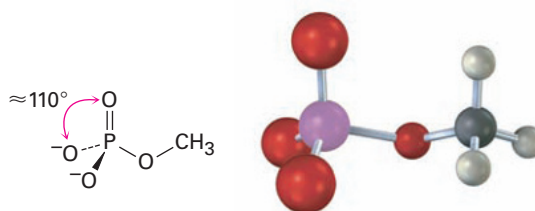
Like the carbon atom in methane and the nitrogen atom in methylamine, the oxygen atom in methanol (methyl alcohol) and many other organic molecules can be described as  $sp^3$ -hybridized. The C–O–H bond angle in methanol is  $108.5^\circ$ , very close to the  $109.5^\circ$  tetrahedral angle. Two of the four  $sp^3$  hybrid orbitals on oxygen are occupied by nonbonding electron lone pairs, and two are used to form bonds.



**Methanol  
(methyl alcohol)**

Phosphorus and sulfur are the third-row analogs of nitrogen and oxygen, and the bonding in both can be described using hybrid orbitals. Because of their positions in the third row, however, both phosphorus and sulfur can expand their outer-shell octets and form more than the typical number of covalent bonds. Phosphorus, for instance, often forms five covalent bonds, and sulfur often forms four.

Phosphorus is most commonly encountered in biological molecules in *organophosphates*, compounds that contain a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon. Methyl phosphate,  $\text{CH}_3\text{OPO}_3^{2-}$ , is the simplest example. The O–P–O bond angle in such compounds is typically in the range  $110$  to  $112^\circ$ , implying  $sp^3$  hybridization for the phosphorus orbitals.



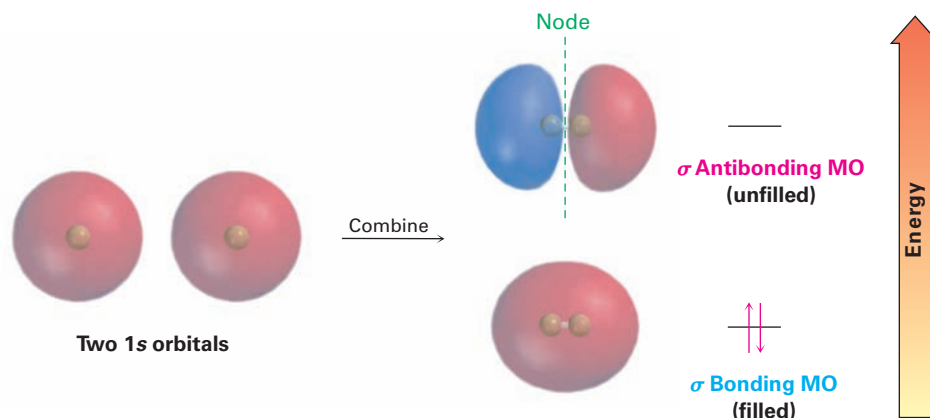
**Methyl phosphate  
(an organophosphate)**



whether unhybridized or hybridized, describes a region of space around an atom where an electron is likely to be found, so a molecular orbital describes a region of space in a *molecule* where electrons are most likely to be found.

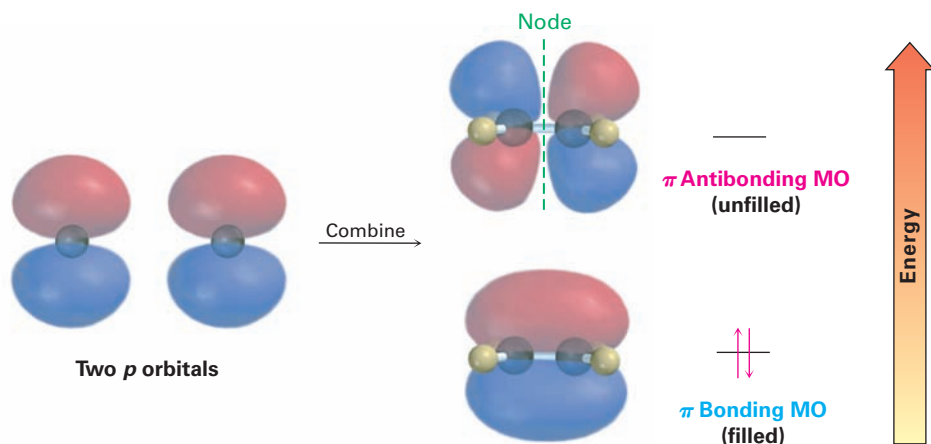
Like an atomic orbital, a molecular orbital has a specific size, shape, and energy. In the  $H_2$  molecule, for example, two singly occupied  $1s$  atomic orbitals combine to form two molecular orbitals. There are two ways for the orbital combination to occur—an additive way and a subtractive way. The additive combination leads to formation of a molecular orbital that is lower in energy and roughly egg-shaped, while the subtractive combination leads to formation of a molecular orbital that is higher in energy and has a node between nuclei (**Figure 1.17**). Note that the additive combination is a *single*, egg-shaped, molecular orbital; it is not the same as the two overlapping  $1s$  atomic orbitals of the valence bond description. Similarly, the subtractive combination is a single molecular orbital with the shape of an elongated dumbbell.

**Figure 1.17** Molecular orbitals of  $H_2$ . Combination of two hydrogen  $1s$  atomic orbitals leads to two  $H_2$  molecular orbitals. The lower-energy, **bonding MO** is filled, and the higher-energy, **antibonding MO** is unfilled.



The additive combination is lower in energy than the two hydrogen  $1s$  atomic orbitals and is called a **bonding MO** because electrons in this MO spend most of their time in the region between the two nuclei, thereby bonding the atoms together. The subtractive combination is higher in energy than the two hydrogen  $1s$  orbitals and is called an **antibonding MO** because any electrons it contains *can't* occupy the central region between the nuclei, where there is a node, and can't contribute to bonding. The two nuclei therefore repel each other.

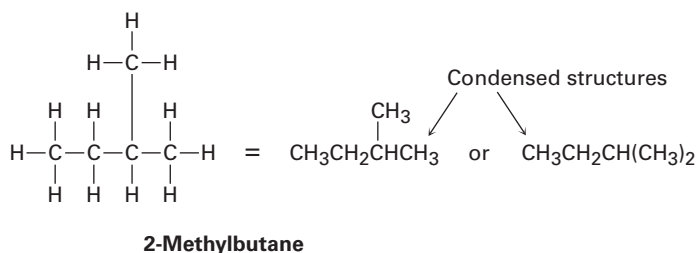
Just as bonding and antibonding  $\sigma$  molecular orbitals result from the head-on combination of two  $s$  atomic orbitals in  $H_2$ , so bonding and antibonding  $\pi$  molecular orbitals result from the sideways combination of two  $p$  atomic orbitals in ethylene. As shown in **Figure 1.18**, the lower-energy,  $\pi$  bonding MO has no node between nuclei and results from combination of  $p$  orbital lobes with the same algebraic sign. The higher-energy,  $\pi$  antibonding MO has a node between nuclei and results from combination of lobes with opposite algebraic signs. Only the bonding MO is occupied; the higher-energy, antibonding MO is vacant. We'll see in Chapters 14, 15, and 30 that molecular orbital theory is particularly useful for describing  $\pi$  bonds in compounds that have more than one double bond.



**Figure 1.18** A molecular orbital description of the C–C  $\pi$  bond in ethylene. The lower-energy,  $\pi$  bonding MO results from an additive combination of  $p$  orbital lobes with the same algebraic sign and is filled. The higher-energy,  $\pi$  antibonding MO results from a subtractive combination of  $p$  orbital lobes with the opposite algebraic signs and is unfilled.

## 1.12 Drawing Chemical Structures

Let's cover just one more point before ending this introductory chapter. In the structures we've been drawing until now, a line between atoms has represented the two electrons in a covalent bond. Drawing every bond and every atom is tedious, however, so chemists have devised several shorthand ways for writing structures. In **condensed structures**, carbon–hydrogen and carbon–carbon single bonds aren't shown; instead, they're understood. If a carbon has three hydrogens bonded to it, we write  $\text{CH}_3$ ; if a carbon has two hydrogens bonded to it, we write  $\text{CH}_2$ ; and so on. The compound called 2-methylbutane, for example, is written as follows:



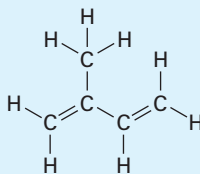
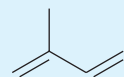
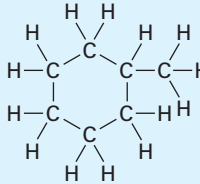
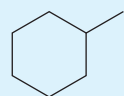
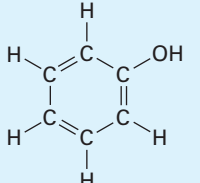
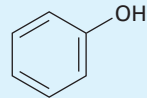
Notice that the horizontal bonds between carbons aren't shown in condensed structures—the  $\text{CH}_3$ ,  $\text{CH}_2$ , and  $\text{CH}$  units are simply placed next to each other—but the vertical carbon–carbon bond in the first of the condensed structures drawn above is shown for clarity. Notice also in the second of the condensed structures that the two  $\text{CH}_3$  units attached to the  $\text{CH}$  carbon are grouped together as  $(\text{CH}_3)_2$ .

Even simpler than condensed structures are **skeletal structures** such as those shown in Table 1.3. The rules for drawing skeletal structures are straightforward.

### RULE 1

Carbon atoms aren't usually shown. Instead, a carbon atom is assumed to be at each intersection of two lines (bonds) and at the end of each line. Occasionally, a carbon atom might be indicated for emphasis or clarity.

**Table 1.3** Kekulé and Skeletal Structures for Some Compounds

Compound	Kekulé structure	Skeletal structure
Isoprene, $C_5H_8$		
Methylcyclohexane, $C_7H_{14}$		
Phenol, $C_6H_6O$		

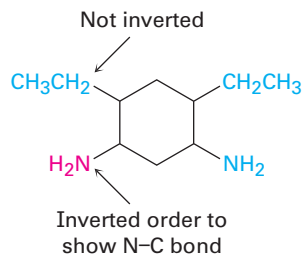
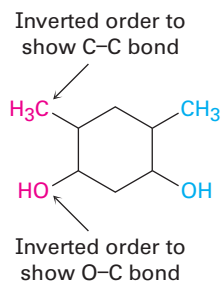
**RULE 2**

Hydrogen atoms bonded to carbon aren't shown. Because carbon always has a valence of 4, we mentally supply the correct number of hydrogen atoms for each carbon.

**RULE 3**

Atoms other than carbon and hydrogen *are* shown.

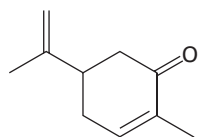
One further comment: although such groupings as  $-CH_3$ ,  $-OH$ , and  $-NH_2$  are usually written with the C, O, or N atom first and the H atom second, the order of writing is sometimes inverted to  $H_3C-$ ,  $HO-$ , and  $H_2N-$  if needed to make the bonding connections in a molecule clearer. Larger units such as  $-CH_2CH_3$  are not inverted, though; we don't write  $H_3CH_2C-$  because it would be confusing. There are, however, no well-defined rules that cover all cases; it's largely a matter of preference.



## Interpreting a Line-Bond Structure

### Worked Example 1.4

Carvone, a substance responsible for the odor of spearmint, has the following structure. Tell how many hydrogens are bonded to each carbon, and give the molecular formula of carvone.

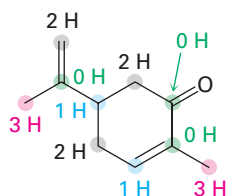


Carvone

### Strategy

The end of a line represents a carbon atom with 3 hydrogens,  $\text{CH}_3$ ; a two-way intersection is a carbon atom with 2 hydrogens,  $\text{CH}_2$ ; a three-way intersection is a carbon atom with 1 hydrogen,  $\text{CH}$ ; and a four-way intersection is a carbon atom with no attached hydrogens.

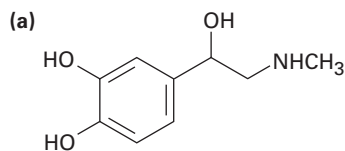
### Solution



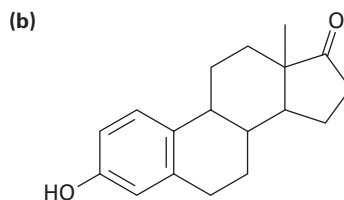
Carvone ( $\text{C}_{10}\text{H}_{14}\text{O}$ )

### Problem 1.15

Tell how many hydrogens are bonded to each carbon in the following compounds, and give the molecular formula of each substance:



Adrenaline



Estrone (a hormone)

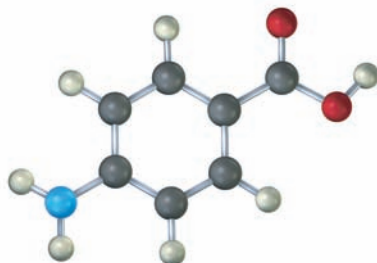
### Problem 1.16

Propose skeletal structures for compounds that satisfy the following molecular formulas. There is more than one possibility in each case.

- (a)  $\text{C}_5\text{H}_{12}$     (b)  $\text{C}_2\text{H}_7\text{N}$     (c)  $\text{C}_3\text{H}_6\text{O}$     (d)  $\text{C}_4\text{H}_9\text{Cl}$

### Problem 1.17

The following molecular model is a representation of *para*-aminobenzoic acid (PABA), the active ingredient in many sunscreens. Indicate the positions of the multiple bonds, and draw a skeletal structure (gray = C, red = O, blue = N, ivory = H).



*para*-Aminobenzoic acid  
(PABA)



## Organic Foods: Risk versus Benefit

### A DEEPER LOOK

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How dangerous is the pesticide being sprayed on this crop?

Contrary to what you may hear in supermarkets or on television, *all* foods are organic—that is, complex mixtures of organic molecules. Even so, when applied to food, the word *organic* has come to mean an absence of synthetic chemicals, typically pesticides, antibiotics, and preservatives. How concerned should we be about traces of pesticides in the food we eat? Or toxins in the water we drink? Or pollutants in the air we breathe?

Life is not risk-free—we all take many risks each day without even thinking about it. We decide to ride a bike rather than drive, even though there is a ten times greater likelihood per mile of dying in a bicycling accident than in a car. We decide to walk down stairs rather than take an elevator, even though 7000 people die from falls each year in the United States. Some of us decide to smoke cigarettes, even though it increases our chance of getting cancer by 50%. But what about risks from chemicals like pesticides?

One thing is certain: without pesticides, whether they target weeds (herbicides), insects (insecticides), or molds and fungi (fungicides), crop production would drop significantly, food prices would increase, and famines would occur in less developed parts of the world. Take the herbicide atrazine, for instance. In the United States alone, approximately 100 million pounds of atrazine are used each year to kill weeds in corn, sorghum, and sugarcane fields, greatly improving the yields of these crops. Nevertheless, the use of atrazine continues to be a concern because traces persist in the environment. Indeed, heavy atrazine exposure *can* pose health risks to humans and some animals, but the United States Environmental Protection Agency (EPA) is unwilling to ban its use because doing so would result in significantly lower crop yields and increased food costs, and because there is no suitable alternative herbicide available.

How can the potential hazards from a chemical like atrazine be determined? Risk evaluation of chemicals is carried out by exposing test animals, usually mice or rats, to the chemical and then monitoring the animals for signs of harm. To limit the expense and time needed, the amounts administered are typically hundreds or thousands of times greater than those a person might normally encounter. The results obtained in animal tests are then distilled into a single number called an  $LD_{50}$ , the amount of substance per kilogram body weight that is a lethal dose for 50% of the test animals. For atrazine, the  $LD_{50}$  value is between 1 and 4 g/kg depending on the animal species. Aspirin, for comparison, has an  $LD_{50}$  of 1.1 g/kg, and ethanol (ethyl alcohol) has an  $LD_{50}$  of 10.6 g/kg.

Table 1.4 lists values for some other familiar substances. The lower the value, the more toxic the substance. Note, though, that  $LD_{50}$  values tell only about the effects of heavy

**Table 1.4** Some  $LD_{50}$  Values

Substance	$LD_{50}$ (g/kg)	Substance	$LD_{50}$ (g/kg)
Strychnine	0.005	Chloroform	1.2
Arsenic trioxide	0.015	Iron(II) sulfate	1.5
DDT	0.115	Ethyl alcohol	10.6
Aspirin	1.1	Sodium cyclamate	17

(continued)

exposure for a relatively short time. They say nothing about the risks of long-term exposure, such as whether the substance can cause cancer or interfere with development in the unborn.

So, should we still use atrazine? All decisions involve tradeoffs, and the answer is rarely obvious. Does the benefit of increased food production outweigh possible health risks of a pesticide? Do the beneficial effects of a new drug outweigh a potentially dangerous side effect in a small number of users? Different people will have different opinions, but an honest evaluation of facts is surely the best way to start. At present, atrazine is approved for continued use in the United States because the EPA believes that the benefits of increased food production outweigh possible health risks. At the same time, though, the use of atrazine is being phased out in Europe.

## Summary

The purpose of this chapter has been to get you up to speed—to review some ideas about atoms, bonds, and molecular geometry. As we've seen, **organic chemistry** is the study of carbon compounds. Although a division into organic and inorganic chemistry occurred historically, there is no scientific reason for the division.

An atom consists of a positively charged nucleus surrounded by one or more negatively charged electrons. The electronic structure of an atom can be described by a quantum mechanical wave equation, in which electrons are considered to occupy **orbitals** around the nucleus. Different orbitals have different energy levels and different shapes. For example, *s* orbitals are spherical and *p* orbitals are dumbbell-shaped. The **ground-state electron configuration** of an atom can be found by assigning electrons to the proper orbitals, beginning with the lowest-energy ones.

A **covalent bond** is formed when an electron pair is shared between atoms. According to **valence bond theory**, electron sharing occurs by overlap of two atomic orbitals. According to **molecular orbital (MO) theory**, bonds result from the mathematical combination of atomic orbitals to give molecular orbitals, which belong to the entire molecule. Bonds that have a circular cross-section and are formed by head-on interaction are called **sigma ( $\sigma$ ) bonds**; bonds formed by sideways interaction of *p* orbitals are called **pi ( $\pi$ ) bonds**.

In the valence bond description, carbon uses hybrid orbitals to form bonds in organic molecules. When forming only single bonds with tetrahedral geometry, carbon uses four equivalent  **$sp^3$  hybrid orbitals**. When forming a double bond with planar geometry, carbon uses three equivalent  **$sp^2$  hybrid orbitals** and one unhybridized *p* orbital. When forming a triple bond with linear geometry, carbon uses two equivalent  **$sp$  hybrid orbitals** and two unhybridized *p* orbitals. Other atoms such as nitrogen, phosphorus, oxygen, and sulfur also use hybrid orbitals to form strong, oriented bonds.

Organic molecules are usually drawn using either condensed structures or skeletal structures. In **condensed structures**, carbon-carbon and carbon-hydrogen bonds aren't shown. In **skeletal structures**, only the bonds and not the atoms are shown. A carbon atom is assumed to be at the ends and at the junctions of lines (bonds), and the correct number of hydrogens is mentally supplied.

## Key words

antibonding MO, 20  
 bond angle, 12  
 bond length, 10  
 bond strength, 10  
 bonding MO, 20  
 condensed structure, 21  
 covalent bond, 7  
 electron-dot structure, 7  
 electron shell, 4  
 ground-state electron configuration, 5  
 isotope, 3  
 line-bond structure, 7  
 lone-pair electrons, 8  
 molecular orbital (MO) theory, 19  
 molecule, 7  
 node, 4  
 orbital, 3  
 organic chemistry, 1  
 pi ( $\pi$ ) bond, 14  
 sigma ( $\sigma$ ) bond, 10  
 skeletal structure, 21  
 $sp$  hybrid orbital, 16  
 $sp^2$  hybrid orbital, 14  
 $sp^3$  hybrid orbital, 11  
 valence bond theory, 9  
 valence shell, 6


## Working Problems

There's no surer way to learn organic chemistry than by working problems. Although careful reading and rereading of this text are important, reading alone isn't enough. You must also be able to use the information you've read and be able to apply your knowledge in new situations. Working problems gives you practice at doing this.

Each chapter in this book provides many problems of different sorts. The in-chapter problems are placed for immediate reinforcement of ideas just learned, while end-of-chapter problems provide additional practice and are of several types. They begin with a short section called "Visualizing Chemistry," which helps you "see" the microscopic world of molecules and provides practice for working in three dimensions. After the visualizations are many "Additional Problems," which are organized by topic. Early problems are primarily of the drill type, providing an opportunity for you to practice your command of the fundamentals. Later problems tend to be more thought-provoking, and some are real challenges.

As you study organic chemistry, take the time to work the problems. Do the ones you can, and ask for help on the ones you can't. If you're stumped by a particular problem, check the accompanying *Study Guide and Solutions Manual* for an explanation that will help clarify the difficulty. Working problems takes effort, but the payoff in knowledge and understanding is immense.

## Exercises

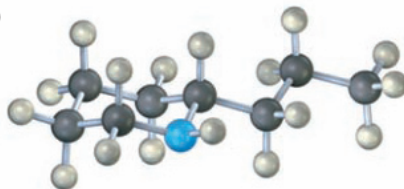
 Interactive versions of these problems are assignable in OWL for Organic Chemistry.

## Visualizing Chemistry

(Problems 1.1–1.17 appear within the chapter.)

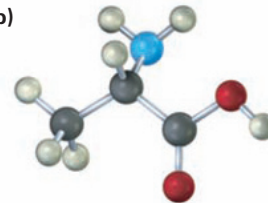
- 1.18** Convert each of the following molecular models into a skeletal structure, and give the formula of each. Only the connections between atoms are shown; multiple bonds are not indicated (gray = C, red = O, blue = N, ivory = H).

(a)



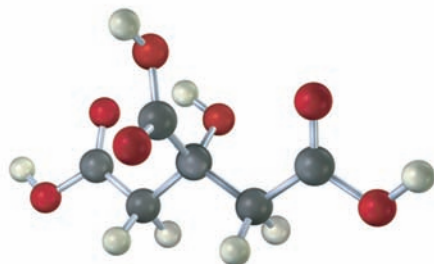
Coniine (the toxic substance in poison hemlock)

(b)

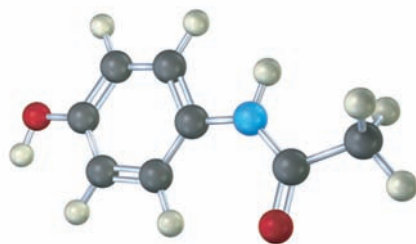


Alanine (an amino acid)

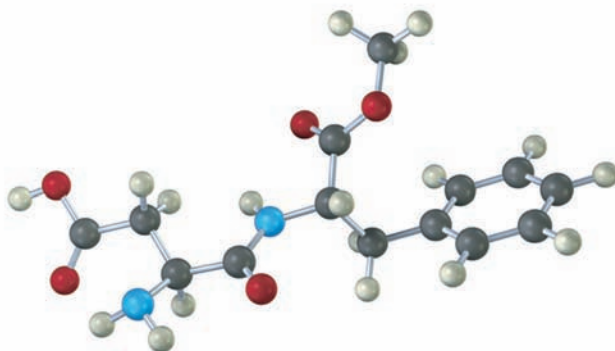
- 1.19** The following model is a representation of citric acid, the key substance in the so-called citric acid cycle by which food molecules are metabolized in the body. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure by indicating the positions of multiple bonds and lone-pair electrons (gray = C, red = O, ivory = H).



- 1.20** The following model is a representation of acetaminophen, a pain reliever sold in drugstores under a variety of names, including Tylenol. Identify the hybridization of each carbon atom in acetaminophen, and tell which atoms have lone pairs of electrons (gray = C, red = O, blue = N, ivory = H).



- 1.21** The following model is a representation of aspartame,  $C_{14}H_{18}N_2O_5$ , known commercially under many names, including NutraSweet. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure for aspartame, and indicate the positions of multiple bonds (gray = C, red = O, blue = N, ivory = H).



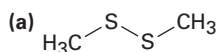
## Additional Problems

### Electron Configurations

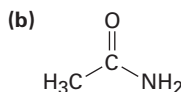
- 1.22** How many valence electrons does each of the following dietary trace elements have?  
 (a) Zinc                    (b) Iodine                    (c) Silicon                    (d) Iron
- 1.23** Give the ground-state electron configuration for each of the following elements:  
 (a) Potassium            (b) Arsenic                    (c) Aluminum                    (d) Germanium

### Electron-Dot and Line-Bond Structures

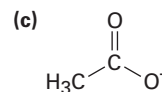
- 1.24** What are likely formulas for the following molecules?  
 (a)  $\text{NH}_? \text{OH}$             (b)  $\text{AlCl}_?$                     (c)  $\text{CF}_2 \text{Cl}_?$                     (d)  $\text{CH}_? \text{O}$
- 1.25** Why can't molecules with the following formulas exist?  
 (a)  $\text{CH}_5$                     (b)  $\text{C}_2\text{H}_6\text{N}$                     (c)  $\text{C}_3\text{H}_5\text{Br}_2$
- 1.26** Draw an electron-dot structure for acetonitrile,  $\text{C}_2\text{H}_3\text{N}$ , which contains a carbon–nitrogen triple bond. How many electrons does the nitrogen atom have in its outer shell? How many are bonding, and how many are nonbonding?
- 1.27** Draw a line-bond structure for vinyl chloride,  $\text{C}_2\text{H}_3\text{Cl}$ , the starting material from which PVC [poly(vinyl chloride)] plastic is made.
- 1.28** Fill in any nonbonding valence electrons that are missing from the following structures:



**Dimethyl disulfide**

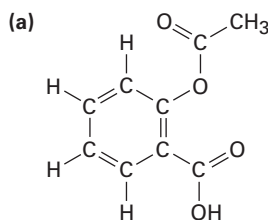


**Acetamide**

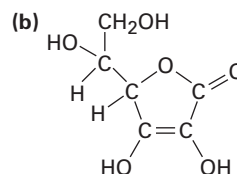


**Acetate ion**

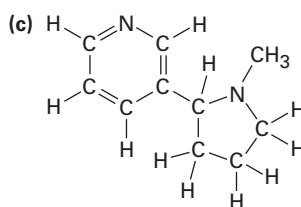
- 1.29** Convert the following line-bond structures into molecular formulas:



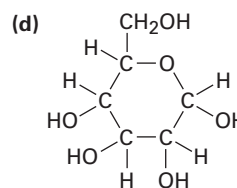
**Aspirin**  
(acetylsalicylic acid)



**Vitamin C**  
(ascorbic acid)



**Nicotine**

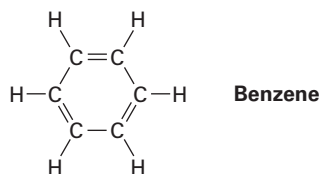


**Glucose**

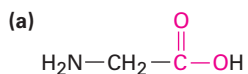
- 1.30** Convert the following molecular formulas into line-bond structures that are consistent with valence rules:
- (a)  $C_3H_8$                       (b)  $CH_5N$   
 (c)  $C_2H_6O$  (2 possibilities)    (d)  $C_3H_7Br$  (2 possibilities)  
 (e)  $C_2H_4O$  (3 possibilities)    (f)  $C_3H_9N$  (4 possibilities)
- 1.31** Draw a three-dimensional representation of the oxygen-bearing carbon atom in ethanol,  $CH_3CH_2OH$ , using the standard convention of solid, wedged, and dashed lines.
- 1.32** Oxaloacetic acid, an important intermediate in food metabolism, has the formula  $C_4H_4O_5$  and contains three  $C=O$  bonds and two  $O-H$  bonds. Propose two possible structures.
- 1.33** Draw structures for the following molecules, showing lone pairs:
- (a) Acrylonitrile,  $C_3H_3N$ , which contains a carbon-carbon double bond and a carbon-nitrogen triple bond  
 (b) Ethyl methyl ether,  $C_3H_8O$ , which contains an oxygen atom bonded to two carbons  
 (c) Butane,  $C_4H_{10}$ , which contains a chain of four carbon atoms  
 (d) Cyclohexene,  $C_6H_{10}$ , which contains a ring of six carbon atoms and one carbon-carbon double bond
- 1.34** Potassium methoxide,  $KOCH_3$ , contains both covalent and ionic bonds. Which do you think is which?

### Hybridization

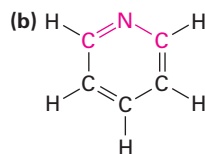
- 1.35** What is the hybridization of each carbon atom in acetonitrile (Problem 1.26)?
- 1.36** What kind of hybridization do you expect for each carbon atom in the following molecules?
- (a) Propane,  $CH_3CH_2CH_3$                       (b) 2-Methylpropene,  $\begin{array}{c} CH_3 \\ | \\ CH_3C=CH_2 \end{array}$
- (c) 1-Butene-3-yne,  $H_2C=CH-C\equiv CH$     (d) Acetic acid,  $\begin{array}{c} O \\ || \\ CH_3COH \end{array}$
- 1.37** What is the shape of benzene, and what hybridization do you expect for each carbon?



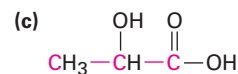
**1.38** What bond angles do you expect for each of the following, and what kind of hybridization do you expect for the central atom in each?



**Glycine**  
(an amino acid)



**Pyridine**

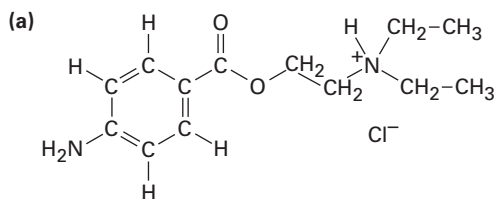


**Lactic acid**  
(in sour milk)

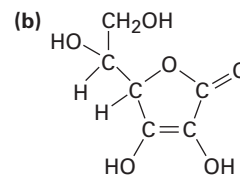
**1.39** Propose structures for molecules that meet the following descriptions:

- (a) Contains two  $sp^2$ -hybridized carbons and two  $sp^3$ -hybridized carbons  
 (b) Contains only four carbons, all of which are  $sp^2$ -hybridized  
 (c) Contains two  $sp$ -hybridized carbons and two  $sp^2$ -hybridized carbons

**1.40** What kind of hybridization do you expect for each carbon atom in the following molecules?

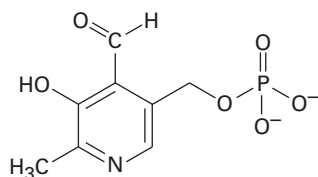


**Procaine**



**Vitamin C**  
(ascorbic acid)

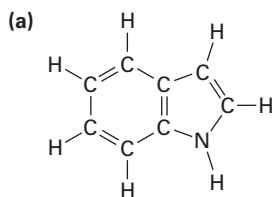
**1.41** Pyridoxal phosphate, a close relative of vitamin B<sub>6</sub>, is involved in a large number of metabolic reactions. Tell the hybridization, and predict the bond angles for each nonterminal atom.



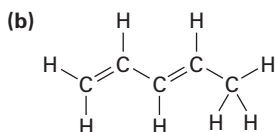
**Pyridoxal phosphate**

## Skeletal Structures

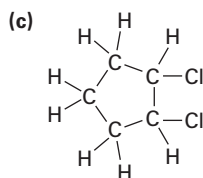
1.42 Convert the following structures into skeletal drawings:



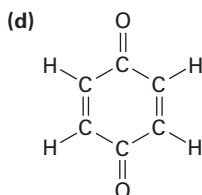
Indole



1,3-Pentadiene

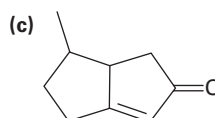
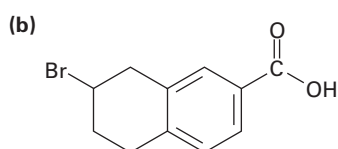
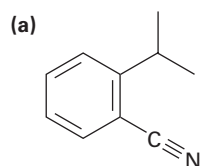


1,2-Dichlorocyclopentane

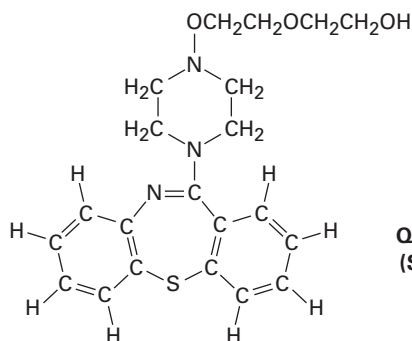


Benzoquinone

1.43 Tell the number of hydrogens bonded to each carbon atom in the following substances, and give the molecular formula of each:

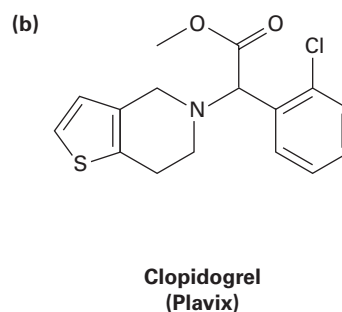
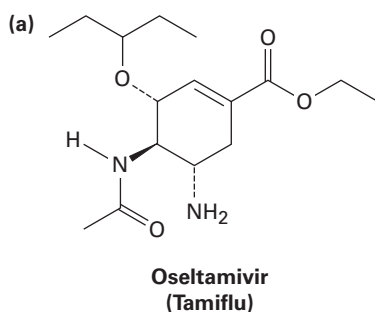


1.44 Quetiapine, marketed as Seroquel, is a heavily prescribed antipsychotic drug used in the treatment of schizophrenia and bipolar disorder. Convert the following representation into a skeletal structure, and give the molecular formula of quetiapine.

Quetiapine  
(Seroquel)



- 1.45 Tell the number of hydrogens bonded to each carbon atom in (a) the anti-influenza agent oseltamivir, marketed as Tamiflu, and (b) the platelet aggregation inhibitor clopidogrel, marketed as Plavix. Give the molecular formula of each.



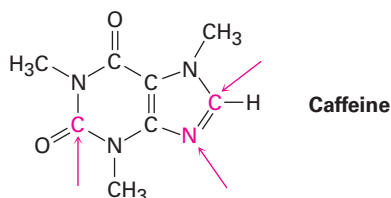
### General Problems

- 1.46 Why do you suppose no one has ever been able to make cyclopentyne as a stable molecule?

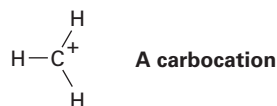


**Cyclopentyne**

- 1.47 Allene,  $\text{H}_2\text{C}=\text{C}=\text{CH}_2$ , is somewhat unusual in that it has two adjacent double bonds. Draw a picture showing the orbitals involved in the  $\sigma$  and  $\pi$  bonds of allene. Is the central carbon atom  $sp^2$ - or  $sp$ -hybridized? What about the hybridization of the terminal carbons? What shape do you predict for allene?
- 1.48 Allene (see Problem 1.47) is related structurally to carbon dioxide,  $\text{CO}_2$ . Draw a picture showing the orbitals involved in the  $\sigma$  and  $\pi$  bonds of  $\text{CO}_2$ , and identify the likely hybridization of carbon.
- 1.49 Complete the electron-dot structure of caffeine, showing all lone-pair electrons, and identify the hybridization of the indicated atoms.

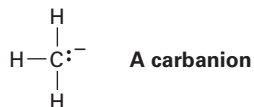


- 1.50 Most stable organic species have tetravalent carbon atoms, but species with trivalent carbon atoms also exist. *Carbocations* are one such class of compounds.

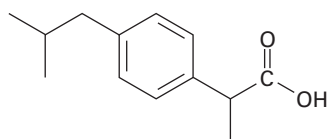


- (a) How many valence electrons does the positively charged carbon atom have?  
 (b) What hybridization do you expect this carbon atom to have?  
 (c) What geometry is the carbocation likely to have?

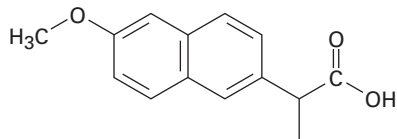
1.51 A *carbanion* is a species that contains a negatively charged, trivalent carbon.



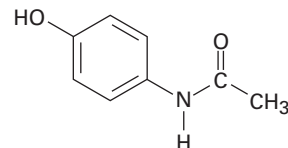
- (a) What is the electronic relationship between a carbanion and a trivalent nitrogen compound such as  $\text{NH}_3$ ?  
 (b) How many valence electrons does the negatively charged carbon atom have?  
 (c) What hybridization do you expect this carbon atom to have?  
 (d) What geometry is the carbanion likely to have?
- 1.52 Divalent carbon species called *carbenes* are capable of fleeting existence. For example, methylene,  $:\text{CH}_2$ , is the simplest carbene. The two unshared electrons in methylene can be either paired in a single orbital or unpaired in different orbitals. Predict the type of hybridization you expect carbon to adopt in singlet (spin-paired) methylene and triplet (spin-unpaired) methylene. Draw a picture of each, and identify the valence orbitals on carbon.
- 1.53 There are two different substances with the formula  $\text{C}_4\text{H}_{10}$ . Draw both, and tell how they differ.
- 1.54 There are two different substances with the formula  $\text{C}_3\text{H}_6$ . Draw both, and tell how they differ.
- 1.55 There are two different substances with the formula  $\text{C}_2\text{H}_6\text{O}$ . Draw both, and tell how they differ.
- 1.56 There are three different substances that contain a carbon-carbon double bond and have the formula  $\text{C}_4\text{H}_8$ . Draw them, and tell how they differ.
- 1.57 Among the most common over-the-counter drugs you might find in a medicine cabinet are mild pain relievers such ibuprofen (Advil, Motrin), naproxen (Aleve), and acetaminophen (Tylenol).



Ibuprofen



Naproxen



Acetaminophen

- (a) How many  $sp^3$ -hybridized carbons does each molecule have?  
 (b) How many  $sp^2$ -hybridized carbons does each molecule have?  
 (c) Can you spot any similarities in their structures?

# 2



The opium poppy is the source of morphine, one of the first “vegetable alkali,” or *alkaloids*, to be isolated. Image copyright Igor Plotnikov, 2010. Used under license from Shutterstock.com

## Polar Covalent Bonds; Acids and Bases

- 2.1 Polar Covalent Bonds: Electronegativity
- 2.2 Polar Covalent Bonds: Dipole Moments
- 2.3 Formal Charges
- 2.4 Resonance
- 2.5 Rules for Resonance Forms
- 2.6 Drawing Resonance Forms
- 2.7 Acids and Bases: The Brønsted–Lowry Definition
- 2.8 Acid and Base Strength
- 2.9 Predicting Acid–Base Reactions from  $pK_a$  Values
- 2.10 Organic Acids and Organic Bases
- 2.11 Acids and Bases: The Lewis Definition
- 2.12 Noncovalent Interactions Between Molecules  
A Deeper Look—Alkaloids: From Cocaine to Dental Anesthetics

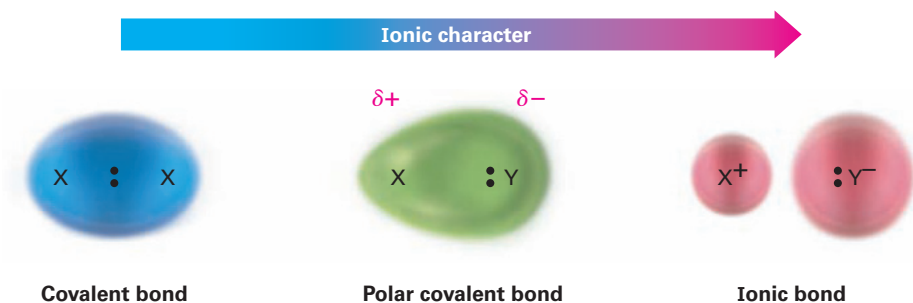
We saw in the last chapter how covalent bonds between atoms are described, and we looked at the valence bond model, which uses hybrid orbitals to account for the observed shapes of organic molecules. Before going on to a systematic study of organic chemistry, however, we still need to review a few fundamental topics. In particular, we need to look more closely at how electrons are distributed in covalent bonds and at some of the consequences that arise when the electrons in a bond are not shared equally between atoms.

**Why This Chapter?** Understanding organic and biological chemistry means knowing not just what happens but also why and how it happens at the molecular level. In this chapter, we’ll look at some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation to understand the specific reactions discussed in subsequent chapters. Topics such as bond polarity, the acid–base behavior of molecules, and hydrogen-bonding are a particularly important part of that foundation.

### 2.1 Polar Covalent Bonds: Electronegativity

Up to this point, we’ve treated chemical bonds as either ionic or covalent. The bond in sodium chloride, for instance, is ionic. Sodium transfers an electron to chlorine to give  $\text{Na}^+$  and  $\text{Cl}^-$  ions, which are held together in the solid by electrostatic attractions between unlike charges. The C–C bond in ethane, however, is covalent. The two bonding electrons are shared equally by the two equivalent carbon atoms, resulting in a symmetrical electron distribution in the bond. Most bonds, however, are neither fully ionic nor fully covalent but are somewhere between the two extremes. Such bonds are called **polar covalent bonds**, meaning that the bonding electrons are attracted more strongly by one atom than the other so that the electron distribution between atoms is not symmetrical (**Figure 2.1**).

**OWL** Sign in to OWL for Organic Chemistry at [www.cengage.com/owl](http://www.cengage.com/owl) to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.



**Figure 2.1** The continuum in bonding from covalent to ionic is a result of an unequal distribution of bonding electrons between atoms. The symbol  $\delta$  (lowercase Greek delta) means *partial* charge, either partial positive ( $\delta^+$ ) for the electron-poor atom or partial negative ( $\delta^-$ ) for the electron-rich atom.

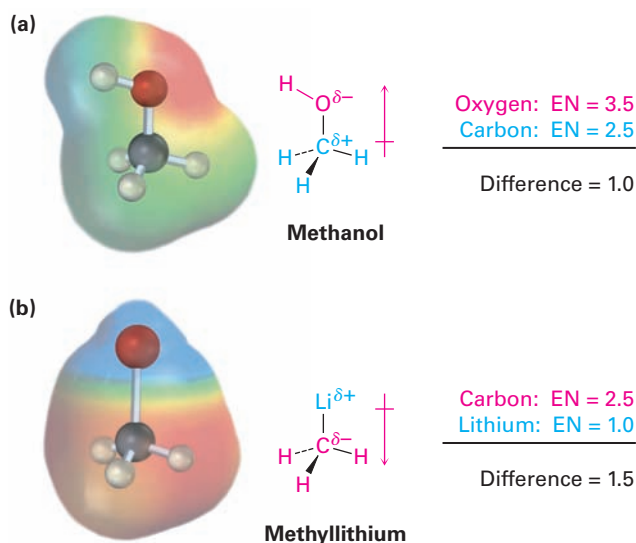
Bond polarity is due to differences in **electronegativity (EN)**, the intrinsic ability of an atom to attract the shared electrons in a covalent bond. As shown in **Figure 2.2**, electronegativities are based on an arbitrary scale, with fluorine the most electronegative (EN = 4.0) and cesium the least (EN = 0.7). Metals on the left side of the periodic table attract electrons weakly and have lower electronegativities, while oxygen, nitrogen, and halogens on the right side of the periodic table attract electrons strongly and have higher electronegativities. Carbon, the most important element in organic compounds, has an electronegativity value of 2.5.

H 2.1																	He
Li 1.0	Be 1.6											B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	Ne
Na 0.9	Mg 1.2											Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	Ar
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.9	Ni 1.9	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	Br 2.8	Kr
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	I 2.5	Xe
Cs 0.7	Ba 0.9	La 1.0	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.9	Bi 1.9	Po 2.0	At 2.1	Rn

**Figure 2.2** Electronegativity values and trends. Electronegativity generally increases from left to right across the periodic table and decreases from top to bottom. The values are on an arbitrary scale, with F = 4.0 and Cs = 0.7. Elements in **red** are the most electronegative, those in **yellow** are medium, and those in **green** are the least electronegative.

As a rough guide, bonds between atoms whose electronegativities differ by less than 0.5 are nonpolar covalent, bonds between atoms whose electronegativities differ by 0.5–2 are polar covalent, and bonds between atoms whose electronegativities differ by more than 2 are largely ionic. Carbon–hydrogen bonds, for example, are relatively nonpolar because carbon (EN = 2.5) and hydrogen (EN = 2.1) have similar electronegativities. Bonds between carbon and *more* electronegative elements such as oxygen (EN = 3.5) and nitrogen (EN = 3.0), by contrast, are polarized so that the bonding electrons are drawn away from carbon toward the electronegative atom. This leaves carbon with a partial positive charge, denoted by  $\delta^+$ , and the electronegative atom with a partial negative charge,  $\delta^-$  ( $\delta$  is the lowercase Greek letter delta). An example, is the C–O bond in methanol,  $\text{CH}_3\text{OH}$  (**Figure 2.3a**). Bonds between carbon and *less* electronegative elements are polarized so that carbon bears a partial negative charge and the other atom bears a partial positive charge. An example is the C–Li bond in methyllithium,  $\text{CH}_3\text{Li}$  (**Figure 2.3b**).

**Figure 2.3** (a) Methanol,  $\text{CH}_3\text{OH}$ , has a polar covalent C–O bond, and (b) methyllithium,  $\text{CH}_3\text{Li}$ , has a polar covalent C–Li bond. The computer-generated representations, called electrostatic potential maps, use color to show calculated charge distributions, ranging from red (electron-rich;  $\delta^-$ ) to blue (electron-poor;  $\delta^+$ ).



Note in the representations of methanol and methyllithium in Figure 2.3 that a crossed arrow  $\dashrightarrow$  is used to indicate the direction of bond polarity. By convention, *electrons are displaced in the direction of the arrow*. The tail of the arrow (which looks like a plus sign) is electron-poor ( $\delta^+$ ), and the head of the arrow is electron-rich ( $\delta^-$ ).

Note also in Figure 2.3 that calculated charge distributions in molecules can be displayed visually with what are called *electrostatic potential maps*, which use color to indicate electron-rich (red;  $\delta^-$ ) and electron-poor (blue;  $\delta^+$ ) regions. In methanol, oxygen carries a partial negative charge and is colored red, while the carbon and hydrogen atoms carry partial positive charges and are colored blue-green. In methyllithium, lithium carries a partial positive charge (blue), while carbon and the hydrogen atoms carry partial negative charges (red). Electrostatic potential maps are useful because they show at a glance the electron-rich and electron-poor atoms in molecules. We'll make frequent use of these maps throughout the text and will see many examples of how electronic structure correlates with chemical reactivity.

When speaking of an atom's ability to polarize a bond, we often use the term *inductive effect*. An **inductive effect** is simply the shifting of electrons in a  $\sigma$  bond in response to the electronegativity of nearby atoms. Metals, such as lithium and magnesium, inductively donate electrons, whereas reactive nonmetals, such as oxygen and nitrogen, inductively withdraw electrons. Inductive effects play a major role in understanding chemical reactivity, and we'll use them many times throughout this text to explain a variety of chemical observations.

### Problem 2.1

Which element in each of the following pairs is more electronegative?

- (a) Li or H (b) B or Br (c) Cl or I (d) C or H

### Problem 2.2

Use the  $\delta^+/\delta^-$  convention to indicate the direction of expected polarity for each of the bonds indicated.

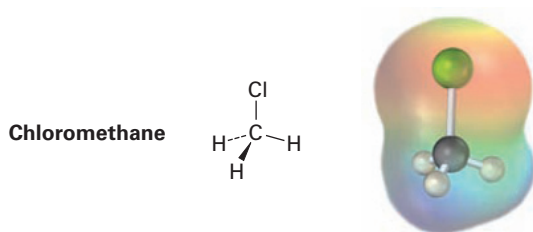
- (a)  $\text{H}_3\text{C}-\text{Cl}$  (b)  $\text{H}_3\text{C}-\text{NH}_2$  (c)  $\text{H}_2\text{N}-\text{H}$   
(d)  $\text{H}_3\text{C}-\text{SH}$  (e)  $\text{H}_3\text{C}-\text{MgBr}$  (f)  $\text{H}_3\text{C}-\text{F}$

**Problem 2.3**

Use the electronegativity values shown in Figure 2.2 to rank the following bonds from least polar to most polar:  $\text{H}_3\text{C}-\text{Li}$ ,  $\text{H}_3\text{C}-\text{K}$ ,  $\text{H}_3\text{C}-\text{F}$ ,  $\text{H}_3\text{C}-\text{MgBr}$ ,  $\text{H}_3\text{C}-\text{OH}$

**Problem 2.4**

Look at the following electrostatic potential map of chloromethane, and tell the direction of polarization of the C–Cl bond:



## 2.2 Polar Covalent Bonds: Dipole Moments

Just as individual bonds are often polar, molecules as a whole are often polar also. Molecular polarity results from the vector summation of all individual bond polarities and lone-pair contributions in the molecule. As a practical matter, strongly polar substances are often soluble in polar solvents like water, whereas less polar substances are insoluble in water.

Net molecular polarity is measured by a quantity called the *dipole moment* and can be thought of in the following way: assume that there is a center of mass of all positive charges (nuclei) in a molecule and a center of mass of all negative charges (electrons). If these two centers don't coincide, then the molecule has a net polarity.

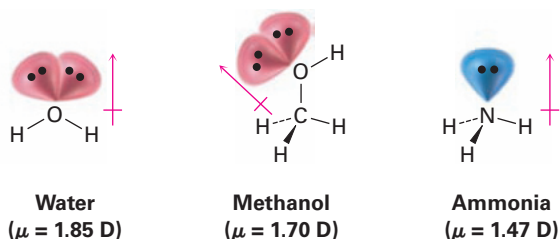
The **dipole moment**,  $\mu$  (Greek mu), is defined as the magnitude of the charge  $Q$  at either end of the molecular dipole times the distance  $r$  between the charges,  $\mu = Q \times r$ . Dipole moments are expressed in *debyes* (D), where  $1 \text{ D} = 3.336 \times 10^{-30}$  coulomb meter ( $\text{C} \cdot \text{m}$ ) in SI units. For example, the unit charge on an electron is  $1.60 \times 10^{-19} \text{ C}$ . Thus, if one positive charge and one negative charge are separated by 100 pm (a bit less than the length of a typical covalent bond), the dipole moment is  $1.60 \times 10^{-29} \text{ C} \cdot \text{m}$ , or 4.80 D.

$$\mu = Q \times r$$


$$\mu = (1.60 \times 10^{-19} \text{ C})(100 \times 10^{-12} \text{ m}) \left( \frac{1 \text{ D}}{3.336 \times 10^{-30} \text{ C} \cdot \text{m}} \right) = 4.80 \text{ D}$$

Dipole moments for some common substances are given in Table 2.1. Of the compounds shown in the table, sodium chloride has the largest dipole moment (9.00 D) because it is ionic. Even small molecules like water ( $\mu = 1.85 \text{ D}$ ), methanol ( $\text{CH}_3\text{OH}$ ;  $\mu = 1.70 \text{ D}$ ), and ammonia ( $\mu = 1.47 \text{ D}$ ), have substantial dipole moments, however, both because they contain strongly

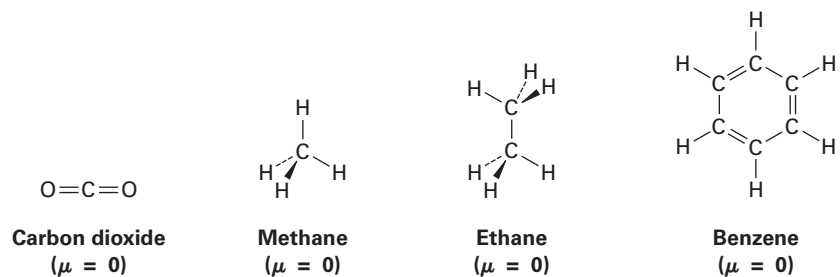
electronegative atoms (oxygen and nitrogen) and because all three molecules have lone-pair electrons. The lone-pair electrons on oxygen and nitrogen atom stick out into space away from the positively charged nuclei, giving rise to a considerable charge separation and making a large contribution to the dipole moment.



**Table 2.1** Dipole Moments of Some Compounds

Compound	Dipole moment (D)	Compound	Dipole moment (D)
NaCl	9.00	NH <sub>3</sub>	1.47
CH <sub>2</sub> O	2.33	CH <sub>3</sub> NH <sub>2</sub>	1.31
CH <sub>3</sub> Cl	1.87	CO <sub>2</sub>	0
H <sub>2</sub> O	1.85	CH <sub>4</sub>	0
CH <sub>3</sub> OH	1.70	CH <sub>3</sub> CH <sub>3</sub>	0
CH <sub>3</sub> CO <sub>2</sub> H	1.70	 <b>Benzene</b>	0
CH <sub>3</sub> SH	1.52		

In contrast with water, methanol, and ammonia, molecules such as carbon dioxide, methane, ethane, and benzene have zero dipole moments. Because of the symmetrical structures of these molecules, the individual bond polarities and lone-pair contributions exactly cancel.



## Predicting the Direction of a Dipole Moment

### Worked Example 2.1

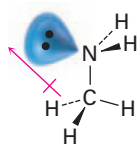
Make a three-dimensional drawing of methylamine,  $\text{CH}_3\text{NH}_2$ , a substance responsible for the odor of rotting fish, and show the direction of its dipole moment ( $\mu = 1.31$ ).

#### Strategy

Look for any lone-pair electrons, and identify any atom with an electronegativity substantially different from that of carbon. (Usually, this means O, N, F, Cl, or Br.) Electron density will be displaced in the general direction of the electronegative atoms and the lone pairs.

#### Solution

Methylamine contains an electronegative nitrogen atom with a lone-pair electrons. The dipole moment thus points generally from  $-\text{CH}_3$  toward the lone pair.



**Methylamine**  
( $\mu = 1.31$ )

#### Problem 2.5

Ethylene glycol,  $\text{HOCH}_2\text{CH}_2\text{OH}$ , has zero dipole moment even though carbon–oxygen bonds are strongly polar and oxygen has two lone-pairs of electrons. Explain.

#### Problem 2.6

Make three-dimensional drawings of the following molecules, and predict whether each has a dipole moment. If you expect a dipole moment, show its direction.

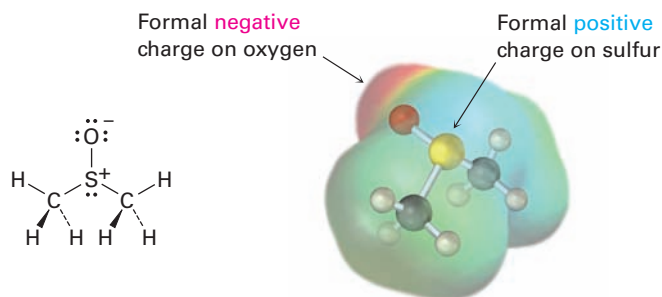
- (a)  $\text{H}_2\text{C}=\text{CH}_2$  (b)  $\text{CHCl}_3$  (c)  $\text{CH}_2\text{Cl}_2$  (d)  $\text{H}_2\text{C}=\text{CCl}_2$

## 2.3 Formal Charges

Closely related to the ideas of bond polarity and dipole moment is the concept of assigning *formal charges* to specific atoms within a molecule, particularly atoms that have an apparently “abnormal” number of bonds. Look at dimethyl sulfoxide ( $\text{CH}_3\text{SOCH}_3$ ), for instance, a solvent commonly used for preserving biological cell lines at low temperature. The sulfur atom in dimethyl sulfoxide has three bonds rather than the usual two and has a formal positive charge. The oxygen atom, by contrast, has one bond rather than the usual two and has a formal negative charge. Note that an electrostatic potential map of dimethyl sulfoxide shows the oxygen as negative

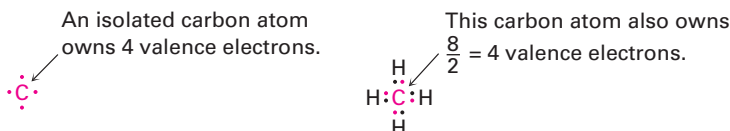


(red) and the sulfur as relatively positive (blue), in accordance with the formal charges.

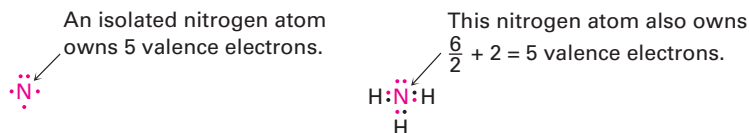


**Dimethyl sulfoxide**

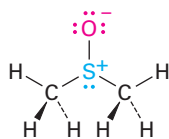
Formal charges, as the name suggests, are a formalism and don't imply the presence of actual ionic charges in a molecule. Instead, they're a device for electron "bookkeeping" and can be thought of in the following way: a typical covalent bond is formed when each atom donates one electron. Although the bonding electrons are shared by both atoms, each atom can still be considered to "own" one electron for bookkeeping purposes. In methane, for instance, the carbon atom owns one electron in each of the four C–H bonds, for a total of four. Because a neutral, isolated carbon atom has four valence electrons, and because the carbon atom in methane still owns four, the methane carbon atom is neutral and has no formal charge.



The same is true for the nitrogen atom in ammonia, which has three covalent N–H bonds and two nonbonding electrons (a lone pair). Atomic nitrogen has five valence electrons, and the ammonia nitrogen also has five—one in each of three shared N–H bonds plus two in the lone pair. Thus, the nitrogen atom in ammonia has no formal charge.



The situation is different in dimethyl sulfoxide. Atomic sulfur has six valence electrons, but the dimethyl sulfoxide sulfur owns only *five*—one in each of the two S–C single bonds, one in the S–O single bond, and two in a lone pair. Thus, the sulfur atom has formally lost an electron and therefore has a positive charge. A similar calculation for the oxygen atom shows that it has formally gained an electron and has a negative charge. Atomic oxygen has six valence electrons, but the oxygen in dimethyl sulfoxide has seven—one in the O–S bond and two in each of three lone pairs.

**For sulfur:**

Sulfur valence electrons = 6

Sulfur bonding electrons = 6

Sulfur nonbonding electrons = 2

Formal charge =  $6 - 6/2 - 2 = +1$

**For oxygen:**

Oxygen valence electrons = 6

Oxygen bonding electrons = 2

Oxygen nonbonding electrons = 6

Formal charge =  $6 - 2/2 - 6 = -1$

To express the calculations in a general way, the **formal charge** on an atom is equal to the number of valence electrons in a neutral, isolated atom minus the number of electrons owned by that bonded atom in a molecule. The number of electrons in the bonded atom, in turn, is equal to half the number of bonding electrons plus the nonbonding, lone-pair electrons.

$$\text{Formal charge} = \left( \begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in free atom} \end{array} \right) - \left( \begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in bonded atom} \end{array} \right)$$

$$= \left( \begin{array}{c} \text{Number of} \\ \text{valence electrons} \\ \text{in free atom} \end{array} \right) - \left( \frac{\text{Number of} \\ \text{bonding electrons}}{2} \right) - \left( \begin{array}{c} \text{Number of} \\ \text{nonbonding} \\ \text{electrons} \end{array} \right)$$

A summary of commonly encountered formal charges and the bonding situations in which they occur is given in Table 2.2. Although only a bookkeeping device, formal charges often give clues about chemical reactivity, so it's helpful to be able to identify and calculate them correctly.

**Table 2.2** A Summary of Common Formal Charges

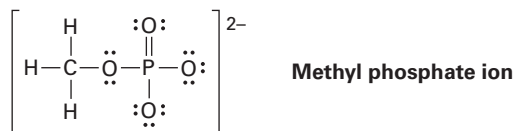
Atom	C			N		O		S		P
Structure										
Valence electrons	4	4	4	5	5	6	6	6	6	5
Number of bonds	3	3	3	4	2	3	1	3	1	4
Number of nonbonding electrons	1	0	2	0	4	2	6	2	6	0
Formal charge	0	+1	-1	+1	-1	+1	-1	+1	-1	+1

**Problem 2.7**

Calculate formal charges for the nonhydrogen atoms in the following molecules:

**Problem 2.8**

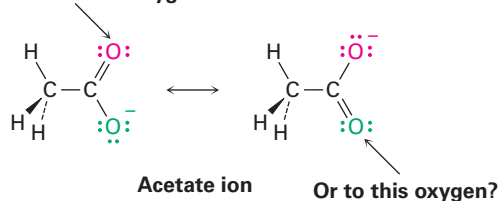
Organic phosphate groups occur commonly in biological molecules. Calculate formal charges on the four O atoms in the methyl phosphate dianion.



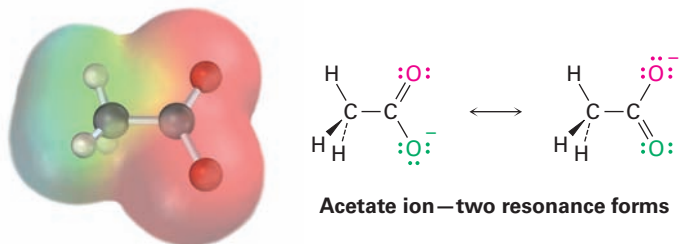
## 2.4 Resonance

Most substances can be represented unambiguously by the Kekulé line-bond structures we've been using up to this point, but an interesting problem sometimes arises. Look at the acetate ion, for instance. When we draw a line-bond structure for acetate, we need to show a double bond to one oxygen and a single bond to the other. But which oxygen is which? Should we draw a double bond to the "top" oxygen and a single bond to the "bottom" oxygen, or vice versa?

Double bond to this oxygen?



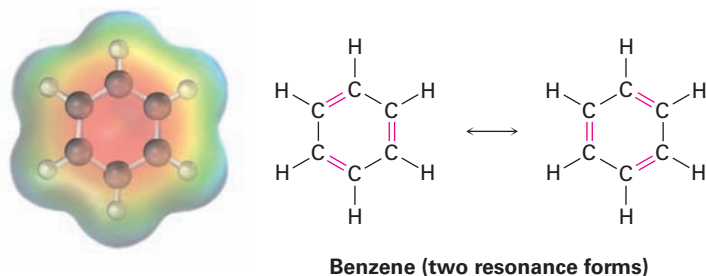
Although the two oxygen atoms in the acetate ion appear different in line-bond structures, experiments show that they are equivalent. Both carbon-oxygen bonds, for example, are 127 pm in length, midway between the length of a typical C–O single bond (135 pm) and a typical C=O double bond (120 pm). In other words, *neither* of the two structures for acetate is correct by itself. The true structure is intermediate between the two, and an electrostatic potential map shows that both oxygen atoms share the negative charge and have equal electron densities (red).



The two individual line-bond structures for acetate ion are called **resonance forms**, and their special resonance relationship is indicated by the double-headed arrow between them. *The only difference between resonance forms is the placement of the  $\pi$  and nonbonding valence electrons.* The atoms themselves occupy exactly the same place in both resonance forms, the connections between atoms are the same, and the three-dimensional shapes of the resonance forms are the same.

A good way to think about resonance forms is to realize that a substance like the acetate ion is the same as any other. Acetate doesn't jump back and forth between two resonance forms, spending part of the time looking like one and part of the time looking like the other. Rather, acetate has a single unchanging structure that we say is a **resonance hybrid** of the two individual forms and has characteristics of both. The only "problem" with acetate is that we can't draw it accurately using a familiar line-bond structure—line-bond structures just don't work well for resonance hybrids. The difficulty, however, is with the *representation* of acetate on paper, not with acetate itself.

Resonance is a very useful concept that we'll return to on numerous occasions throughout the rest of this book. We'll see in Chapter 15, for instance, that the six carbon-carbon bonds in aromatic compounds, such as benzene, are equivalent and that benzene is best represented as a hybrid of two resonance forms. Although each individual resonance form seems to imply that benzene has alternating single and double bonds, neither form is correct by itself. The true benzene structure is a hybrid of the two individual forms, and all six carbon-carbon bonds are equivalent. This symmetrical distribution of electrons around the molecule is evident in an electrostatic potential map.



## 2.5 Rules for Resonance Forms

When first dealing with resonance forms, it's useful to have a set of guidelines that describe how to draw and interpret them. The following rules should be helpful:

### RULE 1

**Individual resonance forms are imaginary, not real.** The real structure is a composite, or resonance hybrid, of the different forms. Species such as the acetate ion and benzene are no different from any other. They have single, unchanging structures, and they do not switch back and forth between resonance forms. The only difference between these and other substances is in the way they must be represented in drawings on paper.

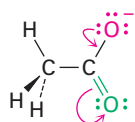
### Key IDEAS

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

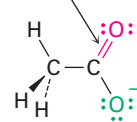
**RULE 2**

**Resonance forms differ only in the placement of their  $\pi$  or nonbonding electrons.** Neither the position nor the hybridization of any atom changes from one resonance form to another. In the acetate ion, for instance, the carbon atom is  $sp^2$ -hybridized and the oxygen atoms remain in exactly the same place in both resonance forms. Only the positions of the  $\pi$  electrons in the C=O bond and the lone-pair electrons on oxygen differ from one form to another. This movement of electrons from one resonance structure to another can be indicated by using curved arrows. A *curved arrow always indicates the movement of electrons, not the movement of atoms*. An arrow shows that a pair of electrons moves *from* the atom or bond at the tail of the arrow *to* the atom or bond at the head of the arrow.

The red curved arrow indicates that a lone pair of electrons moves from the top oxygen atom to become part of a C=O bond.



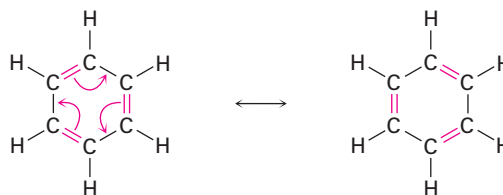
The new resonance form has a double bond here...



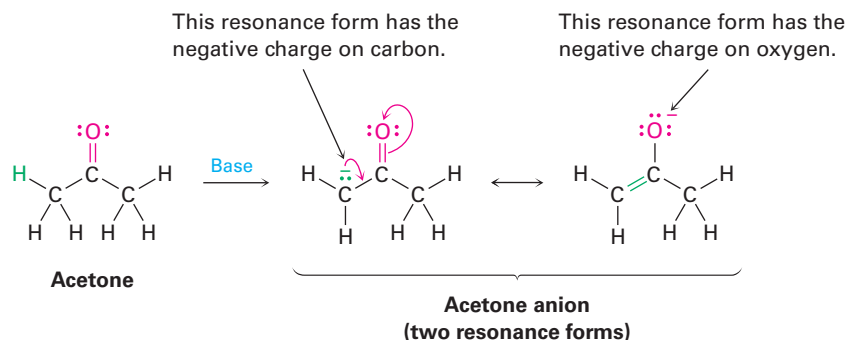
Simultaneously, two electrons from the C=O bond move onto the bottom oxygen atom to become a lone pair.

and has a lone pair of electrons here.

The situation with benzene is similar to that with acetate. The  $\pi$  electrons in the double bonds move, as shown with curved arrows, but the carbon and hydrogen atoms remain in place.

**RULE 3**

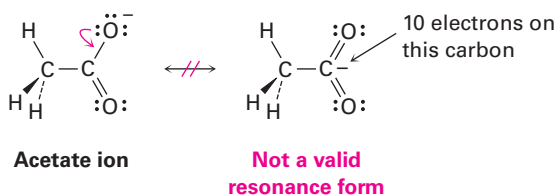
**Different resonance forms of a substance don't have to be equivalent.** As an example, we'll see in Chapter 22 that a compound such as acetone, which contains a C=O bond, can be converted into its anion by reaction with a strong base. The resultant anion has two resonance forms. One form contains a carbon–oxygen double bond and has a negative charge on *carbon*; the other contains a carbon–carbon double bond and has a negative charge on *oxygen*. Even though the two resonance forms aren't equivalent, both contribute to the overall resonance hybrid.



When two resonance forms are nonequivalent, the actual structure of the resonance hybrid resembles the more stable form more than it resembles the less stable form. Thus, we might expect the true structure of the acetone anion to be more like that of the form that places the negative charge on the electronegative oxygen atom rather than on carbon.

#### RULE 4

**Resonance forms obey normal rules of valency.** A resonance form is like any other structure: the octet rule still applies to second-row, main-group atoms. For example, one of the following structures for the acetate ion is not a valid resonance form because the carbon atom has five bonds and ten valence electrons:



#### RULE 5

**The resonance hybrid is more stable than any individual resonance form.** In other words, resonance leads to stability. Generally speaking, the larger the number of resonance forms, the more stable a substance is because its electrons are spread out over a larger part of the molecule and are closer to more nuclei. We'll see in Chapter 15, for instance, that a benzene ring is more stable because of resonance than might otherwise be expected.

## 2.6 Drawing Resonance Forms

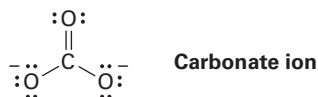
Look back at the resonance forms of the acetate ion and the acetone anion shown in the previous section. The pattern seen there is a common one that



## Drawing Resonance Forms for an Anion

### Worked Example 2.2

Draw three resonance structures for the carbonate ion,  $\text{CO}_3^{2-}$ .

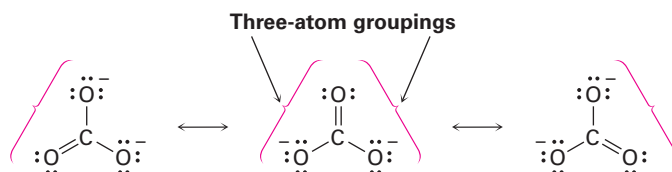


#### Strategy

Look for three-atom groupings that contain a multiple bond next to an atom with a  $p$  orbital. Then exchange the positions of the multiple bond and the electrons in the  $p$  orbital. In the carbonate ion, each of the singly bonded oxygen atoms with its lone pairs and negative charge is next to the  $\text{C}=\text{O}$  double bond, giving the grouping  $\text{O}=\text{C}-\text{O}^-$ .

#### Solution

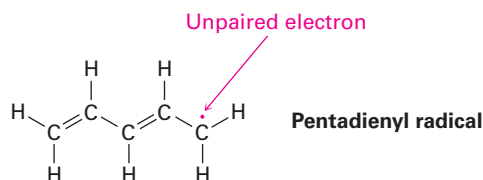
Exchanging the position of the double bond and an electron lone pair in each grouping generates three resonance structures.



## Drawing Resonance Forms for a Radical

### Worked Example 2.3

Draw three resonance forms for the pentadienyl radical, where a *radical* is a substance that contains a single, unpaired electron in one of its orbitals, denoted by a dot ( $\cdot$ ).

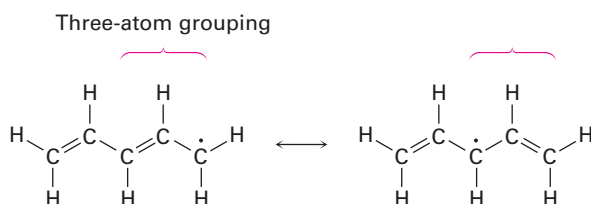


#### Strategy

Find the three-atom groupings that contain a multiple bond next to a  $p$  orbital.

#### Solution

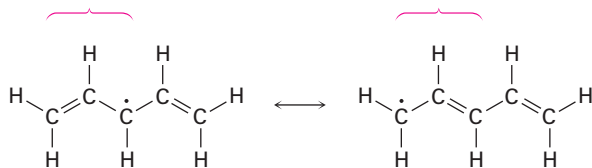
The unpaired electron is on a carbon atom next to a  $\text{C}=\text{C}$  bond, giving a typical three-atom grouping that has two resonance forms.



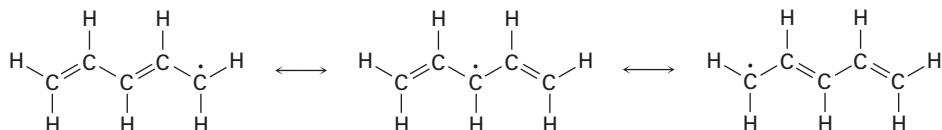


In the second resonance form, the unpaired electron is next to another double bond, giving another three-atom grouping and leading to another resonance form.

Three-atom grouping



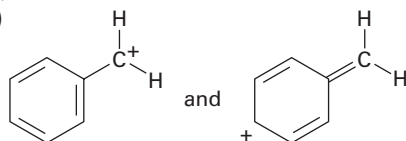
Thus, the three resonance forms for the pentadienyl radical are:



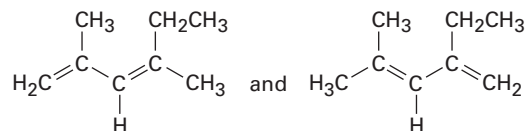
### Problem 2.9

Which of the following pairs of structures represent resonance forms, and which do not? Explain.

(a)



(b)



### Problem 2.10

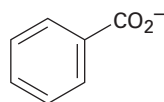
Draw the indicated number of resonance forms for each of the following species:

(a) The methyl phosphate anion,  $\text{CH}_3\text{OPO}_3^{2-}$  (3)

(b) The nitrate anion,  $\text{NO}_3^-$  (3)

(c) The allyl cation,  $\text{H}_2\text{C}=\text{CH}-\text{CH}_2^+$  (2)

(d) The benzoate anion (4)

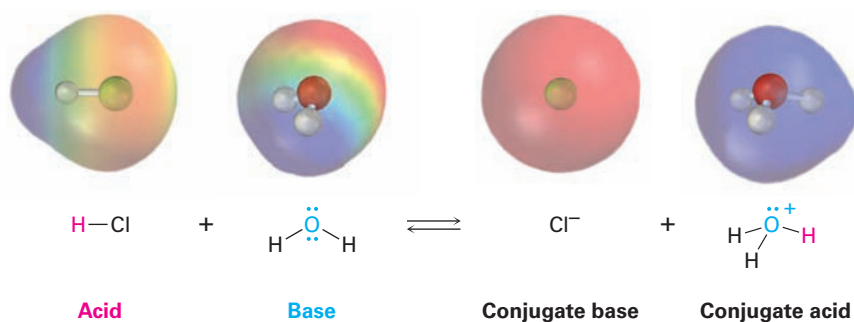


## 2.7 Acids and Bases: The Brønsted–Lowry Definition

Perhaps the most important of all concepts related to electronegativity and polarity is that of *acidity* and *basicity*. We'll soon see, in fact, that the acid–base behavior of organic molecules explains much of their chemistry. You may recall

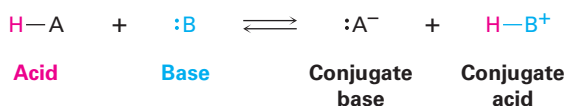
from a course in general chemistry that two definitions of acidity are frequently used: the *Brønsted–Lowry definition* and the *Lewis definition*. We'll look at the Brønsted–Lowry definition in this and the following three sections and then discuss the Lewis definition in **Section 2.11**.

A **Brønsted–Lowry acid** is a substance that donates a hydrogen ion,  $\text{H}^+$ , and a **Brønsted–Lowry base** is a substance that accepts a hydrogen ion. (The name *proton* is often used as a synonym for  $\text{H}^+$  because loss of the valence electron from a neutral hydrogen atom leaves only the hydrogen nucleus—a proton.) When gaseous hydrogen chloride dissolves in water, for example, a polar HCl molecule acts as an acid and donates a proton, while a water molecule acts as a base and accepts the proton, yielding chloride ion ( $\text{Cl}^-$ ) and hydronium ion ( $\text{H}_3\text{O}^+$ ). This and other acid–base reactions are reversible, so we'll write them with double, forward-and-backward arrows.

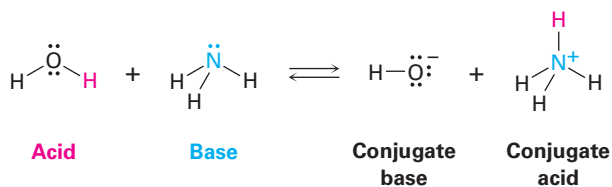
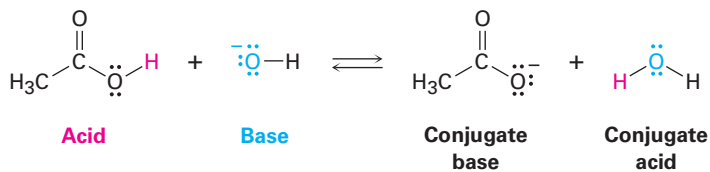


Chloride ion, the product that results when the acid HCl loses a proton, is called the **conjugate base** of the acid, and hydronium ion, the product that results when the base  $\text{H}_2\text{O}$  gains a proton, is called the **conjugate acid** of the base. Other common mineral acids such as  $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$  behave similarly, as do organic acids such as acetic acid,  $\text{CH}_3\text{CO}_2\text{H}$ .

In a general sense,



For example:



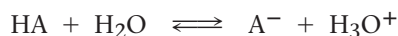
Notice that water can act either as an acid or as a base, depending on the circumstances. In its reaction with HCl, water is a base that accepts a proton to give the hydronium ion,  $\text{H}_3\text{O}^+$ . In its reaction with ammonia ( $\text{NH}_3$ ), however, water is an acid that donates a proton to give ammonium ion ( $\text{NH}_4^+$ ) and hydroxide ion,  $\text{HO}^-$ .

### Problem 2.11

Nitric acid ( $\text{HNO}_3$ ) reacts with ammonia ( $\text{NH}_3$ ) to yield ammonium nitrate. Write the reaction, and identify the acid, the base, the conjugate acid product, and the conjugate base product.

## 2.8 Acid and Base Strength

Acids differ in their ability to donate  $\text{H}^+$ . Stronger acids, such as HCl, react almost completely with water, whereas weaker acids, such as acetic acid ( $\text{CH}_3\text{CO}_2\text{H}$ ), react only slightly. The exact strength of a given acid HA in water solution is described using the **acidity constant** ( $K_a$ ) for the acid-dissociation equilibrium. Remember from general chemistry that the concentration of solvent is ignored in the equilibrium expression and that brackets [ ] around a substance refer to the concentration of the enclosed species in moles per liter.



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

Stronger acids have their equilibria toward the right and thus have larger acidity constants, whereas weaker acids have their equilibria toward the left and have smaller acidity constants. The range of  $K_a$  values for different acids is enormous, running from about  $10^{15}$  for the strongest acids to about  $10^{-60}$  for the weakest. The common inorganic acids such as  $\text{H}_2\text{SO}_4$ ,  $\text{HNO}_3$ , and HCl have  $K_a$ 's in the range of  $10^2$  to  $10^9$ , while organic acids generally have  $K_a$ 's in the range of  $10^{-5}$  to  $10^{-15}$ . As you gain more experience, you'll develop a rough feeling for which acids are "strong" and which are "weak" (always remembering that the terms are relative).

Acid strengths are normally expressed using  $\text{p}K_a$  values rather than  $K_a$  values, where the  $\text{p}K_a$  is the negative common logarithm of the  $K_a$ :

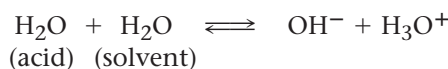
$$\text{p}K_a = -\log K_a$$

A *stronger* acid (larger  $K_a$ ) has a *smaller*  $\text{p}K_a$ , and a *weaker* acid (smaller  $K_a$ ) has a *larger*  $\text{p}K_a$ . Table 2.3 lists the  $\text{p}K_a$ 's of some common acids in order of their strength, and a more comprehensive table is given in Appendix B.

Table 2.3 Relative Strengths of Some Common Acids and Their Conjugate Bases

	Acid	Name	pK <sub>a</sub>	Conjugate base	Name	
	CH <sub>3</sub> CH <sub>2</sub> OH	Ethanol	16.00	CH <sub>3</sub> CH <sub>2</sub> O <sup>-</sup>	Ethoxide ion	
	H <sub>2</sub> O	Water	15.74	HO <sup>-</sup>	Hydroxide ion	
	H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	Dihydrogen phosphate ion	7.21	HPO <sub>4</sub> <sup>2-</sup>	Hydrogen phosphate ion	
	CH <sub>3</sub> CO <sub>2</sub> H	Acetic acid	4.76	CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	Acetate ion	
	H <sub>3</sub> PO <sub>4</sub>	Phosphoric acid	2.16	H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	Dihydrogen phosphate ion	
	HNO <sub>3</sub>	Nitric acid	-1.3	NO <sub>3</sub> <sup>-</sup>	Nitrate ion	
	HCl	Hydrochloric acid	-7.0	Cl <sup>-</sup>	Chloride ion	

Notice that the pK<sub>a</sub> value shown in Table 2.3 for water is 15.74, which results from the following calculation. Because water is both the acid and the solvent, the equilibrium expression is



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} = \frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]} = \frac{[1.0 \times 10^{-7}][1.0 \times 10^{-7}]}{[55.4]} = 1.8 \times 10^{-16}$$

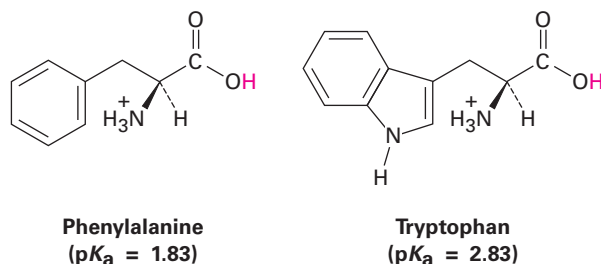
$$\text{p}K_a = 15.74$$

The numerator in this expression is the so-called ion-product constant for water,  $K_w = [\text{H}_3\text{O}^+][\text{OH}^-] = 1.00 \times 10^{-14}$ , and the denominator is the molar concentration of pure water,  $[\text{H}_2\text{O}] = 55.4 \text{ M}$  at 25 °C. The calculation is artificial in that the concentration of “solvent” water is ignored while the concentration of “acid” water is not, but it is nevertheless useful for making a comparison of water with other weak acids on a similar footing.

Notice also in Table 2.3 that there is an inverse relationship between the acid strength of an acid and the base strength of its conjugate base. A *strong* acid has a *weak* conjugate base, and a *weak* acid has a *strong* conjugate base. To understand this inverse relationship, think about what is happening to the acidic hydrogen in an acid–base reaction. A strong acid is one that loses H<sup>+</sup> easily, meaning that its conjugate base holds the H<sup>+</sup> weakly and is therefore a weak base. A weak acid is one that loses H<sup>+</sup> with difficulty, meaning that its conjugate base holds the proton tightly and is therefore a strong base. The fact that HCl is a strong acid, for example, means that Cl<sup>-</sup> does not hold H<sup>+</sup> tightly and is thus a weak base. Water, on the other hand, is a weak acid, meaning that OH<sup>-</sup> holds H<sup>+</sup> tightly and is a strong base.

**Problem 2.12**

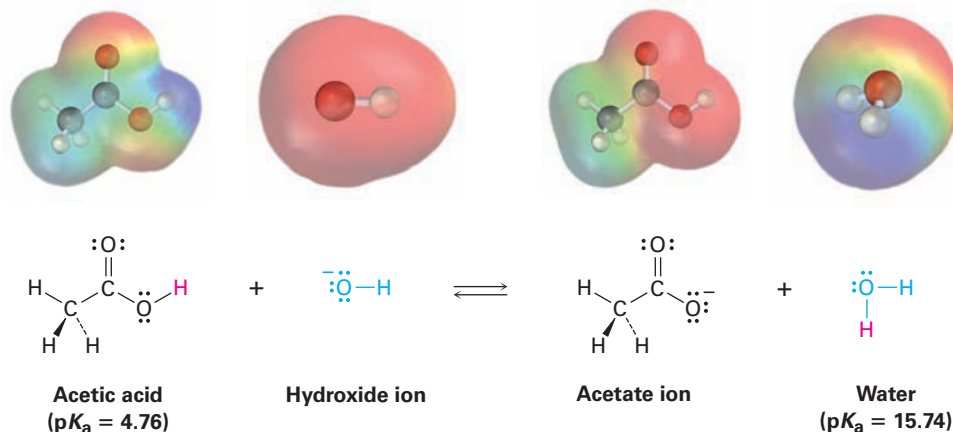
The amino acid phenylalanine has  $pK_a = 1.83$ , and tryptophan has  $pK_a = 2.83$ . Which is the stronger acid?

**Problem 2.13**

Amide ion,  $H_2N^-$ , is a much stronger base than hydroxide ion,  $HO^-$ . Which is the stronger acid,  $NH_3$  or  $H_2O$ ? Explain.

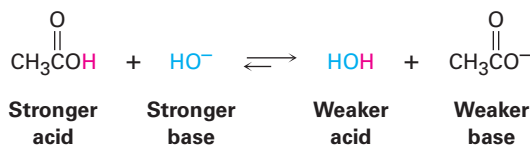
## 2.9 Predicting Acid–Base Reactions from $pK_a$ Values

Compilations of  $pK_a$  values like those in Table 2.3 and Appendix B are useful for predicting whether a given acid–base reaction will take place because  $H^+$  will always go *from* the stronger acid *to* the stronger base. That is, an acid will donate a proton to the conjugate base of a weaker acid, and the conjugate base of a weaker acid will remove the proton from a stronger acid. Since water ( $pK_a = 15.74$ ) is a weaker acid than acetic acid ( $pK_a = 4.76$ ), for example, hydroxide ion holds a proton more tightly than acetate ion does. Hydroxide ion will therefore react to a large extent with acetic acid,  $CH_3CO_2H$ , to yield acetate ion and  $H_2O$ .



Another way to predict acid–base reactivity is to remember that the product conjugate acid in an acid–base reaction must be weaker and less reactive than the starting acid and the product conjugate base must be weaker and less

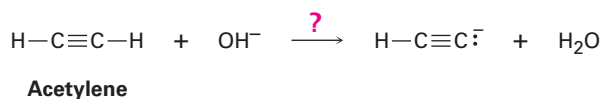
reactive than the starting base. In the reaction of acetic acid with hydroxide ion, for example, the product conjugate acid ( $H_2O$ ) is weaker than the starting acid ( $CH_3CO_2H$ ), and the product conjugate base ( $CH_3CO_2^-$ ) is weaker than the starting base ( $OH^-$ ).



## Predicting Acid Strengths from $pK_a$ Values

### Worked Example 2.4

Water has  $pK_a = 15.74$ , and acetylene has  $pK_a = 25$ . Which is the stronger acid? Does hydroxide ion react to a significant extent with acetylene?



#### Strategy

In comparing two acids, the one with the lower  $pK_a$  is stronger. Thus, water is a stronger acid than acetylene and gives up  $H^+$  more easily.

#### Solution

Because water is a stronger acid and gives up  $H^+$  more easily than acetylene does, the  $HO^-$  ion must have less affinity for  $H^+$  than the  $HC\equiv C:^-$  ion has. In other words, the anion of acetylene is a stronger base than hydroxide ion, and the reaction will not proceed significantly as written.

## Calculating $K_a$ from $pK_a$

### Worked Example 2.5

According to the data in Table 2.3, acetic acid has  $pK_a = 4.76$ . What is its  $K_a$ ?

#### Strategy

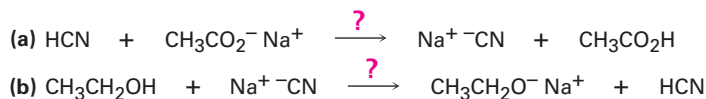
Since  $pK_a$  is the negative logarithm of  $K_a$ , it's necessary to use a calculator with an ANTILOG or INV LOG function. Enter the value of the  $pK_a$  (4.76), change the sign ( $-4.76$ ), and then find the antilog ( $1.74 \times 10^{-5}$ ).

#### Solution

$$K_a = 1.74 \times 10^{-5}$$

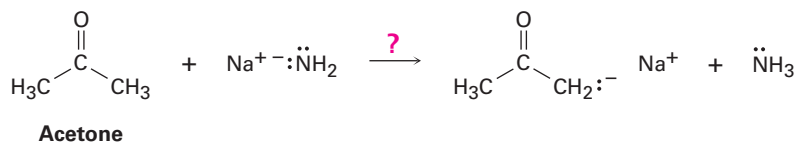
#### Problem 2.14

Will either of the following reactions take place to a significant extent as written, according to the data in Table 2.3?



**Problem 2.15**

Ammonia,  $\text{NH}_3$ , has  $\text{p}K_a \approx 36$ , and acetone has  $\text{p}K_a \approx 19$ . Will the following reaction take place to a significant extent?

**Problem 2.16**

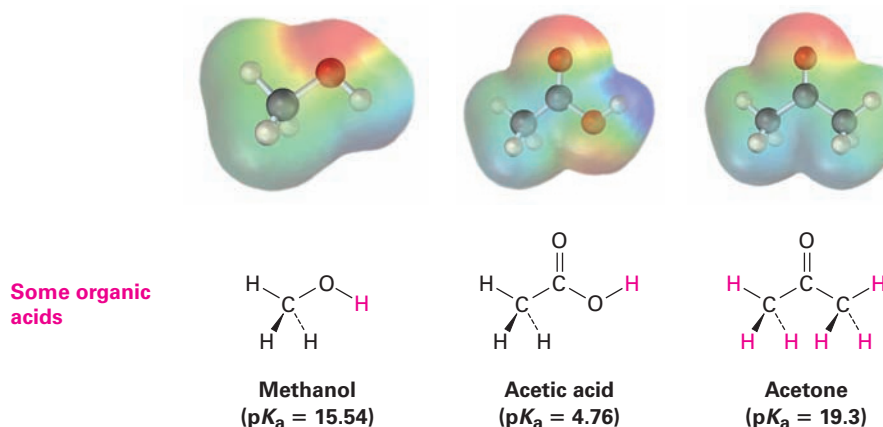
What is the  $K_a$  of HCN if its  $\text{p}K_a = 9.31$ ?

## 2.10 Organic Acids and Organic Bases

Many of the reactions we'll be seeing in future chapters, including practically all biological reactions, involve organic acids and organic bases. Although it's too early to go into the details of these processes now, you might keep the following generalities in mind:

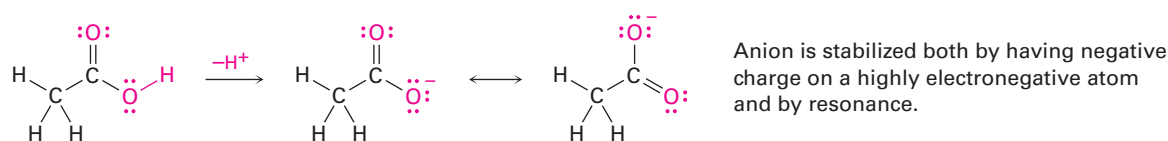
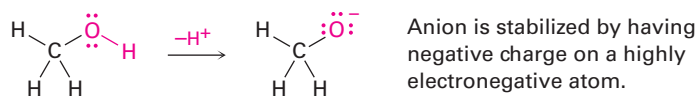
### Organic Acids

Organic acids are characterized by the presence of a positively polarized hydrogen atom (blue in electrostatic potential maps) and are of two main kinds: those acids such as methanol and acetic acid that contain a hydrogen atom bonded to an electronegative oxygen atom (O–H) and those such as acetone (**Section 2.5**) that contain a hydrogen atom bonded to a carbon atom next to a C=O bond (O=C–C–H).

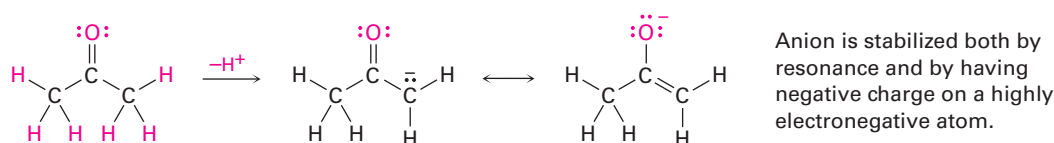


Methanol contains an O–H bond and is a weak acid, while acetic acid also contains an O–H bond and is a somewhat stronger acid. In both cases, acidity is due to the fact that the conjugate base resulting from loss of  $\text{H}^+$  is stabilized by having its negative charge on a strongly electronegative oxygen atom. In

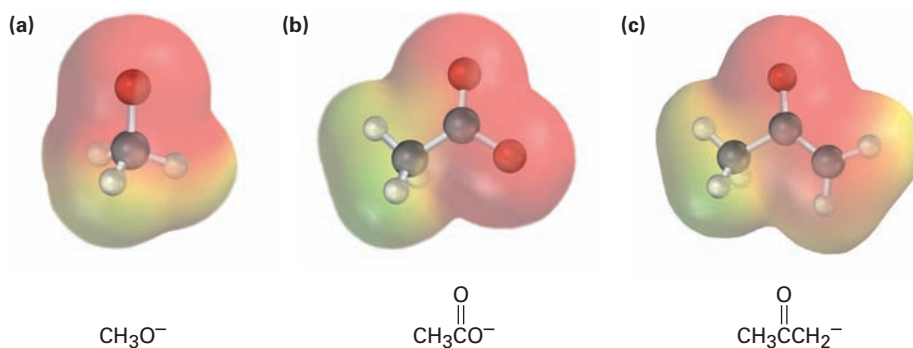
addition, the conjugate base of acetic acid is stabilized by resonance (**Sections 2.4 and 2.5**).



The acidity of acetone and other compounds with C=O bonds is due to the fact that the conjugate base resulting from loss of H<sup>+</sup> is stabilized by resonance. In addition, one of the resonance forms stabilizes the negative charge by placing it on an electronegative oxygen atom.

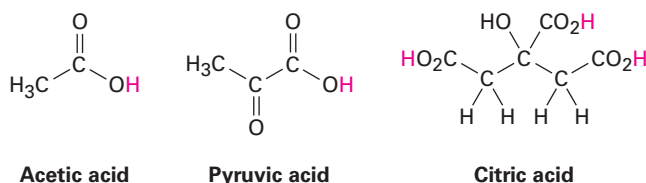


Electrostatic potential maps of the conjugate bases from methanol, acetic acid, and acetone are shown in **Figure 2.4**. As you might expect, all three show a substantial amount of negative charge (red) on oxygen.



**Figure 2.4** Electrostatic potential maps of the conjugate bases of (a) methanol, (b) acetic acid, and (c) acetone. The electronegative oxygen atoms stabilize the negative charge in all three.

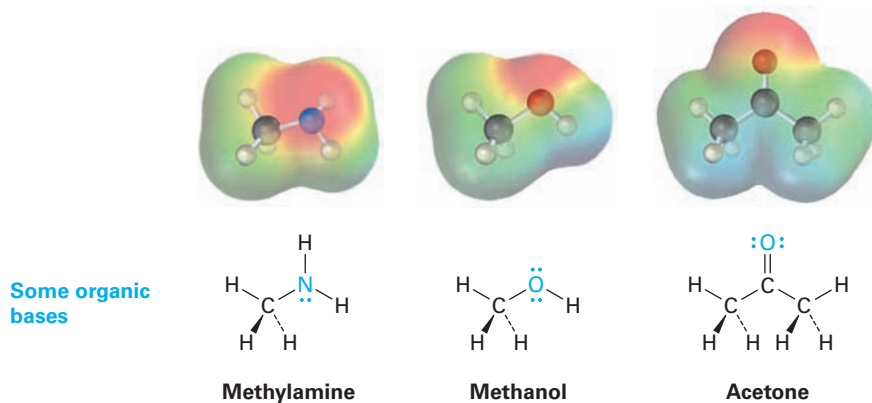
Compounds called *carboxylic acids*, which contain the  $-\text{CO}_2\text{H}$  grouping, occur abundantly in all living organisms and are involved in almost all metabolic pathways. Acetic acid, pyruvic acid, and citric acid are examples. You might note that at the typical pH of 7.3 found within cells, carboxylic acids are usually dissociated and exist as their carboxylate anions,  $-\text{CO}_2^-$ .



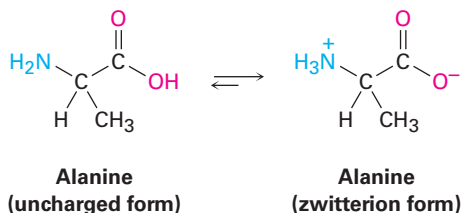


## Organic Bases

Organic bases are characterized by the presence of an atom (reddish in electrostatic potential maps) with a lone pair of electrons that can bond to  $H^+$ . Nitrogen-containing compounds such as methylamine are the most common organic bases and are involved in almost all metabolic pathways, but oxygen-containing compounds can also act as bases when reacting with a sufficiently strong acid. Note that some oxygen-containing compounds can act both as acids and as bases depending on the circumstances, just as water can. Methanol and acetone, for instance, act as *acids* when they donate a proton but as *bases* when their oxygen atom accepts a proton.



We'll see in Chapter 26 that substances called *amino acids*, so-named because they are both amines ( $-NH_2$ ) and carboxylic acids ( $-CO_2H$ ), are the building blocks from which the proteins present in all living organisms are made. Twenty different amino acids go into making up proteins—alanine is an example. Interestingly, alanine and other amino acids exist primarily in a doubly charged form called a *zwitterion* rather than in the uncharged form. The zwitterion form arises because amino acids have both acidic and basic sites within the same molecule and therefore undergo an internal acid–base reaction.



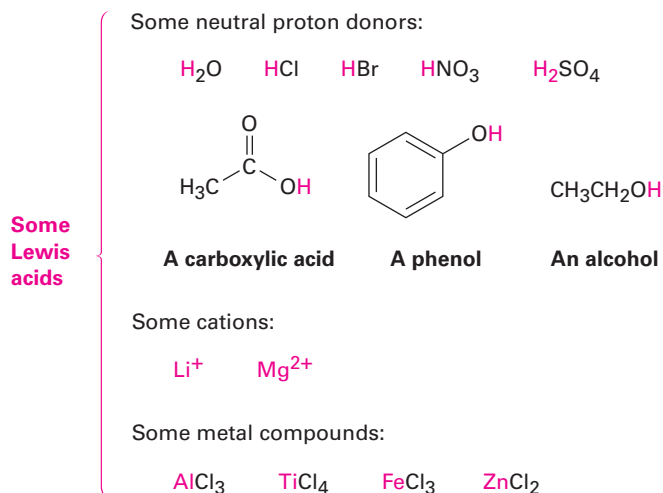
## 2.11 Acids and Bases: The Lewis Definition

The Lewis definition of acids and bases is broader and more encompassing than the Brønsted–Lowry definition because it's not limited to substances that donate or accept just protons. A **Lewis acid** is a substance that *accepts an electron pair*, and a **Lewis base** is a substance that *donates an electron pair*. The donated electron pair is shared between the acid and the base in a covalent bond.



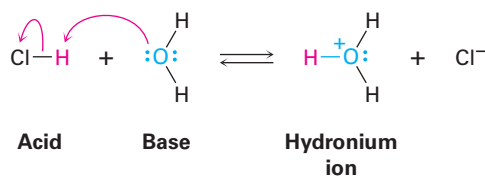
Look closely at the acid–base reaction in Figure 2.5, and note how it is shown. Dimethyl ether, the Lewis base, donates an electron pair to a vacant valence orbital of the boron atom in  $\text{BF}_3$ , a Lewis acid. The direction of electron-pair flow from the base to acid is shown using curved arrows, just as the direction of electron flow in going from one resonance structure to another was shown using curved arrows in **Section 2.5**. A curved arrow always means that a pair of electrons moves from the atom at the tail of the arrow to the atom at the head of the arrow. We'll use this curved-arrow notation throughout the remainder of this text to indicate electron flow during reactions.

Some further examples of Lewis acids follow:



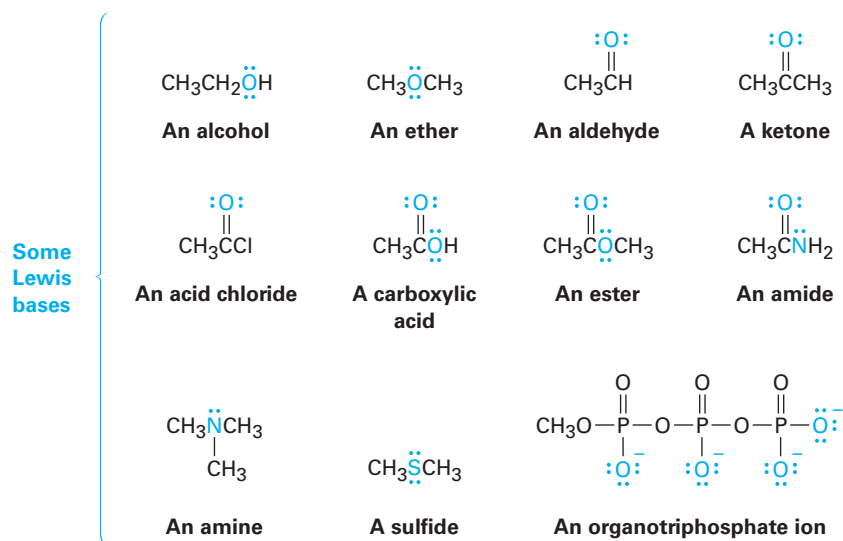
## Lewis Bases

The Lewis definition of a base—a compound with a pair of nonbonding electrons that it can use to bond to a Lewis acid—is similar to the Brønsted–Lowry definition. Thus,  $\text{H}_2\text{O}$ , with its two pairs of nonbonding electrons on oxygen, acts as a Lewis base by donating an electron pair to an  $\text{H}^+$  in forming the hydronium ion,  $\text{H}_3\text{O}^+$ .

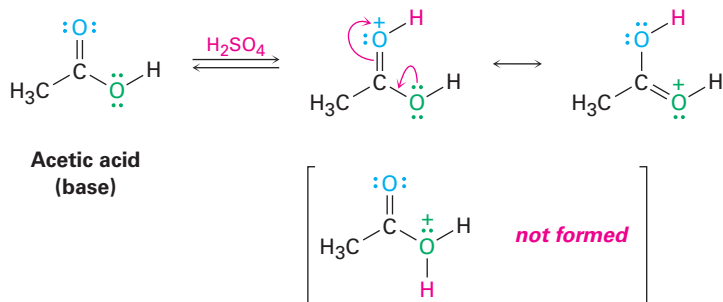


In a more general sense, most oxygen- and nitrogen-containing organic compounds can act as Lewis bases because they have lone pairs of electrons. A divalent oxygen compound has two lone pairs of electrons, and a trivalent nitrogen compound has one lone pair. Note in the following examples that some compounds can act as both acids and bases, just as water can. Alcohols

and carboxylic acids, for instance, act as acids when they donate an  $\text{H}^+$  but as bases when their oxygen atom accepts an  $\text{H}^+$ .



Notice in the list of Lewis bases just given that some compounds, such as carboxylic acids, esters, and amides, have more than one atom with a lone pair of electrons and can therefore react at more than one site. Acetic acid, for example, can be protonated either on the doubly bonded oxygen atom or on the singly bonded oxygen atom. Reaction normally occurs only once in such instances, and the more stable of the two possible protonation products is formed. For acetic acid, protonation by reaction with sulfuric acid occurs on the doubly bonded oxygen because that product is stabilized by two resonance forms.



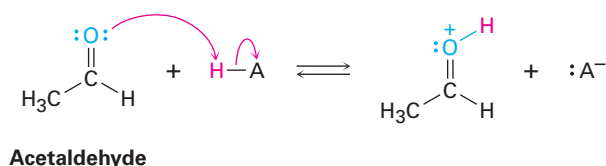
## Using Curved Arrows to Show Electron Flow

## Worked Example 2.6

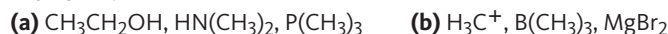
Using curved arrows, show how acetaldehyde,  $\text{CH}_3\text{CHO}$ , can act as a Lewis base.

### Strategy

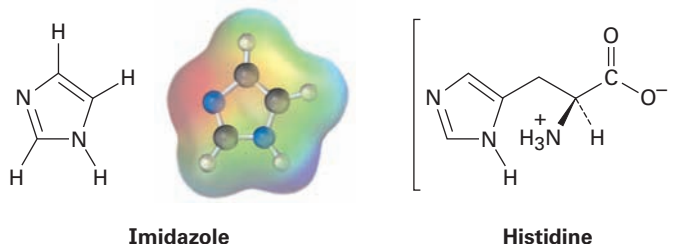
A Lewis base donates an electron pair to a Lewis acid. We therefore need to locate the electron lone pairs on acetaldehyde and use a curved arrow to show the movement of a pair toward the H atom of the acid.

**Solution****Problem 2.17**

Using curved arrows, show how the species in part **(a)** can act as Lewis bases in their reactions with HCl, and show how the species in part **(b)** can act as Lewis acids in their reaction with OH<sup>-</sup>.

**Problem 2.18**

Imidazole forms part of the structure of the amino acid histidine and can act as both an acid and a base.



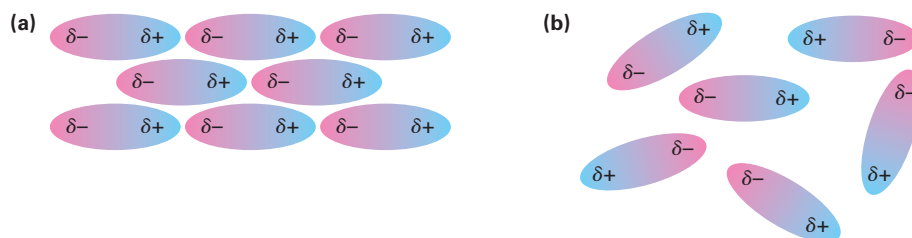
- (a)** Look at the electrostatic potential map of imidazole, and identify the most acidic hydrogen atom and the most basic nitrogen atom.
- (b)** Draw structures for the resonance forms of the products that result when imidazole is protonated by an acid and deprotonated by a base.

## 2.12 Noncovalent Interactions Between Molecules

When thinking about chemical reactivity, chemists usually focus their attention on bonds, the covalent interactions between atoms *within* molecules. Also important, however, particularly in large biomolecules like proteins and nucleic acids, are a variety of interactions *between* molecules that strongly affect molecular properties. Collectively called either *intermolecular forces*, *van der Waals forces*, or **noncovalent interactions**, they are of several different types: dipole-dipole forces, dispersion forces, and hydrogen bonds.

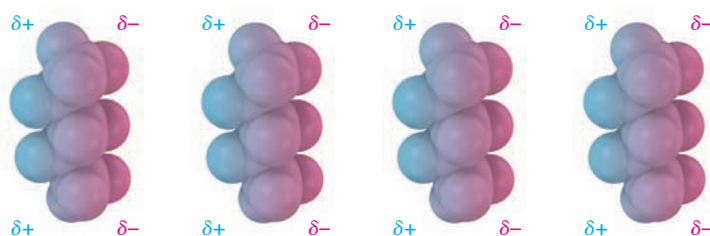
*Dipole-dipole forces* occur between polar molecules as a result of electrostatic interactions among dipoles. The forces can be either attractive or repulsive depending on the orientation of the molecules—attractive when unlike charges

are together and repulsive when like charges are together. The attractive geometry is lower in energy and therefore predominates (**Figure 2.6**).



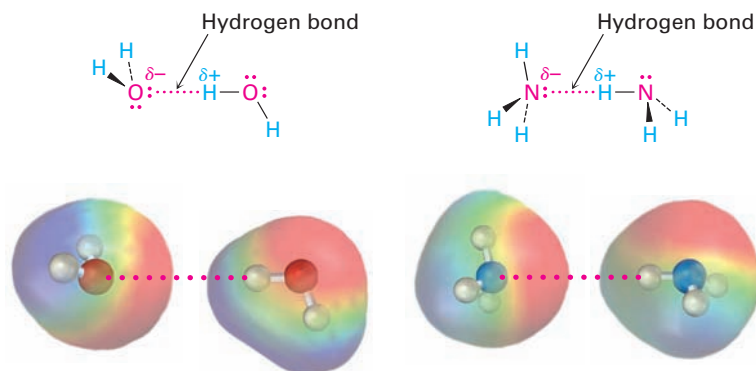
**Figure 2.6** Dipole–dipole forces cause polar molecules **(a)** to attract one another when they orient with unlike charges together, but **(b)** to repel one another when they orient with like charges together.

*Dispersion forces* occur between all neighboring molecules and arise because the electron distribution within molecules is constantly changing. Although uniform on a time-averaged basis, the electron distribution even in nonpolar molecules is likely to be nonuniform at any given instant. One side of a molecule may, by chance, have a slight excess of electrons relative to the opposite side, giving the molecule a temporary dipole. This temporary dipole in one molecule causes a nearby molecule to adopt a temporarily opposite dipole, with the result that a tiny attraction is induced between the two (**Figure 2.7**). Temporary molecular dipoles have only a fleeting existence and are constantly changing, but their cumulative effect is often strong enough to hold molecules close together so that a substance is a liquid or solid rather than a gas.

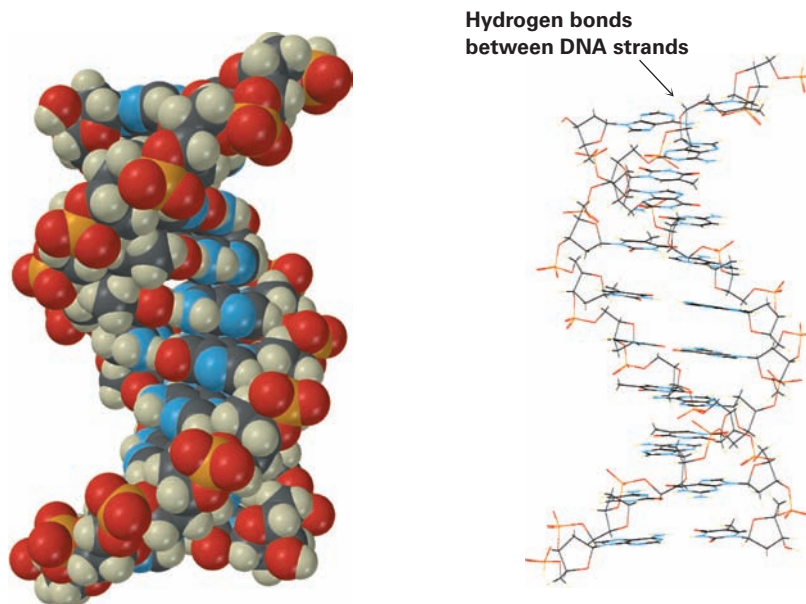


**Figure 2.7** Attractive dispersion forces in nonpolar molecules are caused by temporary dipoles, as shown in these models of pentane,  $C_5H_{12}$ .

Perhaps the most important noncovalent interaction in biological molecules is the **hydrogen bond**, an attractive interaction between a hydrogen bonded to an electronegative O or N atom and an unshared electron pair on another O or N atom. In essence, a hydrogen bond is a very strong dipole–dipole interaction involving polarized O–H or N–H bonds. Electrostatic potential maps of water and ammonia clearly show the positively polarized hydrogens (blue) and the negatively polarized oxygens and nitrogens (red).



Hydrogen bonding has enormous consequences for living organisms. Hydrogen bonds cause water to be a liquid rather than a gas at ordinary temperatures, they hold enzymes in the shapes necessary for catalyzing biological reactions, and they cause strands of deoxyribonucleic acid (DNA) to pair up and coil into the double helix that stores genetic information.

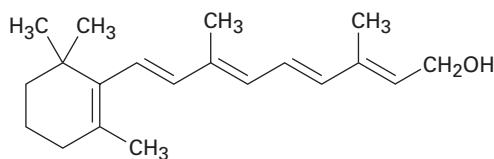


A deoxyribonucleic acid segment

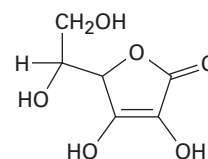
One further point before leaving the subject of noncovalent interactions: biochemists frequently use the term *hydrophilic*, meaning “water-loving,” to describe a substance that is strongly attracted to water and the term *hydrophobic*, meaning “water-fearing,” to describe a substance that is not strongly attracted to water. Hydrophilic substances, such as table sugar, usually have a number of ionic charges or polar  $\text{-OH}$  groups in their structure so they can form hydrogen bonds, whereas hydrophobic substances, such as vegetable oil, do not have groups that form hydrogen bonds, so their attraction to water is limited to weak dispersion forces.

### Problem 2.19

Of the two vitamins A and C, one is hydrophilic and water-soluble while the other is hydrophobic and fat-soluble. Which is which?



Vitamin A  
(retinol)



Vitamin C  
(ascorbic acid)

## A DEEPER LOOK

## Alkaloids: From Cocaine to Dental Anesthetics

Just as ammonia ( $\text{NH}_3$ ) is a weak base, there are a large number of nitrogen-containing organic compounds called *amines* that are also weak bases. In the early days of organic chemistry, basic amines derived from natural sources were known as vegetable alkali, but they are now called *alkaloids*. More than 20,000 alkaloids are known. Their study provided much of the impetus for the growth of organic chemistry in the nineteenth century and remains today an active and fascinating area of research.

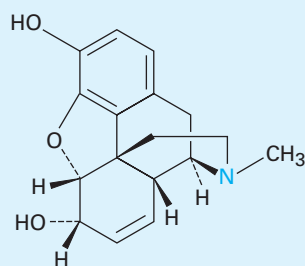
Alkaloids vary widely in structure, from the simple to the enormously complex. The odor of rotting fish, for example, is caused largely by methylamine,  $\text{CH}_3\text{NH}_2$ , a simple relative of ammonia in which one of the  $\text{NH}_3$  hydrogens has been replaced by an organic  $\text{CH}_3$  group. In fact, the use of lemon juice to mask fish odors is simply an acid–base reaction of the citric acid in lemons with methylamine base in the fish.

Many alkaloids have pronounced biological properties, and approximately 50% of the pharmaceutical agents used today are derived from naturally occurring amines. As just three examples, morphine, an analgesic agent, is obtained from the opium poppy *Papaver somniferum*. Ephedrine, a bronchodilator, decongestant, and appetite suppressant, is obtained from the Chinese plant *Ephedra sinica*. Cocaine, both an anesthetic and a stimulant, is obtained from the coca bush *Erythroxylon coca*, endemic to the upland rain forest areas of central South America. (And yes, there really was a small amount of cocaine in the original Coca-Cola recipe, although it was removed in 1906.)

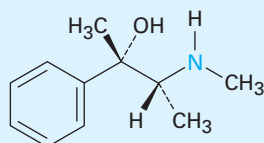


© Gustavo Gilaberti/CORBIS SABA

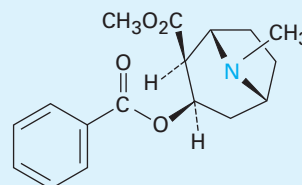
The coca bush *Erythroxylon coca*, native to upland rain forest areas of Colombia, Ecuador, Peru, Bolivia, and western Brazil, is the source of the alkaloid cocaine.



Morphine



Ephedrine



Cocaine

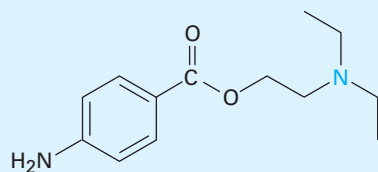
Cocaine itself is no longer used as a medicine because it is too addictive, but its anesthetic properties provoked a search for related but nonaddictive compounds. This search ultimately resulted in the synthesis of the “caine” anesthetics that are commonly used today in dental and surgical anesthesia. Procaine, the first such compound, was synthesized in 1898 and marketed under the name Novocain. It was rapidly adopted and remains in use today as a topical anesthetic. Other related compounds with different activity profiles followed: Lidocaine, marketed as Xylocaine, was introduced in 1943, and mepivacaine (Carbocaine) in the early 1960s. More recently, bupivacaine (Marcaine) and prilocaine (Citanest) have gained popularity. Both are quick-acting, but the effects of

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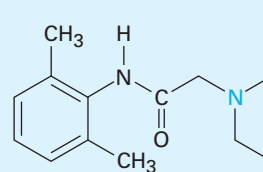


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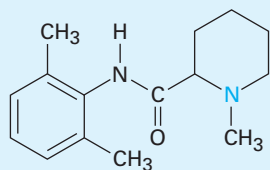
bupivacaine last for 3 to 6 hours while those of prilocaine fade after 45 minutes. Note some structural similarity of all the caines to cocaine itself.



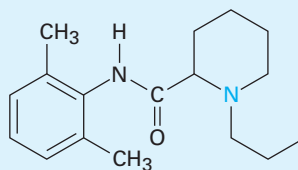
**Procaine**  
(Novocain)



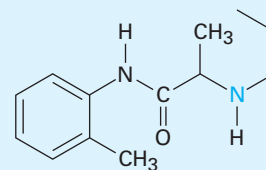
**Lidocaine**  
(Xylocaine)



**Mepivacaine**  
(Carbocaine)



**Bupivacaine**  
(Marcaine)



**Prilocaine**  
(Citanest)

A recent report from the U.S. National Academy of Sciences estimates that less than 1% of all living species have been characterized. Thus, alkaloid chemistry remains today an active area of research, and innumerable substances with potentially useful properties remain to be discovered. Undoubtedly even the caine anesthetics will become obsolete at some point, perhaps supplanted by newly discovered alkaloids.

## Key words

acidity constant ( $K_a$ ), 50  
 Brønsted–Lowry acid, 49  
 Brønsted–Lowry base, 49  
 conjugate acid, 49  
 conjugate base, 49  
 dipole moment ( $\mu$ ), 37  
 electronegativity (EN), 35  
 formal charge, 41  
 hydrogen bond, 61  
 inductive effect, 36  
 Lewis acid, 56  
 Lewis base, 56  
 noncovalent interaction, 60  
 $pK_a$ , 50  
 polar covalent bond, 34  
 resonance form, 43  
 resonance hybrid, 43

## Summary

Understanding both organic and biological chemistry means knowing not just what happens but also why and how it happens at the molecular level. In this chapter, we've reviewed some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation for understanding the specific reactions that will be discussed in subsequent chapters.

Organic molecules often have **polar covalent bonds** as a result of unsymmetrical electron sharing caused by differences in the **electronegativity** of atoms. A carbon–oxygen bond is polar, for example, because oxygen attracts the shared electrons more strongly than carbon does. Carbon–hydrogen bonds are relatively nonpolar. Many molecules as a whole are also polar owing to the presence of individual polar bonds and electron lone pairs. The polarity of a molecule is measured by its **dipole moment**,  $\mu$ .

Plus (+) and minus (–) signs are often used to indicate the presence of **formal charges** on atoms in molecules. Assigning formal charges to specific atoms is a bookkeeping technique that makes it possible to keep track of the valence electrons around an atom and offers some clues about chemical reactivity.

Some substances, such as acetate ion and benzene, can't be represented by a single line-bond structure and must be considered as a **resonance hybrid** of

two or more structures, neither of which is correct by itself. The only difference between two **resonance forms** is in the location of their  $\pi$  and nonbonding electrons. The nuclei remain in the same places in both structures, and the hybridization of the atoms remains the same.

Acidity and basicity are closely related to the ideas of polarity and electronegativity. A **Brønsted–Lowry acid** is a compound that can donate a proton (hydrogen ion,  $H^+$ ), and a **Brønsted–Lowry base** is a compound that can accept a proton. The strength of a Brønsted–Lowry acid or base is expressed by its **acidity constant**,  $K_a$ , or by the negative logarithm of the acidity constant,  $pK_a$ . The larger the  $pK_a$ , the weaker the acid. More useful is the Lewis definition of acids and bases. A **Lewis acid** is a compound that has a low-energy empty orbital that can accept an electron pair;  $Mg^{2+}$ ,  $BF_3$ ,  $AlCl_3$ , and  $H^+$  are examples. A **Lewis base** is a compound that can donate an unshared electron pair;  $NH_3$  and  $H_2O$  are examples. Most organic molecules that contain oxygen and nitrogen can act as Lewis bases toward sufficiently strong acids.

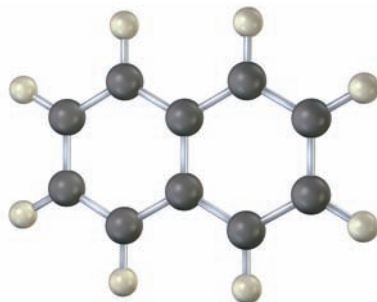
A variety of **noncovalent interactions** have a significant effect on the properties of large biomolecules. **Hydrogen bonding**—the attractive interaction between a positively polarized hydrogen atom bonded to an oxygen or nitrogen atom with an unshared electron pair on another O or N atom, is particularly important in giving proteins and nucleic acids their shapes.

## Exercises

### Visualizing Chemistry

(Problems 2.1–2.19 appear within the chapter.)

- 2.20** Fill in the multiple bonds in the following model of naphthalene,  $C_{10}H_8$  (gray = C, ivory = H). How many resonance structures does naphthalene have? Draw them.

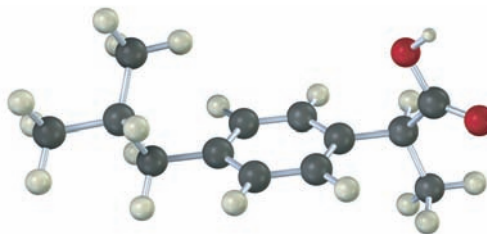


**OWL** Interactive versions of these problems are assignable in OWL for Organic Chemistry.

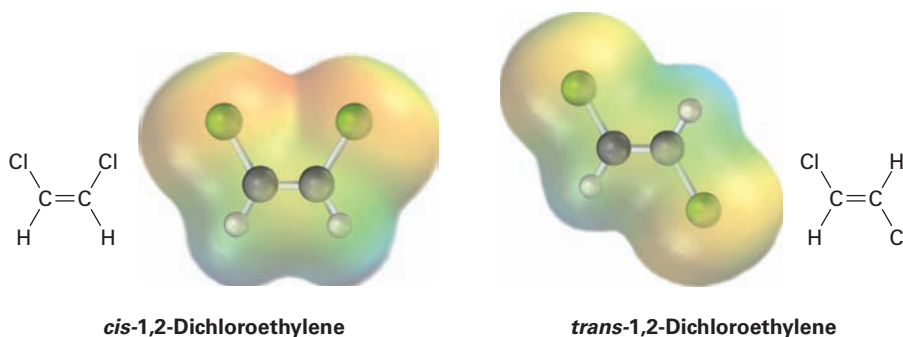
▲ denotes problems linked to the Key Ideas in this chapter.

▲ Problems linked to Key Ideas in this chapter

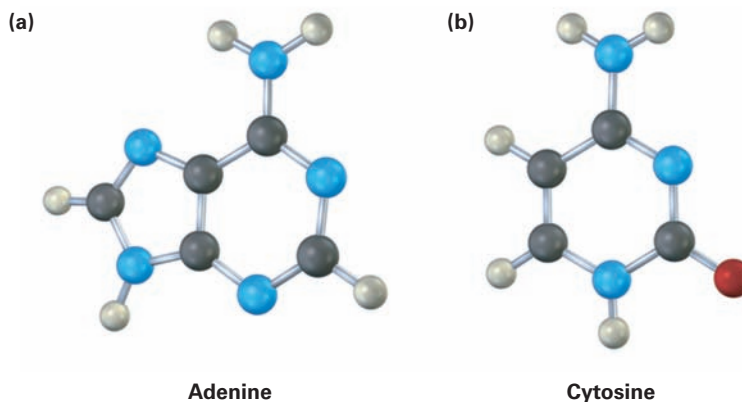
- 2.21 The following model is a representation of ibuprofen, a common over-the-counter pain reliever. Indicate the positions of the multiple bonds, and draw a skeletal structure (gray = C, red = O, ivory = H).



- 2.22 *cis*-1,2-Dichloroethylene and *trans*-dichloroethylene are *isomers*, compounds with the same formula but different chemical structures. Look at the following electrostatic potential maps, and tell whether either compound has a dipole moment.



- 2.23 The following molecular models are representations of (a) adenine and (b) cytosine, constituents of DNA (deoxyribonucleic acid). Indicate the positions of multiple bonds and lone pairs for both, and draw skeletal structures (gray = C, red = O, blue = N, ivory = H).



## Additional Problems

### Electronegativity and Dipole Moments

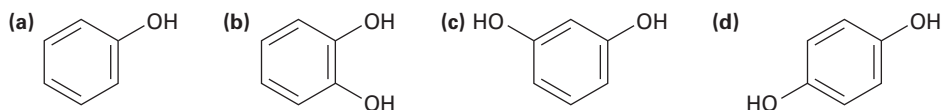
2.24 Identify the most electronegative element in each of the following molecules:

- (a)  $\text{CH}_2\text{FCl}$                       (b)  $\text{FCH}_2\text{CH}_2\text{CH}_2\text{Br}$   
 (c)  $\text{HOCH}_2\text{CH}_2\text{NH}_2$         (d)  $\text{CH}_3\text{OCH}_2\text{Li}$

2.25 Use the electronegativity table given in Figure 2.2 on page 35 to predict which bond in each of the following pairs is more polar, and indicate the direction of bond polarity for each compound.

- (a)  $\text{H}_3\text{C}-\text{Cl}$  or  $\text{Cl}-\text{Cl}$                       (b)  $\text{H}_3\text{C}-\text{H}$  or  $\text{H}-\text{Cl}$   
 (c)  $\text{HO}-\text{CH}_3$  or  $(\text{CH}_3)_3\text{Si}-\text{CH}_3$         (d)  $\text{H}_3\text{C}-\text{Li}$  or  $\text{Li}-\text{OH}$

2.26 Which of the following molecules has a dipole moment? Indicate the expected direction of each.



2.27 (a) The  $\text{H}-\text{Cl}$  bond length is 136 pm. What would the dipole moment of  $\text{HCl}$  be if the molecule were 100% ionic,  $\text{H}^+ \text{Cl}^-$ ?

(b) The actual dipole moment of  $\text{HCl}$  is 1.08 D. What is the percent ionic character of the  $\text{H}-\text{Cl}$  bond?

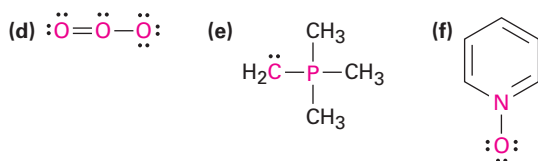
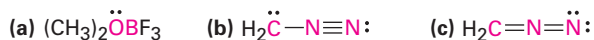
2.28 Phosgene,  $\text{Cl}_2\text{C}=\text{O}$ , has a smaller dipole moment than formaldehyde,  $\text{H}_2\text{C}=\text{O}$ , even though it contains electronegative chlorine atoms in place of hydrogen. Explain.

2.29 Fluoromethane ( $\text{CH}_3\text{F}$ ,  $\mu = 1.81$  D) has a smaller dipole moment than chloromethane ( $\text{CH}_3\text{Cl}$ ,  $\mu = 1.87$  D) even though fluorine is more electronegative than chlorine. Explain.

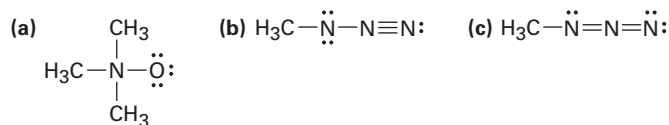
2.30 Methanethiol,  $\text{CH}_3\text{SH}$ , has a substantial dipole moment ( $\mu = 1.52$ ) even though carbon and sulfur have identical electronegativities. Explain.

### Formal Charges

2.31 Calculate the formal charges on the atoms shown in red.

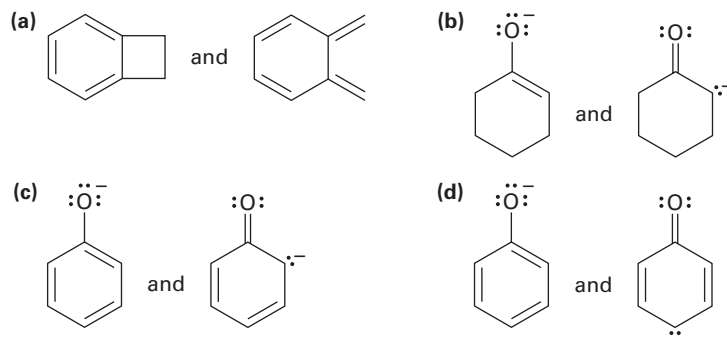


2.32 Assign formal charges to the atoms in each of the following molecules:

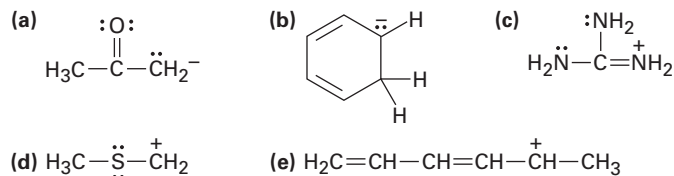


### Resonance

2.33 Which of the following pairs of structures represent resonance forms?



2.34 ▲ Draw as many resonance structures as you can for the following species:



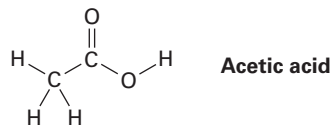
2.35 1,3-Cyclobutadiene is a rectangular molecule with two shorter double bonds and two longer single bonds. Why do the following structures *not* represent resonance forms?



### Acids and Bases

2.36 Alcohols can act either as weak acids or as weak bases, just as water can. Show the reaction of methanol,  $\text{CH}_3\text{OH}$ , with a strong acid such as  $\text{HCl}$  and with a strong base such as  $\text{Na}^+ \text{NH}_2^-$ .

2.37 ▲ The O–H hydrogen in acetic acid is more acidic than any of the C]H hydrogens. Explain this result using resonance structures.



▲ Problems linked to Key Ideas in this chapter

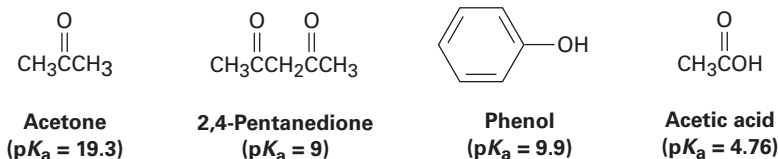
**2.38** Draw electron-dot structures for the following molecules, indicating any unshared electron pairs. Which of the compounds are likely to act as Lewis acids and which as Lewis bases?

- (a)  $\text{AlBr}_3$     (b)  $\text{CH}_3\text{CH}_2\text{NH}_2$     (c)  $\text{BH}_3$   
 (d)  $\text{HF}$     (e)  $\text{CH}_3\text{SCH}_3$     (f)  $\text{TiCl}_4$

**2.39** Write the products of the following acid–base reactions:

- (a)  $\text{CH}_3\text{OH} + \text{H}_2\text{SO}_4 \rightleftharpoons ?$   
 (b)  $\text{CH}_3\text{OH} + \text{NaNH}_2 \rightleftharpoons ?$   
 (c)  $\text{CH}_3\text{NH}_3^+ \text{Cl}^- + \text{NaOH} \rightleftharpoons ?$

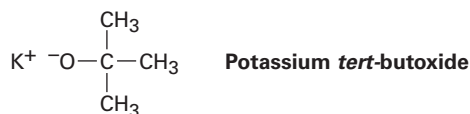
**2.40** Rank the following substances in order of increasing acidity:



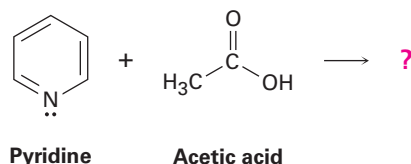
**2.41** Which, if any, of the substances in Problem 2.40 is a strong enough acid to react almost completely with  $\text{NaOH}$ ? (The  $\text{p}K_{\text{a}}$  of  $\text{H}_2\text{O}$  is 15.74.)

**2.42** The ammonium ion ( $\text{NH}_4^+$ ,  $\text{p}K_{\text{a}} = 9.25$ ) has a lower  $\text{p}K_{\text{a}}$  than the methylammonium ion ( $\text{CH}_3\text{NH}_3^+$ ,  $\text{p}K_{\text{a}} = 10.66$ ). Which is the stronger base, ammonia ( $\text{NH}_3$ ) or methylamine ( $\text{CH}_3\text{NH}_2$ )? Explain.

**2.43** Is *tert*-butoxide anion a strong enough base to react significantly with water? In other words, can a solution of potassium *tert*-butoxide be prepared in water? The  $\text{p}K_{\text{a}}$  of *tert*-butyl alcohol is approximately 18.



**2.44** Predict the structure of the product formed in the reaction of the organic base pyridine with the organic acid acetic acid, and use curved arrows to indicate the direction of electron flow.



**2.45** Calculate  $K_{\text{a}}$  values from the following  $\text{p}K_{\text{a}}$ 's:

- (a) Acetone,  $\text{p}K_{\text{a}} = 19.3$     (b) Formic acid,  $\text{p}K_{\text{a}} = 3.75$

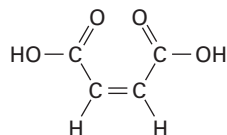
**2.46** Calculate  $\text{p}K_{\text{a}}$  values from the following  $K_{\text{a}}$ 's:

- (a) Nitromethane,  $K_{\text{a}} = 5.0 \times 10^{-11}$     (b) Acrylic acid,  $K_{\text{a}} = 5.6 \times 10^{-5}$

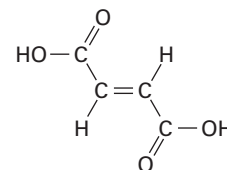
- 2.47** What is the pH of a 0.050 M solution of formic acid,  $pK_a = 3.75$ ?
- 2.48** Sodium bicarbonate,  $\text{NaHCO}_3$ , is the sodium salt of carbonic acid ( $\text{H}_2\text{CO}_3$ ),  $pK_a = 6.37$ . Which of the substances shown in Problem 2.40 will react significantly with sodium bicarbonate?

### General Problems

- 2.49** Maleic acid has a dipole moment, but the closely related fumaric acid, a substance involved in the citric acid cycle by which food molecules are metabolized, does not. Explain.



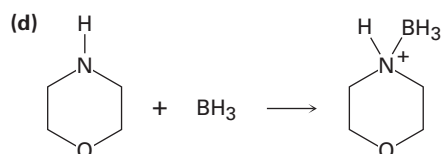
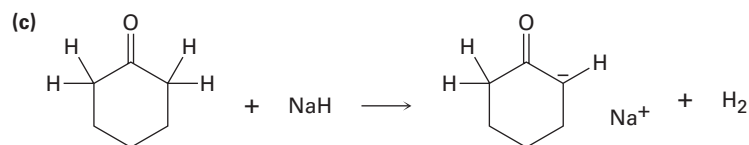
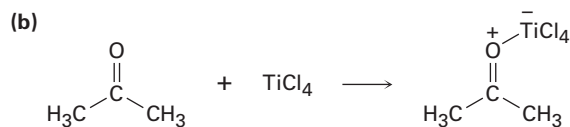
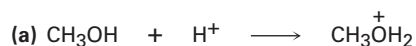
Maleic acid



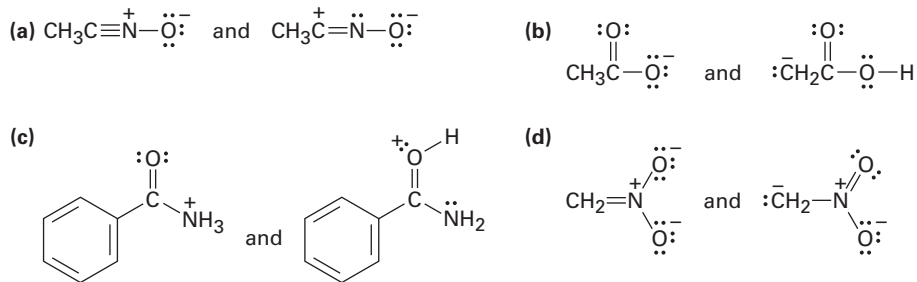
Fumaric acid

- 2.50** Assume that you have two unlabeled bottles, one of which contains phenol ( $pK_a = 9.9$ ) and one of which contains acetic acid ( $pK_a = 4.76$ ). In light of your answer to Problem 2.48, suggest a simple way to determine what is in each bottle.

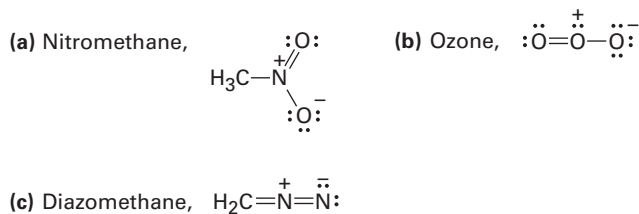
- 2.51** Identify the acids and bases in the following reactions:



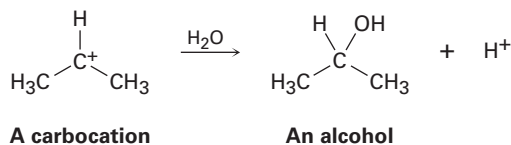
2.52 ▲ Which of the following pairs represent resonance structures?



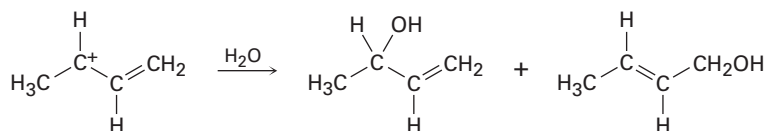
2.53 ▲ Draw as many resonance structures as you can for the following species, adding appropriate formal charges to each:



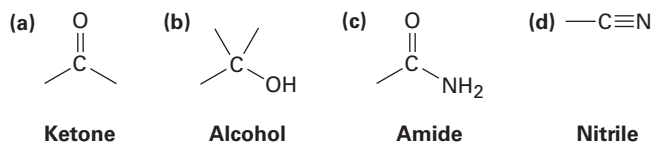
2.54 Carbocations, which contain a trivalent, positively charged carbon atom, react with water to give alcohols:



How can you account for the fact that the following carbocation gives a mixture of *two* alcohols on reaction with water?



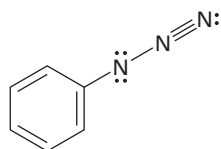
2.55 We'll see in the next chapter that organic molecules can be classified according to the *functional groups* they contain, where a functional group is a collection of atoms with a characteristic chemical reactivity. Use the electronegativity values given in Figure 2.2 on page 35 to predict the direction of polarization of the following functional groups.



▲ Problems linked to Key Ideas in this chapter

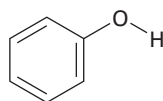
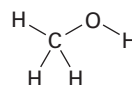


- 2.56 The *azide* functional group (Problem 2.55), such as occurs in azidobenzene, contains three adjacent nitrogen atoms. One resonance structures for azidobenzene is shown. Draw three additional resonance structures, and assign appropriate formal charges to the atoms in all four.

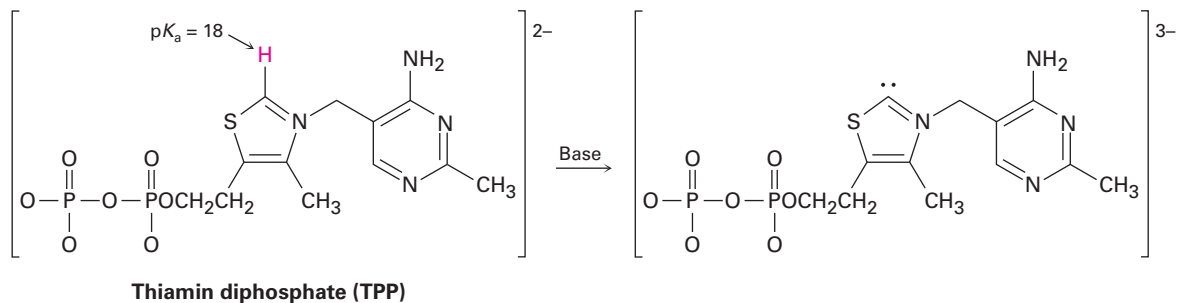


Azidobenzene

- 2.57 Phenol,  $C_6H_5OH$ , is a stronger acid than methanol,  $CH_3OH$ , even though both contain an O–H bond. Draw the structures of the anions resulting from loss of  $H^+$  from phenol and methanol, and use resonance structures to explain the difference in acidity.

Phenol ( $pK_a = 9.89$ )Methanol ( $pK_a = 15.54$ )

**2.58** Thiamin diphosphate (TPP), a derivative of vitamin B<sub>1</sub> required for glucose metabolism, is a weak acid that can be deprotonated by base. Assign formal charges to the appropriate atoms in both TPP and its deprotonation product.



# 3



The bristlecone pine is the oldest living organism on Earth. The waxy coating on its needles contains a mixture of organic compounds called alkanes, the subject of this chapter. Image copyright Mike Norton, 2010. Used under license from Shutterstock.com

## Organic Compounds: Alkanes and Their Stereochemistry

- 3.1 Functional Groups
- 3.2 Alkanes and Alkane Isomers
- 3.3 Alkyl Groups
- 3.4 Naming Alkanes
- 3.5 Properties of Alkanes
- 3.6 Conformations of Ethane
- 3.7 Conformations of Other Alkanes  
A Deeper Look—Gasoline

According to *Chemical Abstracts*, the publication that abstracts and indexes the chemical literature, there are more than 50 million known organic compounds. Each of these compounds has its own physical properties, such as melting point and boiling point, and each has its own chemical reactivity.

Chemists have learned through years of experience that organic compounds can be classified into families according to their structural features and that the members of a given family often have similar chemical behavior. Instead of 40 million compounds with random reactivity, there are a few dozen families of organic compounds whose chemistry is reasonably predictable. We'll study the chemistry of specific families throughout much of this book, beginning in this chapter with a look at the simplest family, the *alkanes*.

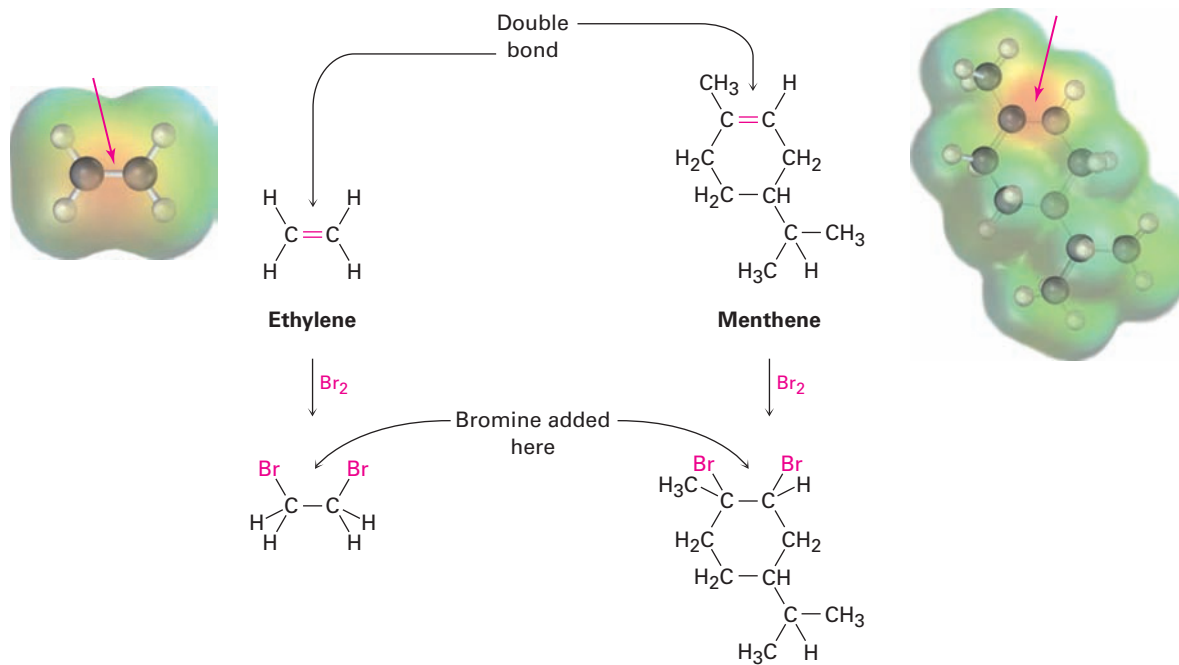
**Why This Chapter?** Alkanes are relatively unreactive and not often involved in chemical reactions, but they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we'll use alkanes to introduce the basic approach to naming organic compounds and to take an initial look at some of the three-dimensional aspects of molecules, a topic of particular importance in understanding biological organic chemistry.

### 3.1 Functional Groups

The structural features that make it possible to classify compounds into families are called *functional groups*. A **functional group** is a group of atoms within a molecule that has a characteristic chemical behavior. Chemically, a given functional group behaves in nearly the same way in every molecule it's a part of. For example, compare ethylene, a plant hormone that causes fruit to ripen, with menthene, a much more complicated molecule found in peppermint oil. Both substances contain a carbon-carbon double-bond functional group, and both therefore react with  $\text{Br}_2$  in the same way to give a product in which a Br atom

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has added to each of the double-bond carbons (**Figure 3.1**). This example is typical: *the chemistry of every organic molecule, regardless of size and complexity, is determined by the functional groups it contains.*



**Figure 3.1** The reactions of ethylene and menthene with bromine. In both molecules, the carbon-carbon double-bond functional group has a similar polarity pattern, so both molecules react with  $\text{Br}_2$  in the same way. The size and complexity of the molecules are not important.

Look at Table 3.1 on pages 76 and 77, which lists many of the common functional groups and gives simple examples of their occurrence. Some functional groups have only carbon-carbon double or triple bonds; others have halogen atoms; and still others contain oxygen, nitrogen, or sulfur. Much of the chemistry you'll be studying is the chemistry of these functional groups.

## Functional Groups with Carbon-Carbon Multiple Bonds

Alkenes, alkynes, and arenes (aromatic compounds) all contain carbon-carbon multiple bonds. *Alkenes* have a double bond, *alkynes* have a triple bond, and *arenes* have alternating double and single bonds in a six-membered ring of carbon atoms. Because of their structural similarities, these compounds also have chemical similarities.

Table 3.1 Structures of Some Common Functional Groups

Name	Structure*	Name ending	Example
Alkene (double bond)		-ene	H <sub>2</sub> C=CH <sub>2</sub> Ethene
Alkyne (triple bond)		-yne	HC≡CH Ethyne
Arene (aromatic ring)		None	 Benzene
Halide	 (X = F, Cl, Br, I)	None	CH <sub>3</sub> Cl Chloromethane
Alcohol		-ol	CH <sub>3</sub> OH Methanol
Ether		ether	CH <sub>3</sub> OCH <sub>3</sub> Dimethyl ether
Monophosphate		phosphate	CH <sub>3</sub> OPO <sub>3</sub> <sup>2-</sup> Methyl phosphate
Diphosphate		diphosphate	CH <sub>3</sub> OP <sub>2</sub> O <sub>6</sub> <sup>3-</sup> Methyl diphosphate
Amine		-amine	CH <sub>3</sub> NH <sub>2</sub> Methylamine
Imine (Schiff base)		None	 CH <sub>3</sub> CCH <sub>3</sub> Acetone imine
Nitrile		-nitrile	CH <sub>3</sub> C≡N Ethanenitrile
Thiol		-thiol	CH <sub>3</sub> SH Methanethiol

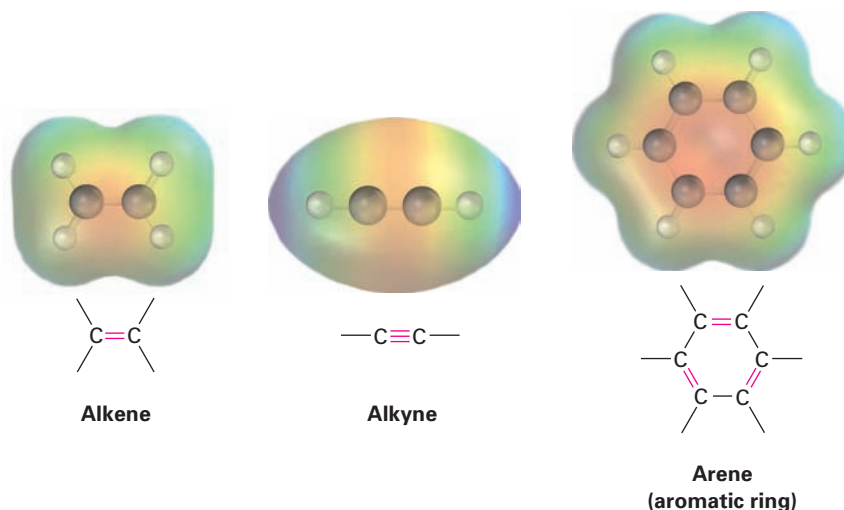
\*The bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule.

Continued

**Table 3.1** Structures of Some Common Functional Groups (*continued*)

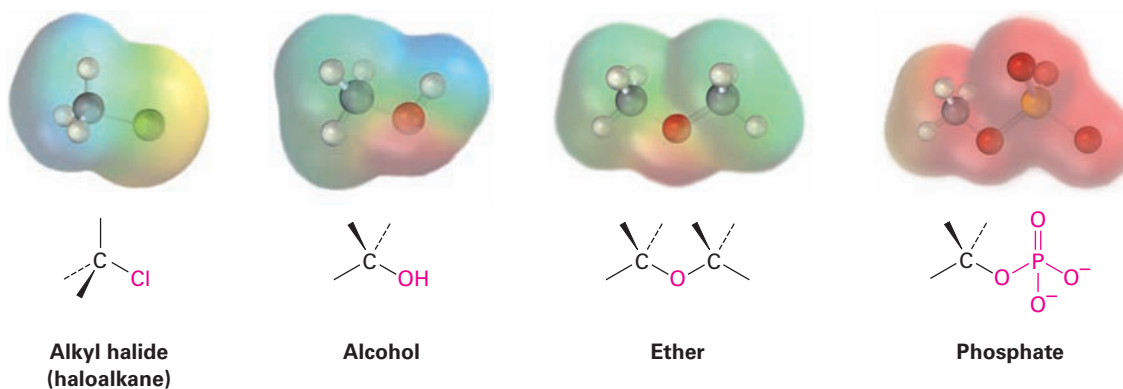
Name	Structure*	Name ending	Example
Sulfide		<i>sulfide</i>	CH <sub>3</sub> SCH <sub>3</sub> Dimethyl sulfide
Disulfide		<i>disulfide</i>	CH <sub>3</sub> SSCH <sub>3</sub> Dimethyl disulfide
Sulfoxide		<i>sulfoxide</i>	 CH <sub>3</sub> S <sup>+</sup> CH <sub>3</sub> Dimethyl sulfoxide
Aldehyde		<i>-al</i>	 CH <sub>3</sub> CH Ethanal
Ketone		<i>-one</i>	 CH <sub>3</sub> CCH <sub>3</sub> Propanone
Carboxylic acid		<i>-oic acid</i>	 CH <sub>3</sub> COH Ethanoic acid
Ester		<i>-oate</i>	 CH <sub>3</sub> COCH <sub>3</sub> Methyl ethanoate
Thioester		<i>-thioate</i>	 CH <sub>3</sub> CSCH <sub>3</sub> Methyl ethanethioate
Amide		<i>-amide</i>	 CH <sub>3</sub> CNH <sub>2</sub> Ethanamide
Acid chloride		<i>-oyl chloride</i>	 CH <sub>3</sub> CCl Ethanoyl chloride
Carboxylic acid anhydride		<i>-oic anhydride</i>	 CH <sub>3</sub> COCH <sub>3</sub> Ethanoic anhydride

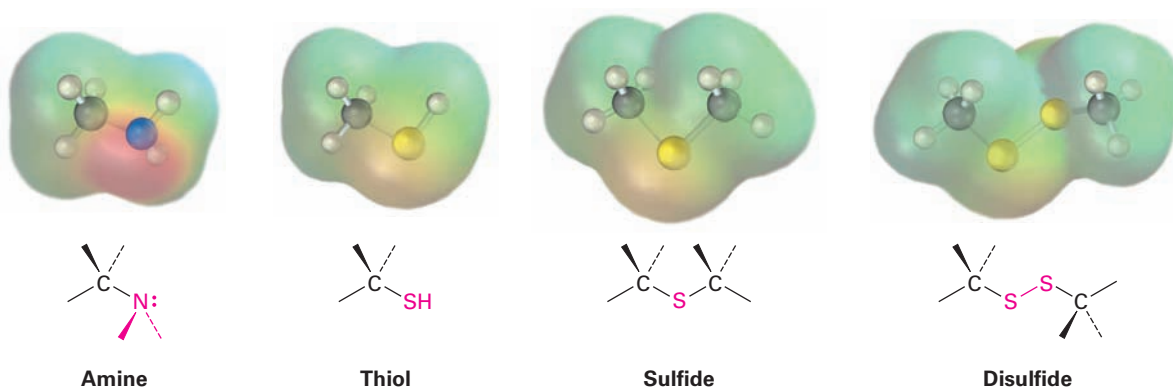
\*The bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule.



### Functional Groups with Carbon Singly Bonded to an Electronegative Atom

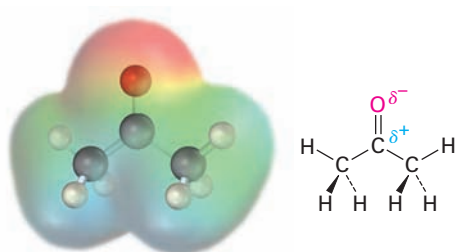
Alkyl halides (haloalkanes), alcohols, ethers, alkyl phosphates, amines, thiols, sulfides, and disulfides all have a carbon atom singly bonded to an electronegative atom—halogen, oxygen, nitrogen, or sulfur. Alkyl halides have a carbon atom bonded to halogen ( $-\text{X}$ ), alcohols have a carbon atom bonded to the oxygen of a hydroxyl group ( $-\text{OH}$ ), ethers have two carbon atoms bonded to the same oxygen, organophosphates have a carbon atom bonded to the oxygen of a phosphate group ( $-\text{OPO}_3^{2-}$ ), amines have a carbon atom bonded to a nitrogen, thiols have a carbon atom bonded to the sulfur of an  $-\text{SH}$  group, sulfides have two carbon atoms bonded to the same sulfur, and disulfides have carbon atoms bonded to two sulfurs that are joined together. In all cases, the bonds are polar, with the carbon atom bearing a partial positive charge ( $\delta+$ ) and the electronegative atom bearing a partial negative charge ( $\delta-$ ).



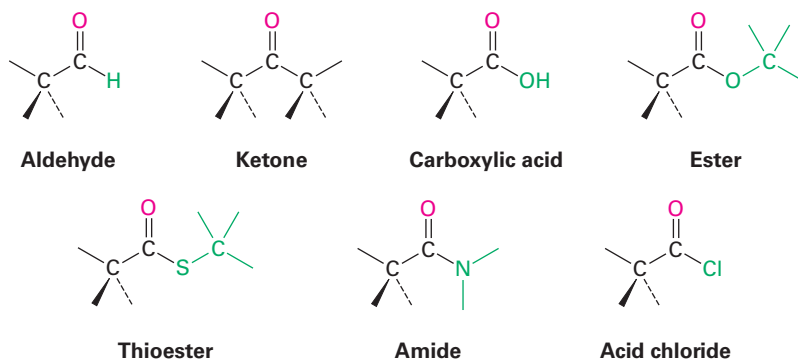


### Functional Groups with a Carbon–Oxygen Double Bond (Carbonyl Groups)

The *carbonyl group*, C=O (pronounced car-bo-**neel**) is common to many of the families listed in Table 3.1. Carbonyl groups are present in a large majority of organic compounds and in practically all biological molecules. These compounds behave similarly in many respects but differ depending on the identity of the atoms bonded to the carbonyl-group carbon. Aldehydes have at least one hydrogen bonded to the C=O, ketones have two carbons bonded to the C=O, carboxylic acids have an –OH group bonded to the C=O, esters have an ether-like oxygen bonded to the C=O, thioesters have a sulfide-like sulfur bonded to the C=O, amides have an amine-like nitrogen bonded to the C=O, acid chlorides have a chlorine bonded to the C=O, and so on. The carbonyl carbon atom bears a partial positive charge ( $\delta^+$ ), and the oxygen bears a partial negative charge ( $\delta^-$ ).



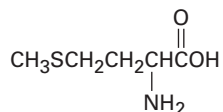
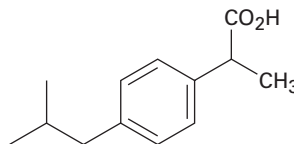
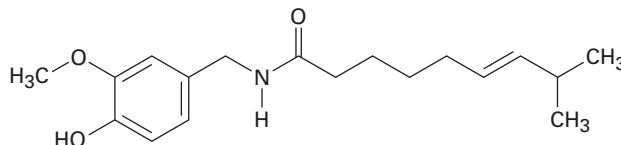
Acetone – a typical carbonyl compound





**Problem 3.1**

Identify the functional groups in each of the following molecules:

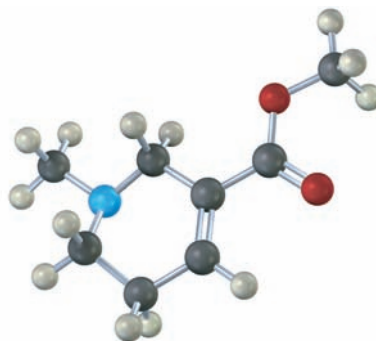
**(a)** Methionine, an amino acid:**(b)** Ibuprofen, a pain reliever:**(c)** Capsaicin, the pungent substance in chili peppers:**Problem 3.2**

Propose structures for simple molecules that contain the following functional groups:

- (a)** Alcohol    **(b)** Aromatic ring    **(c)** Carboxylic acid  
**(d)** Amine    **(e)** Both ketone and amine    **(f)** Two double bonds

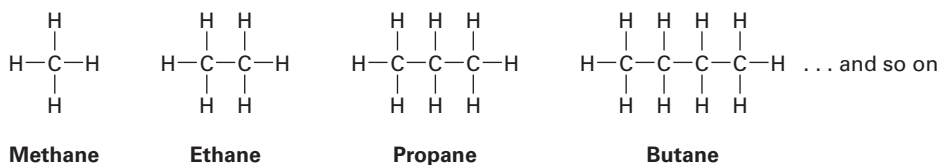
**Problem 3.3**

Identify the functional groups in the following model of arecoline, a veterinary drug used to control worms in animals. Convert the drawing into a line-bond structure and a molecular formula (red = O, blue = N).

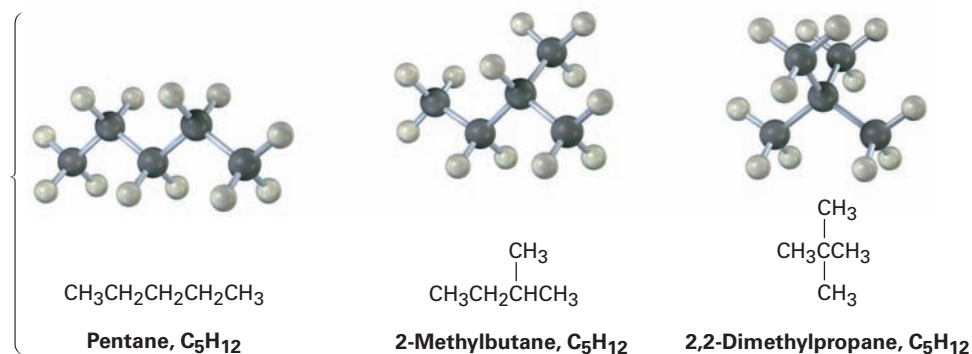


## 3.2 Alkanes and Alkane Isomers

Before beginning a systematic study of the different functional groups, let's look first at the simplest family of molecules—the *alkanes*—to develop some general ideas that apply to all families. We saw in **Section 1.7** that the carbon–carbon single bond in ethane results from  $\sigma$  (head-on) overlap of carbon  $sp^3$  hybrid orbitals. If we imagine joining three, four, five, or even more carbon atoms by C–C single bonds, we can generate the large family of molecules called **alkanes**.







Compounds like butane and pentane, whose carbons are all connected in a row, are called **straight-chain alkanes**, or *normal alkanes*. Compounds like 2-methylpropane (isobutane), 2-methylbutane, and 2,2-dimethylpropane, whose carbon chains branch, are called **branched-chain alkanes**.

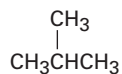
Compounds like the two C<sub>4</sub>H<sub>10</sub> molecules and the three C<sub>5</sub>H<sub>12</sub> molecules, which have the same formula but different structures, are called *isomers*, from the Greek *isos* + *meros*, meaning “made of the same parts.” **Isomers** are compounds that have the same numbers and kinds of atoms but differ in the way the atoms are arranged. Compounds like butane and isobutane, whose atoms are connected differently, are called **constitutional isomers**. We’ll see shortly that other kinds of isomers are also possible, even among compounds whose atoms are connected in the same order. As Table 3.2 shows, the number of possible alkane isomers increases dramatically as the number of carbon atoms increases.

Constitutional isomerism is not limited to alkanes—it occurs widely throughout organic chemistry. Constitutional isomers may have different carbon skeletons (as in isobutane and butane), different functional groups (as in ethanol and dimethyl ether), or different locations of a functional group along the chain (as in isopropylamine and propylamine). Regardless of the reason for the isomerism, constitutional isomers are always different compounds with different properties but with the same formula.

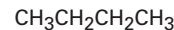
**Table 3.2** Number of Alkane Isomers

Formula	Number of isomers
C <sub>6</sub> H <sub>14</sub>	5
C <sub>7</sub> H <sub>16</sub>	9
C <sub>8</sub> H <sub>18</sub>	18
C <sub>9</sub> H <sub>20</sub>	35
C <sub>10</sub> H <sub>22</sub>	75
C <sub>15</sub> H <sub>32</sub>	4,347
C <sub>20</sub> H <sub>42</sub>	366,319
C <sub>30</sub> H <sub>62</sub>	4,111,846,763

**Different carbon skeletons**  
C<sub>4</sub>H<sub>10</sub>



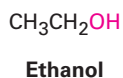
and



**2-Methylpropane (isobutane)**

**Butane**

**Different functional groups**  
C<sub>2</sub>H<sub>6</sub>O

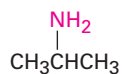


and

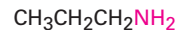


**Dimethyl ether**

**Different position of functional groups**  
C<sub>3</sub>H<sub>9</sub>N



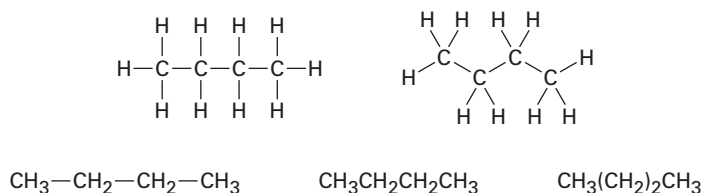
and



**Isopropylamine**

**Propylamine**

A given alkane can be drawn in many ways. For example, the straight-chain, four-carbon alkane called butane can be represented by any of the structures shown in **Figure 3.2**. These structures don't imply any particular three-dimensional geometry for butane; they indicate only the connections among atoms. In practice, as noted in **Section 1.12**, chemists rarely draw all the bonds in a molecule and usually refer to butane by the condensed structure,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$  or  $\text{CH}_3(\text{CH}_2)_2\text{CH}_3$ . Still more simply, butane can be represented as  $n\text{-C}_4\text{H}_{10}$ , where  $n$  denotes *normal* (straight-chain) butane.



**Figure 3.2** Some representations of butane,  $\text{C}_4\text{H}_{10}$ . The molecule is the same regardless of how it's drawn. These structures imply only that butane has a continuous chain of four carbon atoms; they do not imply any specific geometry.

Straight-chain alkanes are named according to the number of carbon atoms they contain, as shown in Table 3.3. With the exception of the first four compounds—methane, ethane, propane, and butane—whose names have historical roots, the alkanes are named based on Greek numbers. The suffix *-ane* is added to the end of each name to indicate that the molecule identified is an alkane. Thus, *pentane* is the five-carbon alkane, *hexane* is the six-carbon alkane, and so on. We'll soon see that these alkane names form the basis for naming all other organic compounds, so at least the first ten should be memorized.

**Table 3.3** Names of Straight-Chain Alkanes

Number of carbons ( $n$ )	Name	Formula ( $\text{C}_n\text{H}_{2n+2}$ )	Number of carbons ( $n$ )	Name	Formula ( $\text{C}_n\text{H}_{2n+2}$ )
1	Methane	$\text{CH}_4$	9	Nonane	$\text{C}_9\text{H}_{20}$
2	Ethane	$\text{C}_2\text{H}_6$	10	Decane	$\text{C}_{10}\text{H}_{22}$
3	Propane	$\text{C}_3\text{H}_8$	11	Undecane	$\text{C}_{11}\text{H}_{24}$
4	Butane	$\text{C}_4\text{H}_{10}$	12	Dodecane	$\text{C}_{12}\text{H}_{26}$
5	Pentane	$\text{C}_5\text{H}_{12}$	13	Tridecane	$\text{C}_{13}\text{H}_{28}$
6	Hexane	$\text{C}_6\text{H}_{14}$	20	Icosane	$\text{C}_{20}\text{H}_{42}$
7	Heptane	$\text{C}_7\text{H}_{16}$	30	triacontane	$\text{C}_{30}\text{H}_{62}$
8	Octane	$\text{C}_8\text{H}_{18}$			

## Drawing the Structures of Isomers

## Worked Example 3.1

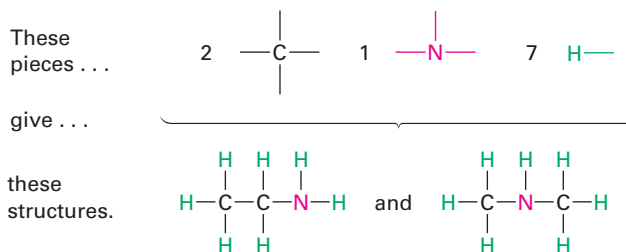
Propose structures for two isomers with the formula  $\text{C}_2\text{H}_7\text{N}$ .

### Strategy

We know that carbon forms four bonds, nitrogen forms three, and hydrogen forms one. Write down the carbon atoms first, and then use a combination of trial and error plus intuition to put the pieces together.

**Solution**

There are two isomeric structures. One has the connection C–C–N, and the other has the connection C–N–C.

**Problem 3.4**

Draw structures of the five isomers of  $\text{C}_6\text{H}_{14}$ .

**Problem 3.5**

Propose structures that meet the following descriptions:

- Two isomeric esters with the formula  $\text{C}_5\text{H}_{10}\text{O}_2$
- Two isomeric nitriles with the formula  $\text{C}_4\text{H}_7\text{N}$
- Two isomeric disulfides with the formula  $\text{C}_4\text{H}_{10}\text{S}_2$

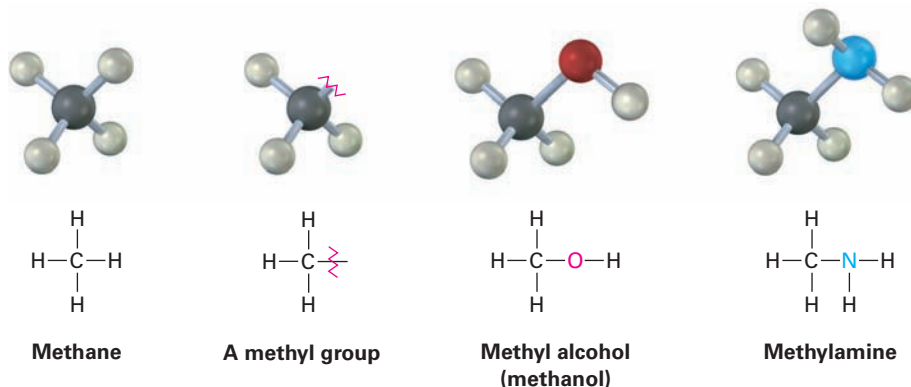
**Problem 3.6**

How many isomers are there with the following descriptions?

- Alcohols with the formula  $\text{C}_3\text{H}_8\text{O}$
- Bromoalkanes with the formula  $\text{C}_4\text{H}_9\text{Br}$
- Thioesters with the formula  $\text{C}_4\text{H}_8\text{OS}$

## 3.3 Alkyl Groups

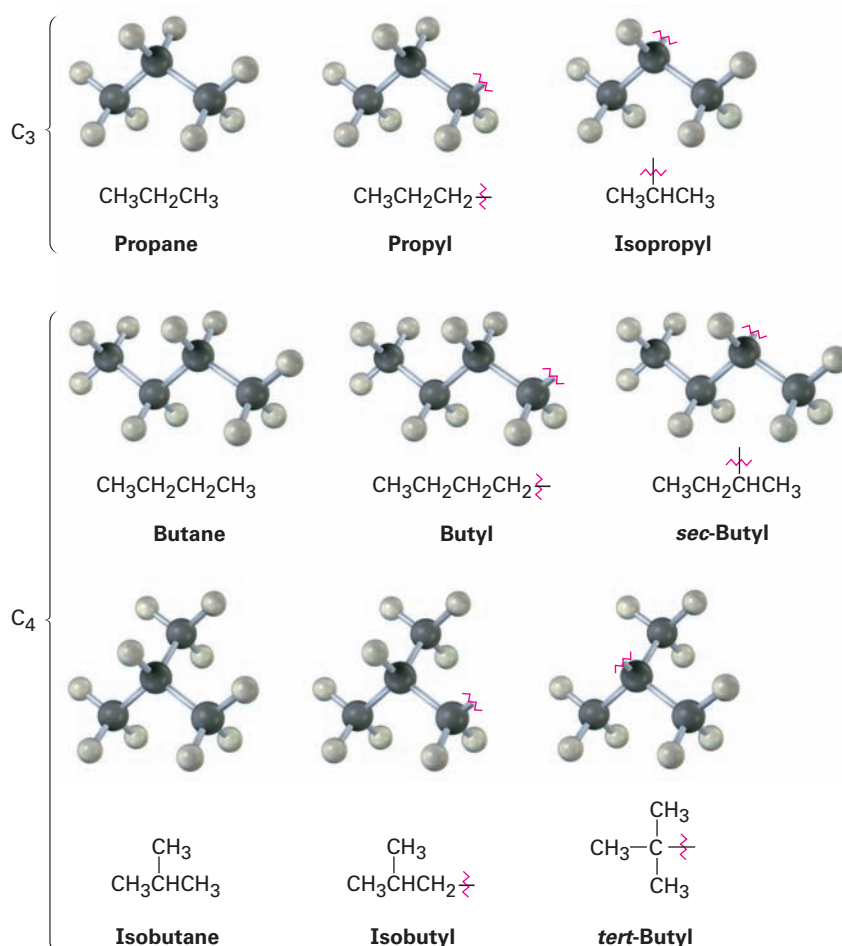
If you imagine removing a hydrogen atom from an alkane, the partial structure that remains is called an **alkyl group**. Alkyl groups are not stable compounds themselves, they are simply parts of larger compounds. Alkyl groups are named by replacing the *-ane* ending of the parent alkane with an *-yl* ending. For example, removal of a hydrogen from methane,  $\text{CH}_4$ , generates a *methyl* group,  $-\text{CH}_3$ , and removal of a hydrogen from ethane,  $\text{CH}_3\text{CH}_3$ , generates an *ethyl* group,  $-\text{CH}_2\text{CH}_3$ . Similarly, removal of a hydrogen atom from the end carbon of any straight-chain alkane gives the series of straight-chain alkyl groups shown in Table 3.4. Combining an alkyl group with any of the functional groups listed earlier makes it possible to generate and name many thousands of compounds. For example:



**Table 3.4** Some Straight-Chain Alkyl Groups

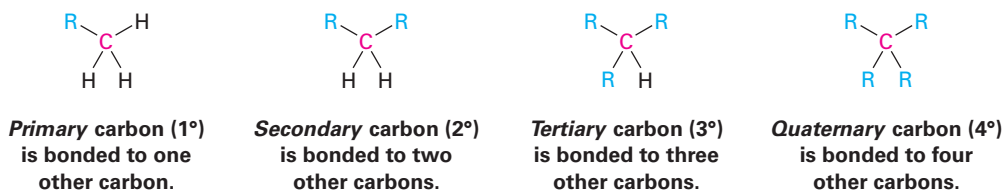
Alkane	Name	Alkyl group	Name (abbreviation)
CH <sub>4</sub>	Methane	–CH <sub>3</sub>	Methyl (Me)
CH <sub>3</sub> CH <sub>3</sub>	Ethane	–CH <sub>2</sub> CH <sub>3</sub>	Ethyl (Et)
CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>	Propane	–CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Propyl (Pr)
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Butane	–CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Butyl (Bu)
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Pentane	–CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	Pentyl, or amyl

Just as straight-chain alkyl groups are generated by removing a hydrogen from an end carbon, branched alkyl groups are generated by removing a hydrogen atom from an internal carbon. Two 3-carbon alkyl groups and four 4-carbon alkyl groups are possible (**Figure 3.3**).

**Figure 3.3** Alkyl groups generated from straight-chain alkanes.

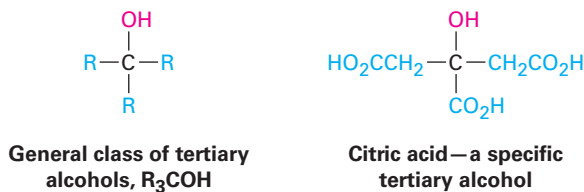
One further comment about naming alkyl groups: the prefixes *sec-* (for secondary) and *tert-* (for tertiary) used for the C<sub>4</sub> alkyl groups in Figure 3.3 refer to

the number of other carbon atoms attached to the branching carbon atom. There are four possibilities: primary ( $1^\circ$ ), secondary ( $2^\circ$ ), tertiary ( $3^\circ$ ), and quaternary ( $4^\circ$ ).

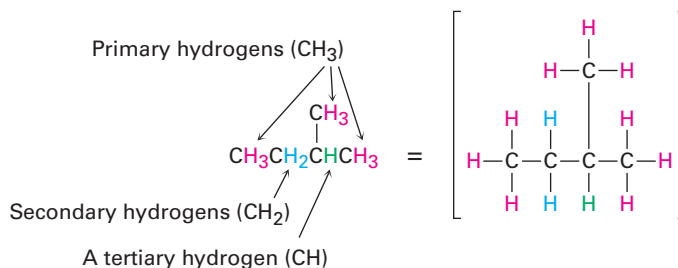


The symbol **R** is used here and throughout organic chemistry to represent a *generalized* organic group. The R group can be methyl, ethyl, propyl, or any of a multitude of others. You might think of **R** as representing the **R**est of the molecule, which isn't specified.

The terms *primary*, *secondary*, *tertiary*, and *quaternary* are routinely used in organic chemistry, and their meanings need to become second nature. For example, if we were to say, "Citric acid is a tertiary alcohol," we would mean that it has an alcohol functional group ( $-\text{OH}$ ) bonded to a carbon atom that is itself bonded to three other carbons. (These other carbons may in turn connect to other functional groups.)



In addition, we also speak about hydrogen atoms as being primary, secondary, or tertiary. Primary hydrogen atoms are attached to primary carbons ( $\text{RCH}_3$ ), secondary hydrogens are attached to secondary carbons ( $\text{R}_2\text{CH}_2$ ), and tertiary hydrogens are attached to tertiary carbons ( $\text{R}_3\text{CH}$ ). There is, of course, no such thing as a quaternary hydrogen. (Why not?)

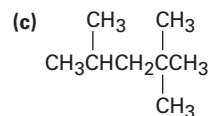
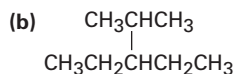
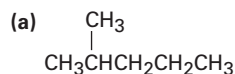


### Problem 3.7

Draw the eight 5-carbon alkyl groups (pentyl isomers).

### Problem 3.8

Identify the carbon atoms in the following molecules as primary, secondary, tertiary, or quaternary:



**Problem 3.9**

Identify the hydrogen atoms on the compounds shown in Problem 3.8 as primary, secondary, or tertiary.

**Problem 3.10**

Draw structures of alkanes that meet the following descriptions:

- (a) An alkane with two tertiary carbons
- (b) An alkane that contains an isopropyl group
- (c) An alkane that has one quaternary and one secondary carbon

## 3.4 Naming Alkanes

In earlier times, when relatively few pure organic chemicals were known, new compounds were named at the whim of their discoverer. Thus, urea ( $\text{CH}_4\text{N}_2\text{O}$ ) is a crystalline substance isolated from urine; morphine ( $\text{C}_{17}\text{H}_{19}\text{NO}_3$ ) is an analgesic (painkiller) named after Morpheus, the Greek god of dreams; and acetic acid, the primary organic constituent of vinegar, is named from the Latin word for vinegar, *acetum*.

As the science of organic chemistry slowly grew in the 19th century, so too did the number of known compounds and the need for a systematic method of naming them. The system of nomenclature we'll use in this book is that devised by the International Union of Pure and Applied Chemistry (IUPAC, usually spoken as eye-you-pac).

A chemical name typically has four parts in the IUPAC system of nomenclature: prefix, parent, locant, and suffix. The prefix identifies the various **substituent** groups in the molecule, the parent selects a main part of the molecule and tells how many carbon atoms are in that part, the locants give the positions of the functional groups and substituents, and the suffix identifies the primary functional group.



As we cover new functional groups in later chapters, the applicable IUPAC rules of nomenclature will be given. In addition, Appendix A at the back of this book gives an overall view of organic nomenclature and shows how compounds that contain more than one functional group are named. (If preferred, you can study that appendix now.) For the present, let's see how to name branched-chain alkanes and learn some general rules that are applicable to all compounds.

All but the most complex branched-chain alkanes can be named by following four steps. For a very few compounds, a fifth step is needed.

**STEP 1****Find the parent hydrocarbon.**

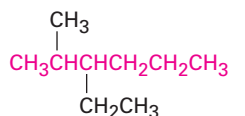
- (a) Find the longest continuous chain of carbon atoms in the molecule, and use the name of that chain as the parent name. The longest chain



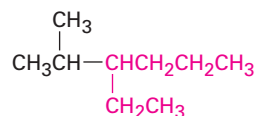
may not always be apparent from the manner of writing; you may have to “turn corners.”



- (b) If two different chains of equal length are present, choose the one with the larger number of branch points as the parent.



Named as a hexane with two substituents



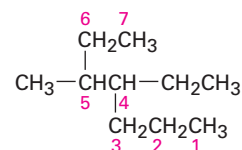
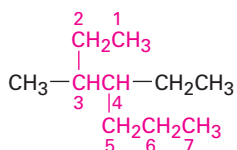
as a hexane with one substituent

NOT

### STEP 2

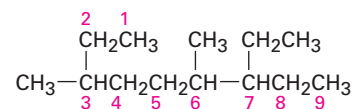
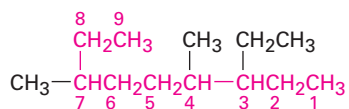
**Number the atoms in the longest chain.**

- (a) Beginning at the end nearer the first branch point, number each carbon atom in the parent chain.



The first branch occurs at C3 in the proper system of numbering, not at C4.

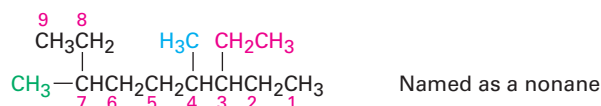
- (b) If there is branching an equal distance away from both ends of the parent chain, begin numbering at the end nearer the second branch point.



### STEP 3

**Identify and number the substituents.**

- (a) Assign a number, or *locant*, to each substituent to locate its point of attachment to the parent chain.



Substituents: On C3,  $\text{CH}_2\text{CH}_3$  (3-ethyl)  
On C4,  $\text{CH}_3$  (4-methyl)  
On C7,  $\text{CH}_3$  (7-methyl)



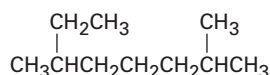


When writing an alkane name, the nonhyphenated prefix *iso-* is considered part of the alkyl-group name for alphabetizing purposes, but the hyphenated and italicized prefixes *sec-* and *tert-* are not. Thus, isopropyl and isobutyl are listed alphabetically under *i*, but *sec*-butyl and *tert*-butyl are listed under *b*.

## Naming Alkanes

### Worked Example 3.2

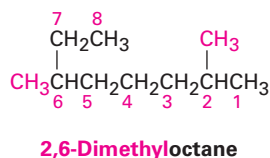
What is the IUPAC name of the following alkane?



#### Strategy

Find the longest continuous carbon chain in the molecule, and use that as the parent name. This molecule has a chain of eight carbons—octane—with two methyl substituents. (You have to turn corners to see it.) Numbering from the end nearer the first methyl substituent indicates that the methyls are at C2 and C6

#### Solution



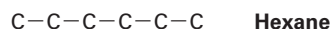
## Converting a Chemical Name into a Structure

### Worked Example 3.3

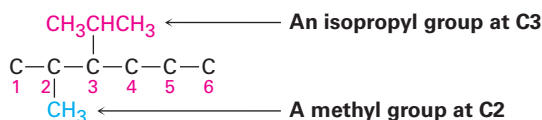
Draw the structure of 3-isopropyl-2-methylhexane.

#### Strategy

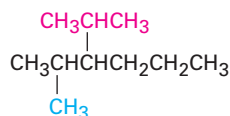
This is the reverse of Worked Example 3.2 and uses a reverse strategy. Look at the parent name (hexane), and draw its carbon structure.



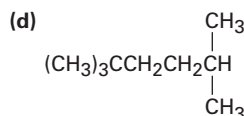
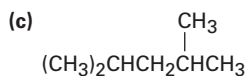
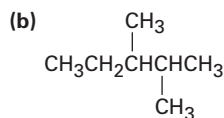
Next, find the substituents (3-isopropyl and 2-methyl), and place them on the proper carbons.



Finally, add hydrogens to complete the structure.

**Solution****3-Isopropyl-2-methylhexane****Problem 3.11**

Give IUPAC names for the following compounds:

(a) The three isomers of  $\text{C}_5\text{H}_{12}$ **Problem 3.12**

Draw structures corresponding to the following IUPAC names:

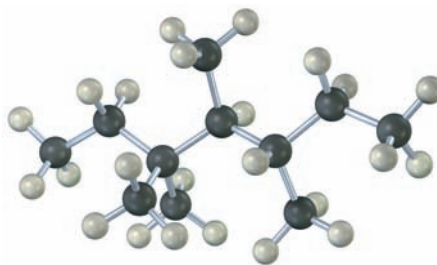
- (a) 3,4-Dimethylnonane      (b) 3-Ethyl-4,4-dimethylheptane  
 (c) 2,2-Dimethyl-4-propyloctane      (d) 2,2,4-Trimethylpentane

**Problem 3.13**

Name the eight 5-carbon alkyl groups you drew in Problem 3.7.

**Problem 3.14**

Give the IUPAC name for the following hydrocarbon, and convert the drawing into a skeletal structure.



## 3.5 Properties of Alkanes

Alkanes are sometimes referred to as *paraffins*, a word derived from the Latin *parum affinis*, meaning “little affinity.” This term aptly describes their behavior, for alkanes show little chemical affinity for other substances and are chemically inert to most laboratory reagents. They are also relatively inert biologically and are not often



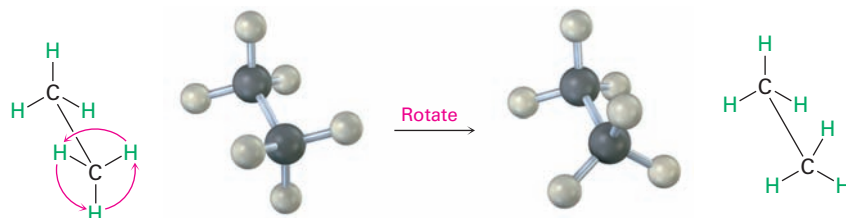
boils at 125.7 °C, whereas isooctane (2,2,4-trimethylpentane) boils at 99.3 °C. Branched-chain alkanes are lower-boiling because they are more nearly spherical than straight-chain alkanes, have smaller surface areas, and consequently have smaller dispersion forces.

## 3.6 Conformations of Ethane

Up to now, we've viewed molecules primarily in a two-dimensional way and have given little thought to any consequences that might arise from the spatial arrangement of atoms in molecules. Now it's time to add a third dimension to our study. **Stereochemistry** is the branch of chemistry concerned with the three-dimensional aspects of molecules. We'll see on many occasions in future chapters that the exact three-dimensional structure of a molecule is often crucial to determining its properties and biological behavior.

We know from **Section 1.5** that  $\sigma$  bonds are cylindrically symmetrical. In other words, the intersection of a plane cutting through a carbon-carbon single-bond orbital looks like a circle. Because of this cylindrical symmetry, rotation is possible around carbon-carbon bonds in open-chain molecules. In ethane, for instance, rotation around the C-C bond occurs freely, constantly changing the spatial relationships between the hydrogens on one carbon and those on the other (**Figure 3.5**).

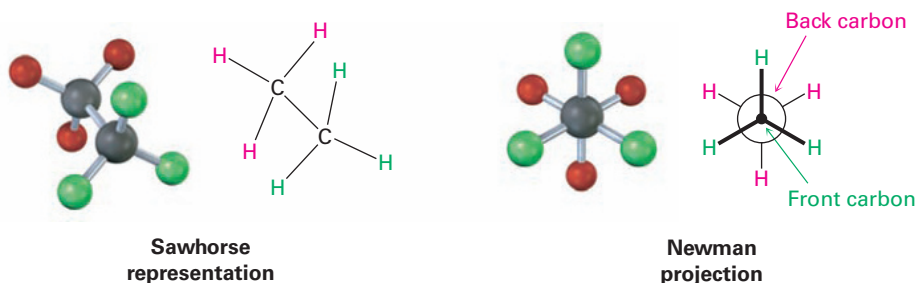
**Figure 3.5** Rotation occurs around the carbon-carbon single bond in ethane because of  $\sigma$  bond cylindrical symmetry.



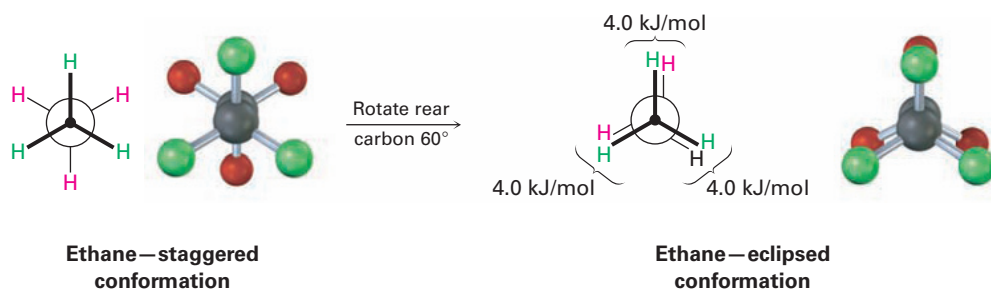
The different arrangements of atoms that result from bond rotation are called **conformations**, and molecules that have different arrangements are called conformational isomers, or **conformers**. Unlike constitutional isomers, however, different conformers often can't be isolated because they interconvert too rapidly.

Conformational isomers are represented in two ways, as shown in **Figure 3.6**. A *sawhorse representation* views the carbon-carbon bond from an oblique angle and indicates spatial orientation by showing all C-H bonds. A **Newman projection** views the carbon-carbon bond directly end-on and represents the two carbon atoms by a circle. Bonds attached to the front carbon are represented by lines to the center of the circle, and bonds attached to the rear carbon are represented by lines to the edge of the circle.

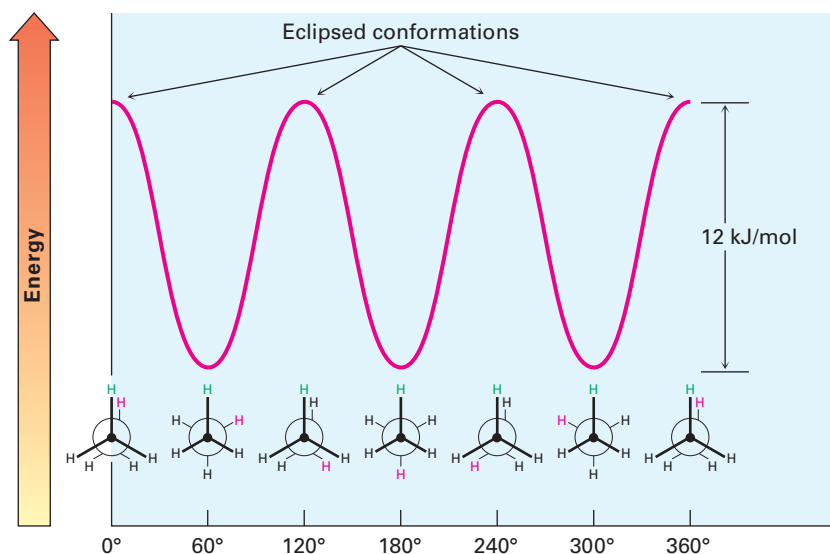
**Figure 3.6** A sawhorse representation and a Newman projection of ethane. The sawhorse representation views the molecule from an oblique angle, while the Newman projection views the molecule end-on. Note that the molecular model of the Newman projection appears at first to have six atoms attached to a single carbon. Actually, the front carbon, with three attached **green atoms**, is directly in front of the rear carbon, with three attached **red atoms**.



Despite what we've just said, we actually don't observe *perfectly* free rotation in ethane. Experiments show that there is a small (12 kJ/mol; 2.9 kcal/mol) barrier to rotation and that some conformations are more stable than others. The lowest-energy, most stable conformation is the one in which all six C–H bonds are as far away from one another as possible—**staggered** when viewed end-on in a Newman projection. The highest-energy, least stable conformation is the one in which the six C–H bonds are as close as possible—**eclipsed** in a Newman projection. At any given instant, about 99% of ethane molecules have an approximately staggered conformation and only about 1% are near the eclipsed conformation.



The extra 12 kJ/mol of energy present in the eclipsed conformation of ethane is called **torsional strain**. Its cause has been the subject of controversy, but the major factor is an interaction between C–H bonding orbitals on one carbon with antibonding orbitals on the adjacent carbon, which stabilizes the staggered conformation relative to the eclipsed one. Because the total strain of 12 kJ/mol arises from three equal hydrogen–hydrogen eclipsing interactions, we can assign a value of approximately 4.0 kJ/mol (1.0 kcal/mol) to each single interaction. The barrier to rotation that results can be represented on a graph of potential energy versus degree of rotation in which the angle between C–H bonds on front and back carbons as viewed end-on (the *dihedral angle*) goes full circle from 0 to 360°. Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations, as shown in **Figure 3.7**.



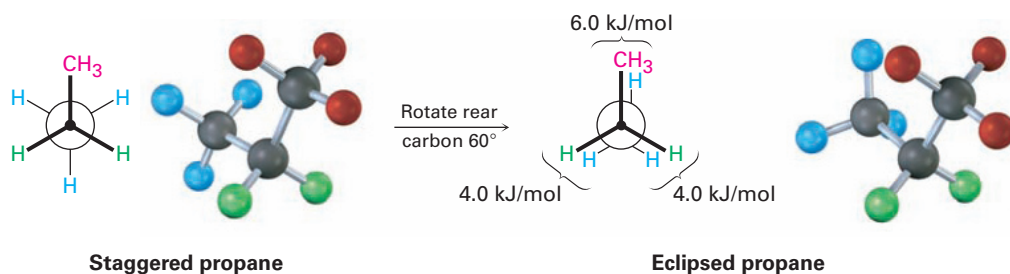
**Figure 3.7** A graph of potential energy versus bond rotation in ethane. The staggered conformations are 12 kJ/mol lower in energy than the eclipsed conformations.



### 3.7 Conformations of Other Alkanes

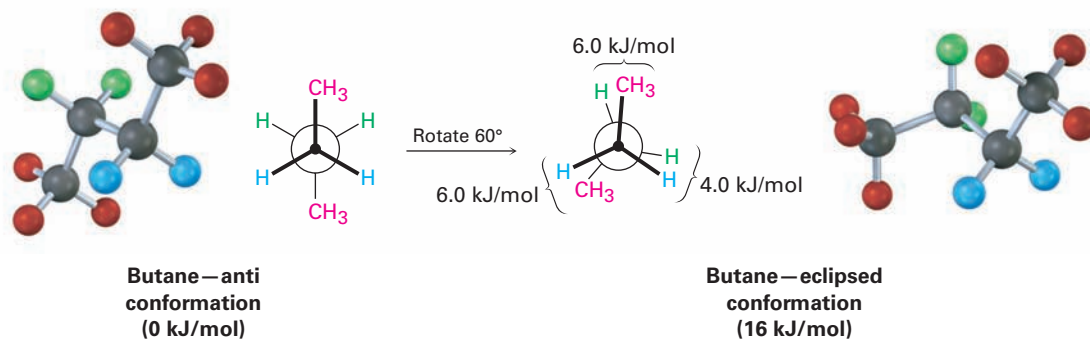
Propane, the next higher member in the alkane series, also has a torsional barrier that results in hindered rotation around the carbon–carbon bonds. The barrier is slightly higher in propane than in ethane—a total of 14 kJ/mol (3.4 kcal/mol) versus 12 kJ/mol.

The eclipsed conformation of propane has three interactions—two ethane-type hydrogen–hydrogen interactions and one additional hydrogen–methyl interaction. Since each eclipsing  $\text{H} \leftrightarrow \text{H}$  interaction is the same as that in ethane and thus has an energy “cost” of 4.0 kJ/mol, we can assign a value of  $14 - (2 \times 4.0) = 6.0$  kJ/mol (1.4 kcal/mol) to the eclipsing  $\text{H} \leftrightarrow \text{CH}_3$  interaction (Figure 3.8).

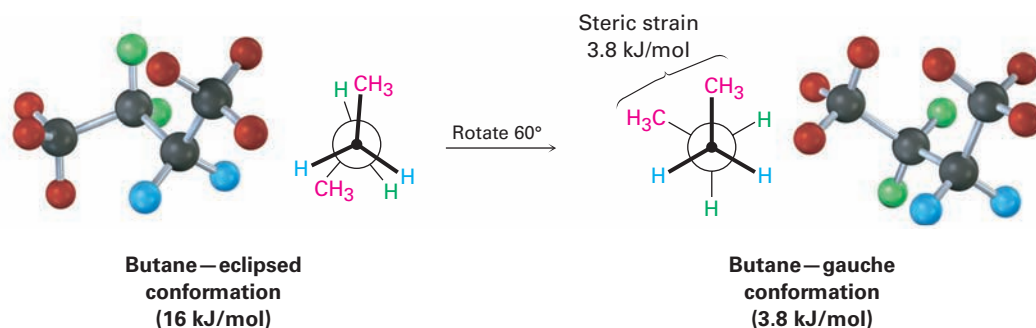


**Figure 3.8** Newman projections of propane showing staggered and eclipsed conformations. The staggered conformer is lower in energy by 14 kJ/mol.

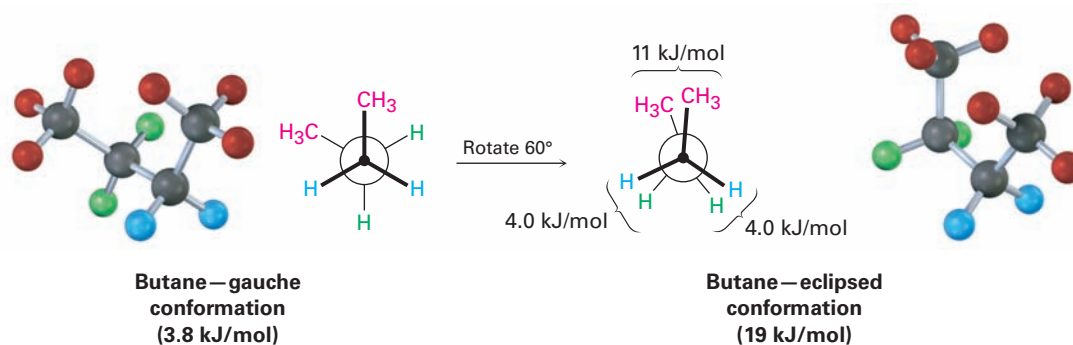
The conformational situation becomes more complex for larger alkanes because not all staggered conformations have the same energy and not all eclipsed conformations have the same energy. In butane, for instance, the lowest-energy arrangement, called the **anti conformation**, is the one in which the two methyl groups are as far apart as possible— $180^\circ$  away from each other. As rotation around the  $\text{C}2-\text{C}3$  bond occurs, an eclipsed conformation is reached in which there are two  $\text{CH}_3 \leftrightarrow \text{H}$  interactions and one  $\text{H} \leftrightarrow \text{H}$  interaction. Using the energy values derived previously from ethane and propane, this eclipsed conformation is more strained than the anti conformation by  $2 \times 6.0$  kJ/mol + 4.0 kJ/mol (two  $\text{CH}_3 \leftrightarrow \text{H}$  interactions plus one  $\text{H} \leftrightarrow \text{H}$  interaction), for a total of 16 kJ/mol (3.8 kcal/mol).



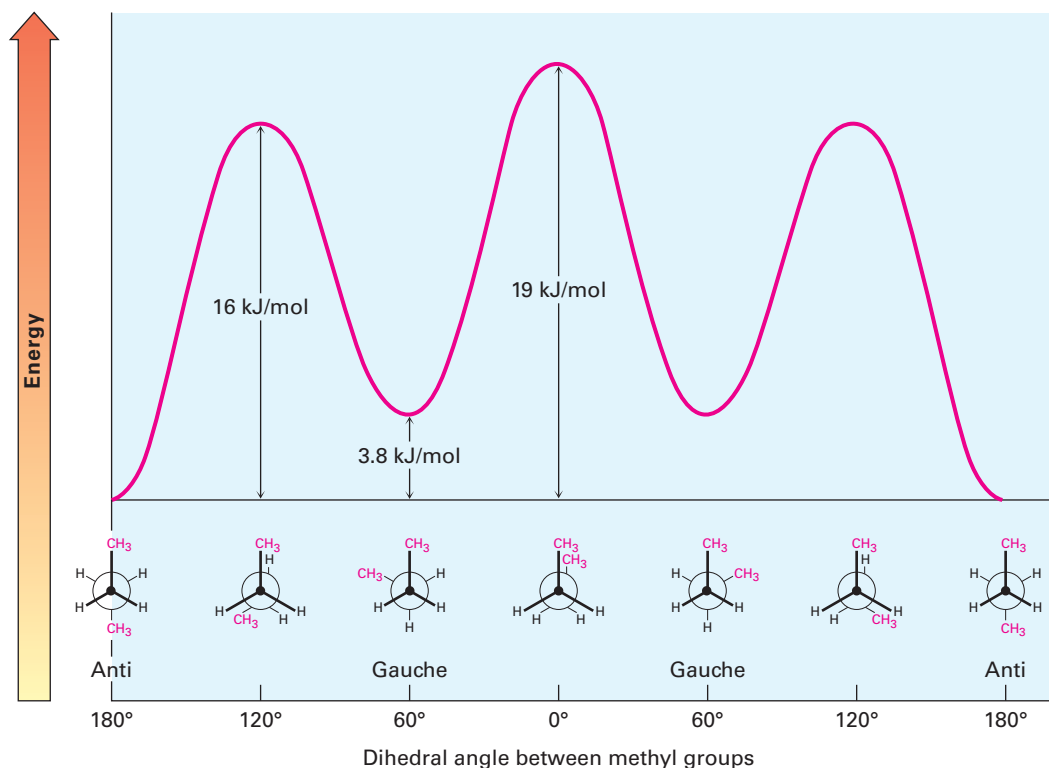
As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are  $60^\circ$  apart. Called the **gauche conformation**, it lies  $3.8 \text{ kJ/mol}$  ( $0.9 \text{ kcal/mol}$ ) higher in energy than the anti conformation even though it has no eclipsing interactions. This energy difference occurs because the hydrogen atoms of the methyl groups are near one another in the gauche conformation, resulting in what is called *steric strain*. **Steric strain** is the repulsive interaction that occurs when atoms are forced closer together than their atomic radii allow. It's the result of trying to force two atoms to occupy the same space.



As the dihedral angle between the methyl groups approaches  $0^\circ$ , an energy maximum is reached at a second eclipsed conformation. Because the methyl groups are forced even closer together than in the gauche conformation, both torsional strain and steric strain are present. A total strain energy of  $19 \text{ kJ/mol}$  ( $4.5 \text{ kcal/mol}$ ) has been estimated for this conformation, making it possible to calculate a value of  $11 \text{ kJ/mol}$  ( $2.6 \text{ kcal/mol}$ ) for the  $\text{CH}_3 \leftrightarrow \text{CH}_3$  eclipsing interaction: total strain of  $19 \text{ kJ/mol}$  less the strain of two  $\text{H} \leftrightarrow \text{H}$  eclipsing interactions ( $2 \times 4.0 \text{ kcal/mol}$ ) equals  $11 \text{ kJ/mol}$ .



After  $0^\circ$ , the rotation becomes a mirror image of what we've already seen: another gauche conformation is reached, another eclipsed conformation, and finally a return to the anti conformation. A plot of potential energy versus rotation about the  $\text{C}_2\text{--C}_3$  bond is shown in **Figure 3.9**.



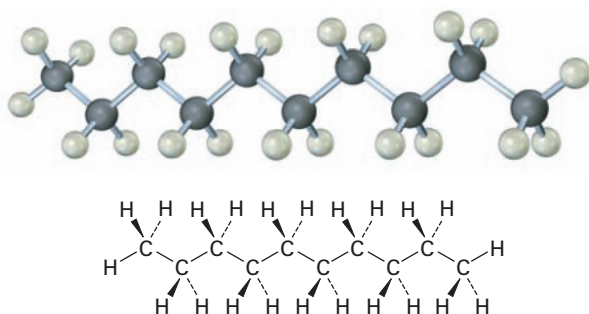
**Figure 3.9** A plot of potential energy versus rotation for the C2–C3 bond in butane. The energy maximum occurs when the two methyl groups eclipse each other, and the energy minimum occurs when the two methyl groups are 180° apart (anti).

The notion of assigning definite energy values to specific interactions within a molecule is a very useful one that we'll return to in the next chapter. A summary of what we've seen thus far is given in Table 3.5.

The same principles just developed for butane apply to pentane, hexane, and all higher alkanes. The most favorable conformation for any alkane has the carbon–carbon bonds in staggered arrangements, with large substituents arranged anti to one another. A generalized alkane structure is shown in **Figure 3.10**.

**Table 3.5** Energy Costs for Interactions in Alkane Conformers

Interaction	Cause	Energy cost	
		(kJ/mol)	(kcal/mol)
H ↔ H eclipsed	Torsional strain	4.0	1.0
H ↔ CH <sub>3</sub> eclipsed	Mostly torsional strain	6.0	1.4
CH <sub>3</sub> ↔ CH <sub>3</sub> eclipsed	Torsional and steric strain	11	2.6
CH <sub>3</sub> ↔ CH <sub>3</sub> gauche	Steric strain	3.8	0.9



**Figure 3.10** The most stable alkane conformation is the one in which all substituents are staggered and the carbon-carbon bonds are arranged in an anti relationship, as shown in this model of decane.

One final point: saying that one particular conformer is “more stable” than another doesn’t mean the molecule adopts and maintains only the more stable conformation. At room temperature, rotations around  $\sigma$  bonds occur so rapidly that all conformers are in equilibrium. At any given instant, however, a larger percentage of molecules will be found in a more stable conformation than in a less stable one.

## Drawing Newman Projections

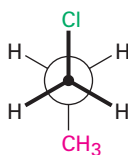
## Worked Example 3.4

Sight along the C1–C2 bond of 1-chloropropane, and draw Newman projections of the most stable and least stable conformations.

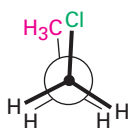
### Strategy

The most stable conformation of a substituted alkane is generally a staggered one in which large groups have an anti relationship. The least stable conformation is generally an eclipsed one in which large groups are as close as possible.

### Solution



Most stable (staggered)



Least stable (eclipsed)

### Problem 3.15

Make a graph of potential energy versus angle of bond rotation for propane, and assign values to the energy maxima.

### Problem 3.16

Sight along the C2–C1 bond, 2-methylpropane (isobutane) and

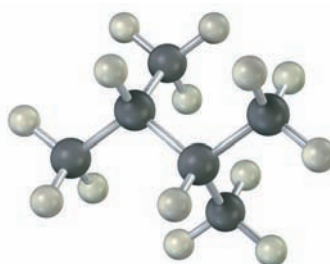
- draw a Newman projection of the most stable conformation.
- draw a Newman projection of the least stable conformation.
- make a graph of energy versus angle of rotation around the C2–C1 bond.
- Since an  $\text{H} \leftrightarrow \text{H}$  eclipsing interaction costs 4.0 kJ/mol and an  $\text{H} \leftrightarrow \text{CH}_3$  eclipsing interaction costs 6.0 kJ/mol, assign relative values to the maxima and minima in your graph.

**Problem 3.17**

Sight along the C2–C3 bond of 2,3-dimethylbutane, and draw a Newman projection of the most stable conformation.

**Problem 3.18**

Draw a Newman projection along the C2–C3 bond of the following conformation of 2,3-dimethylbutane, and calculate a total strain energy:



iStockphoto.com/Sascha Burkard

Gasoline is a finite resource. It won't be around forever.

## Gasoline | A DEEPER LOOK

British Foreign Minister Ernest Bevin once said that “The Kingdom of Heaven runs on righteousness, but the Kingdom of Earth runs on alkanes.” (Actually, he said “runs on oil” not “runs on alkanes,” but they’re essentially the same.) By far, the major sources of alkanes are the world’s natural gas and petroleum deposits. Laid down eons ago, these deposits are thought to be derived primarily from the decomposition of tiny single-celled marine organisms called foraminifera. *Natural gas* consists chiefly of methane but also contains ethane, propane, and butane. *Petroleum* is a complex mixture of hydrocarbons that must be separated into fractions and then further refined before it can be used.

The petroleum era began in August 1859, when the world’s first oil well was drilled by Edwin Drake near Titusville, Pennsylvania. The petroleum was distilled into fractions according to boiling point, but it was high-boiling kerosene, or lamp oil, rather than gasoline that was primarily sought. Literacy was becoming widespread at the time, and people wanted better light for reading than was available from candles. Gasoline was too volatile for use in lamps and was initially considered a waste by-product. The world has changed greatly since those early days, however, and it is now gasoline rather than lamp oil that is prized.

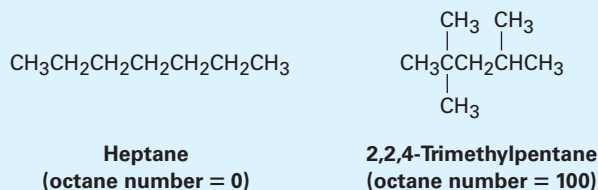
Petroleum refining begins by fractional distillation of crude oil into three principal cuts according to boiling point (bp): straight-run gasoline (bp 30–200 °C), kerosene (bp 175–300 °C), and heating oil, or diesel fuel (bp 275–400 °C). Further distillation under reduced pressure then yields lubricating oils and waxes and leaves a tarry residue of asphalt. The distillation of crude oil is only the first step in gasoline production, however. Straight-run gasoline turns out to be a poor fuel in automobiles because of engine knock, an uncontrolled combustion that can occur in a hot engine.

The *octane number* of a fuel is the measure by which its antiknock properties are judged. It was recognized long ago that straight-chain hydrocarbons are far more prone to induce

(continued)

(continued)

engine knock than are highly branched compounds. Heptane, a particularly bad fuel, is assigned a base value of 0 octane number, and 2,2,4-trimethylpentane, commonly known as isooctane, has a rating of 100.



Because straight-run gasoline burns so poorly in engines, petroleum chemists have devised numerous methods for producing higher-quality fuels. One of these methods, *catalytic cracking*, involves taking the high-boiling kerosene cut ( $\text{C}_{11}$ – $\text{C}_{14}$ ) and “cracking” it into smaller branched molecules suitable for use in gasoline. Another process, called *reforming*, is used to convert  $\text{C}_6$ – $\text{C}_8$  alkanes to aromatic compounds such as benzene and toluene, which have substantially higher octane numbers than alkanes. The final product that goes in your tank has an approximate composition of 15%  $\text{C}_4$ – $\text{C}_8$  straight-chain alkanes, 25% to 40%  $\text{C}_4$ – $\text{C}_{10}$  branched-chain alkanes, 10% cyclic alkanes, 10% straight-chain and cyclic alkenes, and 25% arenes (aromatics).

## Summary

Even though alkanes are relatively unreactive and rarely involved in chemical reactions, they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we’ve used alkanes to introduce the basic approach to naming organic compounds and to take an initial look at some of the three-dimensional aspects of molecules.

A **functional group** is a group of atoms within a larger molecule that has a characteristic chemical reactivity. Because functional groups behave in approximately the same way in all molecules where they occur, the chemical reactions of an organic molecule are largely determined by its functional groups.

**Alkanes** are a class of **saturated hydrocarbons** with the general formula  $\text{C}_n\text{H}_{2n+2}$ . They contain no functional groups, are relatively inert, and can be either **straight-chain** (*normal*) or **branched**. Alkanes are named by a series of IUPAC rules of nomenclature. Compounds that have the same chemical formula but different structures are called **isomers**. More specifically, compounds such as butane and isobutane, which differ in their connections between atoms, are called **constitutional isomers**.

Carbon–carbon single bonds in alkanes are formed by  $\sigma$  overlap of carbon  $sp^3$  hybrid orbitals. Rotation is possible around  $\sigma$  bonds because of their cylindrical symmetry, and alkanes therefore exist in a large number of rapidly interconverting **conformations**. **Newman projections** make it possible to visualize the spatial consequences of bond rotation by sighting directly along a carbon–carbon bond axis. Not all alkane conformations are equally stable. The **staggered** conformation of ethane is 12 kJ/mol (2.9 kcal/mol) more stable than the **eclipsed** conformation because of **torsional strain**. In general, any alkane is most stable when all its bonds are staggered.

## Key words

aliphatic, 81  
 alkane, 80  
 alkyl group, 84  
 anti conformation, 96  
 branched-chain alkane, 82  
 conformation, 94  
 conformers, 94  
 constitutional isomers, 82  
 eclipsed conformation, 95  
 functional group, 74  
 gauche conformation, 97  
 hydrocarbon, 81  
 isomers, 82  
 Newman projection, 94  
 R group, 86  
 saturated, 81  
 staggered conformation, 95  
 stereochemistry, 94  
 steric strain, 97  
 straight-chain alkane, 82  
 substituent, 87  
 torsional strain, 95

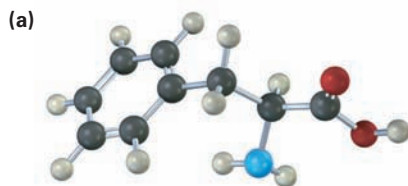
## Exercises

**OWL** Interactive versions of these problems are assignable in OWL for Organic Chemistry.

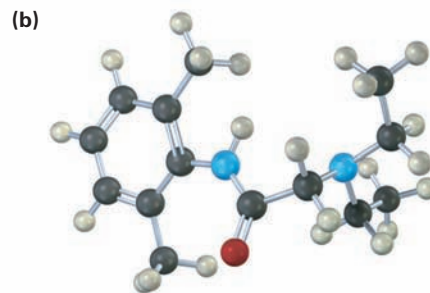
## Visualizing Chemistry

(Problems 3.1–3.18 appear within the chapter.)

**3.19** Identify the functional groups in the following substances, and convert each drawing into a molecular formula (red = O, blue = N).

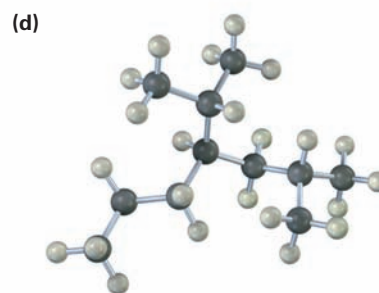
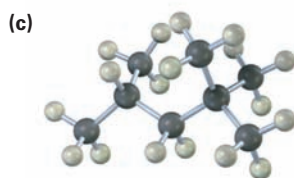
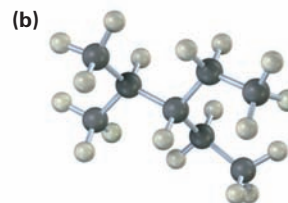
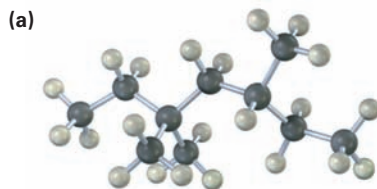


Phenylalanine

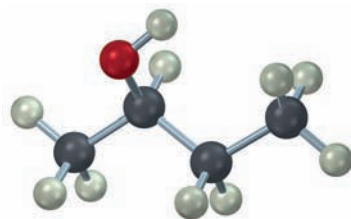


Lidocaine

**3.20** Give IUPAC names for the following alkanes, and convert each drawing into a skeletal structure:



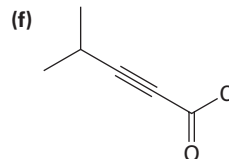
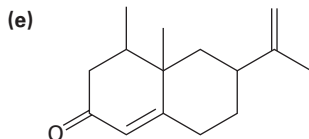
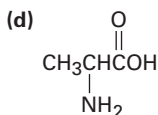
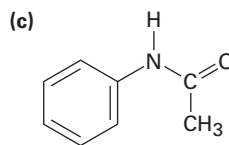
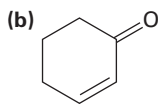
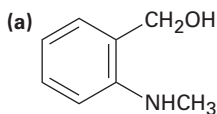
3.21 Draw a Newman projection along the C2-C3 bond of the following conformation of 2-butanol.



## Additional Problems

### Functional Groups

3.22 Locate and identify the functional groups in the following molecules.



3.23 Propose structures that meet the following descriptions:

- (a) A ketone with five carbons      (b) A four-carbon amide  
 (c) A five-carbon ester            (d) An aromatic aldehyde  
 (e) A keto ester                    (f) An amino alcohol

3.24 Propose structures for the following:

- (a) A ketone,  $C_4H_8O$             (b) A nitrile,  $C_5H_9N$   
 (c) A dialdehyde,  $C_4H_6O_2$       (d) A bromoalkene,  $C_6H_{11}Br$   
 (e) An alkane,  $C_6H_{14}$             (f) A cyclic saturated hydrocarbon,  $C_6H_{12}$   
 (g) A diene (dialkene),  $C_5H_8$     (h) A keto alkene,  $C_5H_8O$

3.25 Predict the hybridization of the carbon atom in each of the following functional groups:

- (a) Ketone      (b) Nitrile      (c) Carboxylic acid

3.26 Draw the structures of the following molecules:

- (a) *Biacetyl*,  $C_4H_6O_2$ , a substance with the aroma of butter; it contains no rings or carbon-carbon multiple bonds.  
 (b) *Ethylenimine*,  $C_2H_5N$ , a substance used in the synthesis of melamine polymers; it contains no multiple bonds.  
 (c) *Glycerol*,  $C_3H_8O_3$ , a substance isolated from fat and used in cosmetics; it has an -OH group on each carbon.



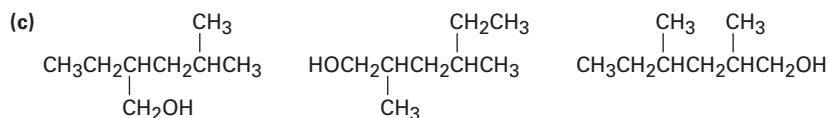
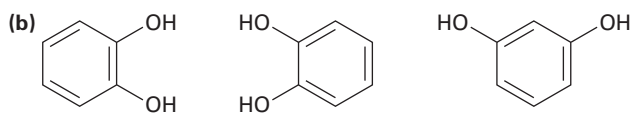
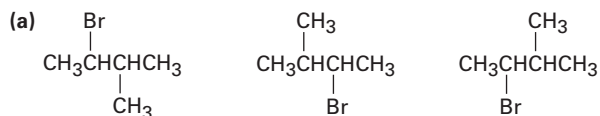
**Isomers**

**3.27** Draw structures that meet the following descriptions (there are many possibilities):

- (a) Three isomers with the formula  $C_8H_{18}$   
 (b) Two isomers with the formula  $C_4H_8O_2$

**3.28** Draw structures of the nine isomers of  $C_7H_{16}$ .

**3.29** In each of the following sets, which structures represent the same compound and which represent different compounds?



**3.30** There are seven constitutional isomers with the formula  $C_4H_{10}O$ . Draw as many as you can.

**3.31** Draw as many compounds as you can that fit the following descriptions:

- (a) Alcohols with formula  $C_4H_{10}O$       (b) Amines with formula  $C_5H_{13}N$   
 (c) Ketones with formula  $C_5H_{10}O$       (d) Aldehydes with formula  $C_5H_{10}O$   
 (e) Esters with formula  $C_4H_8O_2$       (f) Ethers with formula  $C_4H_{10}O$

**3.32** Draw compounds that contain the following:

- (a) A primary alcohol      (b) A tertiary nitrile  
 (c) A secondary thiol      (d) Both primary and secondary alcohols  
 (e) An isopropyl group      (f) A quaternary carbon

**Naming Compounds**

**3.33** Draw and name all monobromo derivatives of pentane,  $C_5H_{11}Br$ .

**3.34** Draw and name all monochloro derivatives of 2,5-dimethylhexane,  $C_8H_{17}Cl$ .

**3.35** Draw structures for the following:

- (a) 2-Methylheptane      (b) 4-Ethyl-2,2-dimethylhexane  
 (c) 4-Ethyl-3,4-dimethyloctane      (d) 2,4,4-Trimethylheptane  
 (e) 3,3-Diethyl-2,5-dimethylnonane      (f) 4-Isopropyl-3-methylheptane

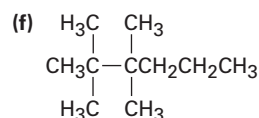
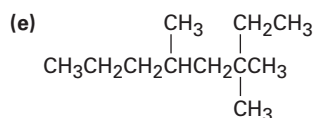
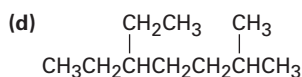
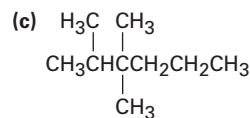
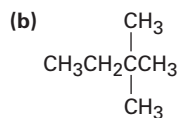
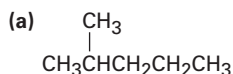
**3.36** Draw a compound that:

- (a) Has only primary and tertiary carbons  
 (b) Has no secondary or tertiary carbons  
 (c) Has four secondary carbons

3.37 Draw a compound that:

- (a) Has nine primary hydrogens  
 (b) Has only primary hydrogens

3.38 Give IUPAC names for the following compounds:



3.39 Name the five isomers of  $\text{C}_6\text{H}_{14}$ .

3.40 Explain why each of the following names is incorrect:

- (a) 2,2-Dimethyl-6-ethylheptane      (b) 4-Ethyl-5,5-dimethylpentane  
 (c) 3-Ethyl-4,4-dimethylhexane      (d) 5,5,6-Trimethyloctane  
 (e) 2-Isopropyl-4-methylheptane

3.41 Propose structures and give IUPAC names for the following:

- (a) A diethyldimethylhexane      (b) A (3-methylbutyl)-substituted alkane

### Conformations

3.42 Consider 2-methylbutane (isopentane). Sighting along the C2–C3 bond:

- (a) Draw a Newman projection of the most stable conformation.  
 (b) Draw a Newman projection of the least stable conformation.  
 (c) If a  $\text{CH}_3 \leftrightarrow \text{CH}_3$  eclipsing interaction costs 11 kJ/mol (2.5 kcal/mol) and a  $\text{CH}_3 \leftrightarrow \text{CH}_3$  gauche interaction costs 3.8 kJ/mol (0.9 kcal/mol), make a quantitative plot of energy versus rotation about the C2–C3 bond.

3.43 What are the relative energies of the three possible staggered conformations around the C2–C3 bond in 2,3-dimethylbutane? (See Problem 3.42.)

3.44 Construct a qualitative potential-energy diagram for rotation about the C–C bond of 1,2-dibromoethane. Which conformation would you expect to be most stable? Label the anti and gauche conformations of 1,2-dibromoethane.

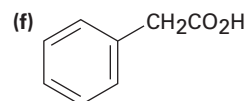
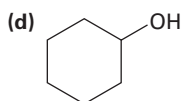
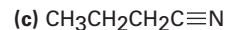
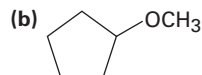
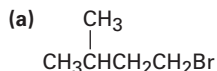
3.45 Which conformation of 1,2-dibromoethane (Problem 3.44) would you expect to have the largest dipole moment? The observed dipole moment of 1,2-dibromoethane is  $\mu = 1.0$  D. What does this tell you about the actual conformation of the molecule?

3.46 Draw the most stable conformation of pentane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

3.47 Draw the most stable conformation of 1,4-dichlorobutane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

## General Problems

**3.48** For each of the following compounds, draw an isomer that has the same functional groups.



**3.49** Malic acid,  $\text{C}_4\text{H}_6\text{O}_5$ , has been isolated from apples. Because this compound reacts with 2 molar equivalents of base, it is a dicarboxylic acid.

(a) Draw at least five possible structures.

(b) If malic acid is a secondary alcohol, what is its structure?

**3.50** Formaldehyde,  $\text{H}_2\text{C}=\text{O}$ , is known to all biologists because of its usefulness as a tissue preservative. When pure, formaldehyde *trimerizes* to give trioxane,  $\text{C}_3\text{H}_6\text{O}_3$ , which, surprisingly enough, has no carbonyl groups. Only one monobromo derivative ( $\text{C}_3\text{H}_5\text{BrO}_3$ ) of trioxane is possible. Propose a structure for trioxane.

**3.51** The barrier to rotation about the C–C bond in bromoethane is 15 kJ/mol (3.6 kcal/mol).

(a) What energy value can you assign to an  $\text{H}\leftrightarrow\text{Br}$  eclipsing interaction?

(b) Construct a quantitative diagram of potential energy versus bond rotation for bromoethane.

**3.52** Increased substitution around a bond leads to increased strain. Take the four substituted butanes listed below, for example. For each compound, sight along the C2–C3 bond and draw Newman projections of the most stable and least stable conformations. Use the data in Table 3.5 to assign strain energy values to each conformation. Which of the eight conformations is most strained? Which is least strained?

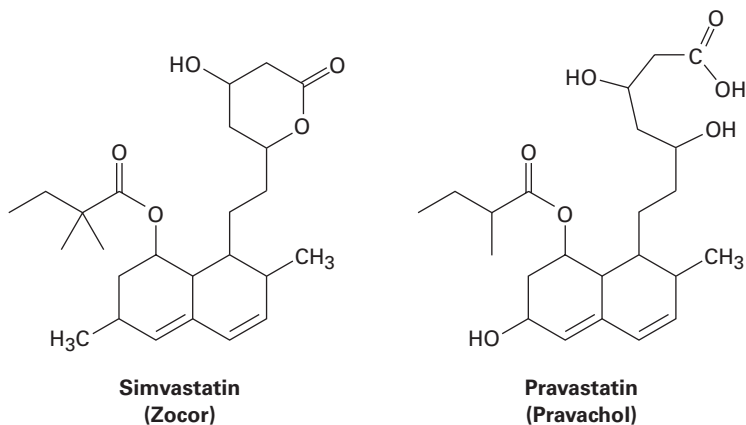
(a) 2-Methylbutane

(b) 2,2-Dimethylbutane

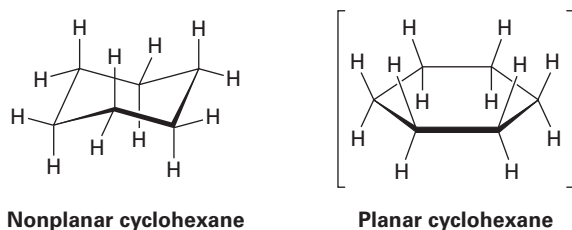
(c) 2,3-Dimethylbutane

(d) 2,2,3-Trimethylbutane

**3.53** The cholesterol-lowering agents called *statins*, such as simvastatin (Zocor) and pravastatin (Pravachol), are among the most widely prescribed drugs in the world, with annual sales estimated at approximately \$15 billion. Identify the functional groups in both, and tell how the two substances differ.



**3.54** We'll look in the next chapter at *cycloalkanes*—saturated cyclic hydrocarbons—and we'll see that the molecules generally adopt puckered, nonplanar conformations. Cyclohexane, for instance, has a puckered shape like a lounge chair rather than a flat shape. Why?



**3.55** We'll see in the next chapter that there are two isomeric substances both named 1,2-dimethylcyclohexane. Explain.



# 4

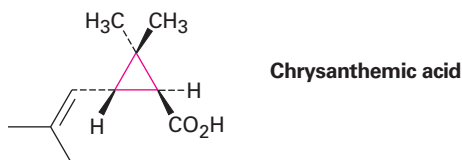


The musk gland of the male Himalayan musk deer secretes a substance once used in perfumery that contains cycloalkanes of 14 to 18 carbons. © Indiapicture/Alamy

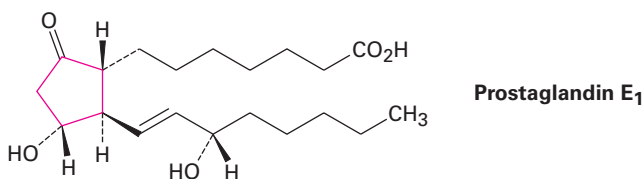
## Organic Compounds: Cycloalkanes and Their Stereochemistry

- 4.1 Naming Cycloalkanes
- 4.2 Cis–Trans Isomerism in Cycloalkanes
- 4.3 Stability of Cycloalkanes: Ring Strain
- 4.4 Conformations of Cycloalkanes
- 4.5 Conformations of Cyclohexane
- 4.6 Axial and Equatorial Bonds in Cyclohexane
- 4.7 Conformations of Monosubstituted Cyclohexanes
- 4.8 Conformations of Disubstituted Cyclohexanes
- 4.9 Conformations of Polycyclic Molecules  
A Deeper Look—  
Molecular Mechanics

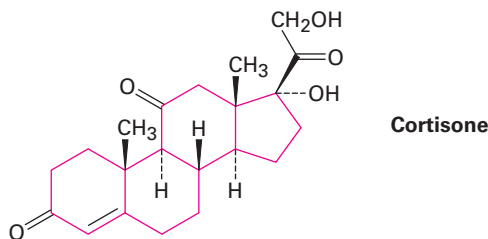
Although we've discussed only open-chain compounds up to now, most organic compounds contain *rings* of carbon atoms. Chrysanthemic acid, for instance, whose esters occur naturally as the active insecticidal constituents of chrysanthemum flowers, contains a three-membered (cyclopropane) ring.



*Prostaglandins*, potent hormones that control an extraordinary variety of physiological functions in humans, contain a five-membered (cyclopentane) ring.



*Steroids*, such as cortisone, contain four rings joined together—3 six-membered (cyclohexane) and 1 five-membered. We'll discuss steroids and their properties in more detail in **Sections 27.6 and 27.7**.

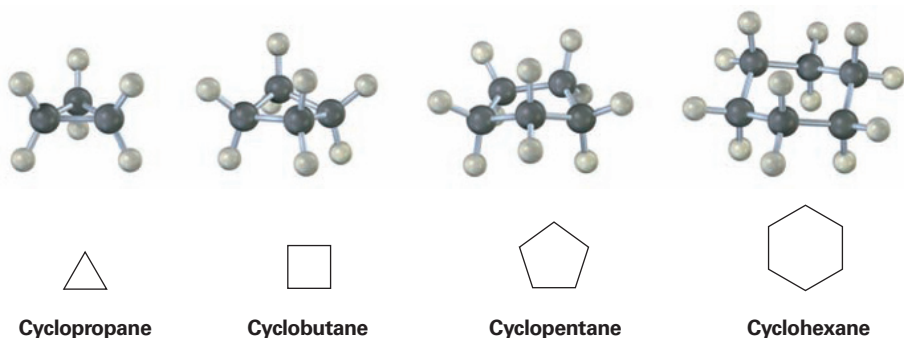


**OWL** Sign in to OWL for Organic Chemistry at [www.cengage.com/owl](http://www.cengage.com/owl) to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

**Why This Chapter?** We'll see numerous instances in future chapters where the chemistry of a given functional group is affected by being in a ring rather than an open chain. Because cyclic molecules are so commonly encountered in most pharmaceuticals and in all classes of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids, it's important to understand the consequences of cyclic structures.

## 4.1 Naming Cycloalkanes

Saturated cyclic hydrocarbons are called **cycloalkanes**, or **alicyclic** compounds (**aliphatic cyclic**). Because cycloalkanes consist of rings of  $-\text{CH}_2-$  units, they have the general formula  $(\text{CH}_2)_n$ , or  $\text{C}_n\text{H}_{2n}$ , and can be represented by polygons in skeletal drawings.

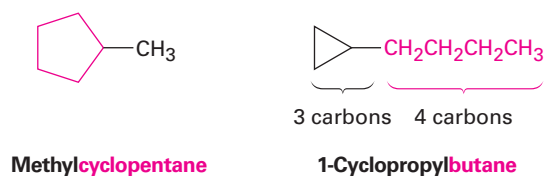


Substituted cycloalkanes are named by rules similar to those we saw in the previous chapter for open-chain alkanes (**Section 3.4**). For most compounds, there are only two steps.

### STEP 1

#### Find the parent.

Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent is greater than the number in the ring, the compound is named as a cycloalkyl-substituted alkane. For example:

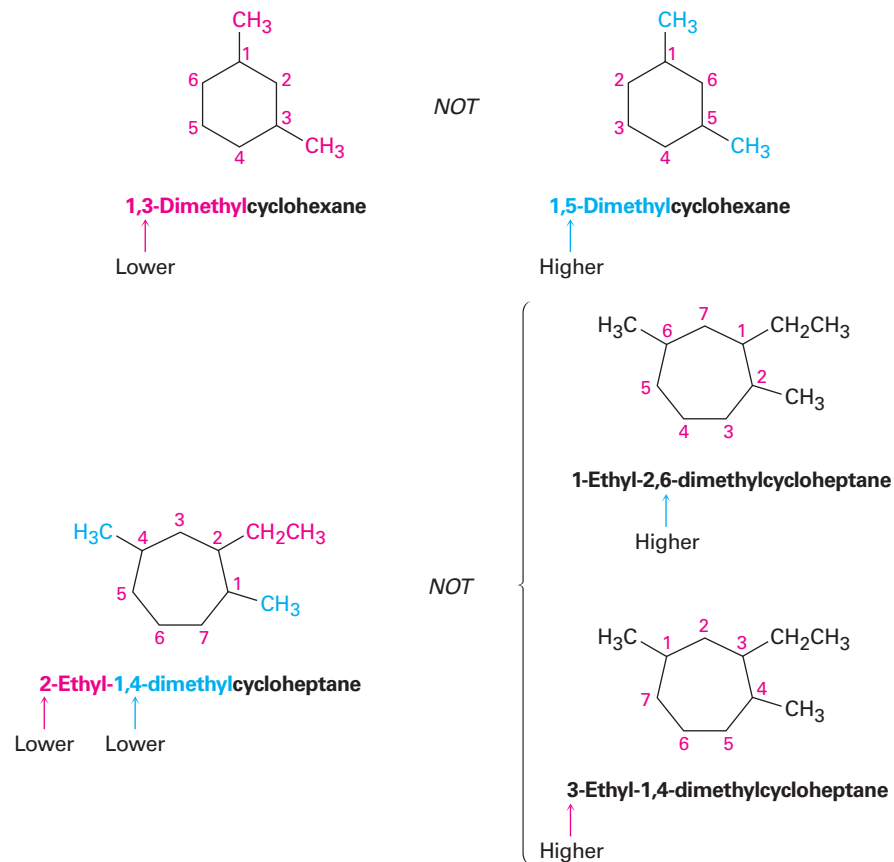


### STEP 2

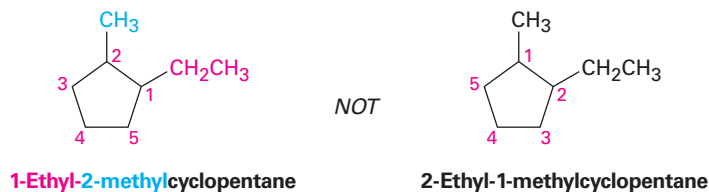
#### Number the substituents, and write the name.

For an alkyl- or halo-substituted cycloalkane, choose a point of attachment as carbon 1 and number the substituents on the ring so that the *second*

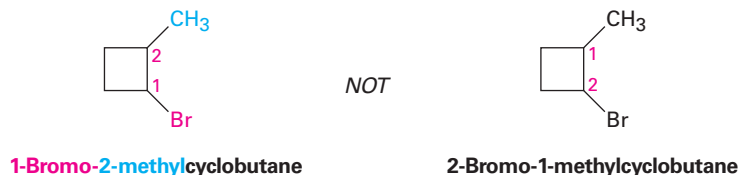
substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found.



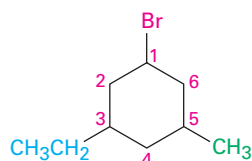
- (a) When two or more different alkyl groups that could potentially receive the same numbers are present, number them by alphabetical priority, ignoring numerical prefixes such as di- and tri-.



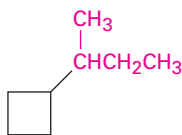
- (b) If halogens are present, treat them just like alkyl groups.



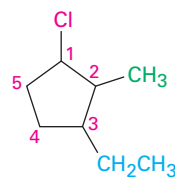
Some additional examples follow:



**1-Bromo-3-ethyl-5-methyl-**  
**cyclohexane**



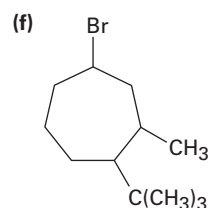
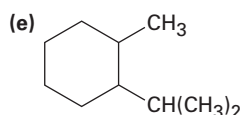
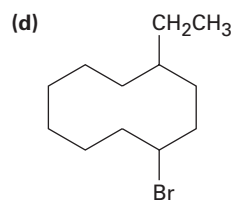
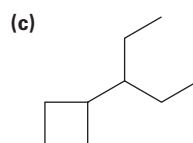
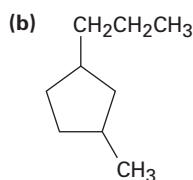
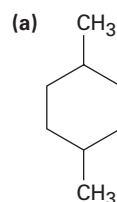
**(1-Methylpropyl)cyclobutane**  
**or *sec*-butylcyclobutane**



**1-Chloro-3-ethyl-2-methyl-**  
**cyclopentane**

### Problem 4.1

Give IUPAC names for the following cycloalkanes:



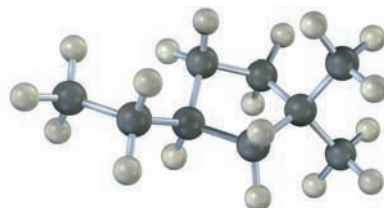
### Problem 4.2

Draw structures corresponding to the following IUPAC names:

- (a) 1,1-Dimethylcyclooctane    (b) 3-Cyclobutylhexane  
(c) 1,2-Dichlorocyclopentane    (d) 1,3-Dibromo-5-methylcyclohexane

### Problem 4.3

Name the following cycloalkane:

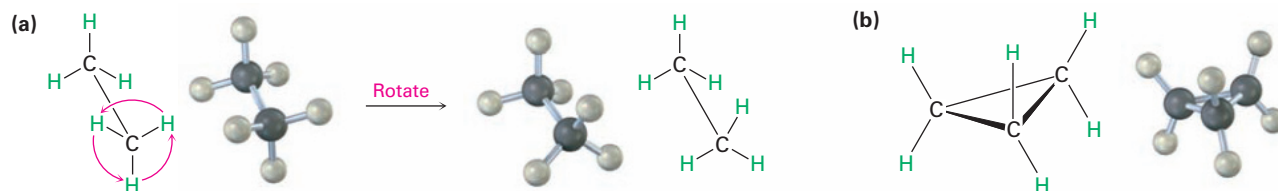


## 4.2 Cis-Trans Isomerism in Cycloalkanes

In many respects, the chemistry of cycloalkanes is like that of open-chain alkanes: both are nonpolar and fairly inert. There are, however, some important differences. One difference is that cycloalkanes are less flexible than open-chain



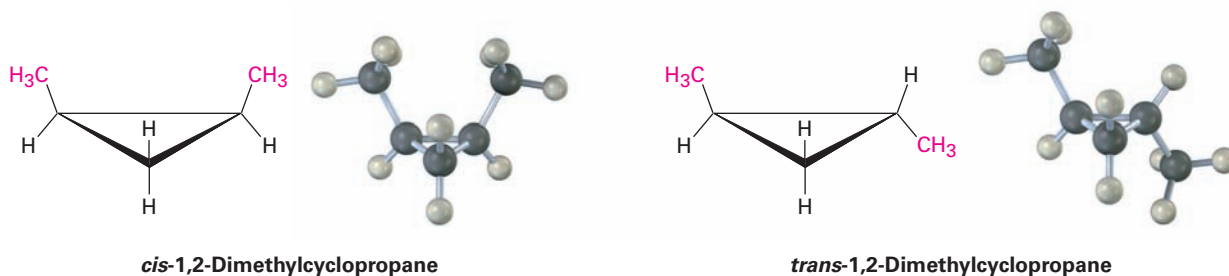
alkanes. In contrast with the relatively free rotation around single bonds in open-chain alkanes (Sections 3.6 and 3.7), there is much less freedom in cycloalkanes. Cyclopropane, for example, must be a rigid, planar molecule because three points (the carbon atoms) define a plane. No bond rotation can take place around a cyclopropane carbon–carbon bond without breaking open the ring (Figure 4.1).



**Figure 4.1** (a) Rotation occurs around the carbon–carbon bond in ethane, but (b) no rotation is possible around the carbon–carbon bonds in cyclopropane without breaking open the ring.

Larger cycloalkanes have increasing rotational freedom, and the very large rings ( $C_{25}$  and up) are so floppy that they are nearly indistinguishable from open-chain alkanes. The common ring sizes ( $C_3$ – $C_7$ ), however, are severely restricted in their molecular motions.

Because of their cyclic structures, cycloalkanes have two faces as viewed edge-on, a “top” face and a “bottom” face. As a result, isomerism is possible in substituted cycloalkanes. For example, there are two different 1,2-dimethylcyclopropane isomers, one with the two methyl groups on the same face of the ring and one with the methyl groups on opposite faces (Figure 4.2). Both isomers are stable compounds, and neither can be converted into the other without breaking and reforming chemical bonds.

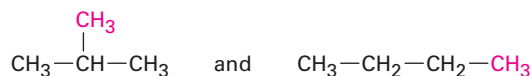


**Figure 4.2** There are two different 1,2-dimethylcyclopropane isomers, one with the methyl groups on the same face of the ring (cis) and the other with the methyl groups on opposite faces of the ring (trans). The two isomers do not interconvert.

Unlike the constitutional isomers butane and isobutane, which have their atoms connected in a different order (Section 3.2), the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, which have their atoms connected in the same order but differ in three-dimensional orientation, are called stereochemical isomers, or **stereoisomers**. More generally, the term **stereochemistry**

is used to refer to the three-dimensional aspects of chemical structure and reactivity.

**Constitutional isomers**  
(different connections  
between atoms)



**Stereoisomers**  
(same connections  
but different three-  
dimensional geometry)



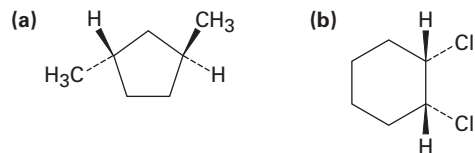
The 1,2-dimethylcyclopropanes are members of a subclass of stereoisomers called *cis-trans* isomers. The prefixes *cis-* (Latin “on the same side”) and *trans-* (Latin “across”) are used to distinguish between them. *Cis-trans* isomerism is a common occurrence in substituted cycloalkanes and in many cyclic biological molecules.



## Naming Cycloalkanes

### Worked Example 4.1

Name the following substances, including the *cis-* or *trans-* prefix:



### Strategy

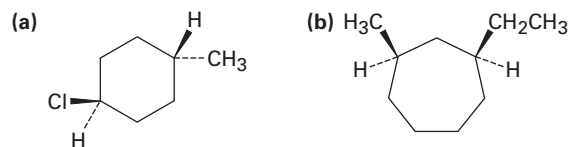
In these views, the ring is roughly in the plane of the page, a wedged bond protrudes out of the page, and a dashed bond recedes into the page. Two substituents are *cis* if they are both out of or both into the page, and they are *trans* if one is out of and one is into the page.

### Solution

(a) *trans*-1,3-Dimethylcyclopentane    (b) *cis*-1,2-Dichlorocyclohexane

### Problem 4.4

Name the following substances, including the *cis-* or *trans-* prefix:



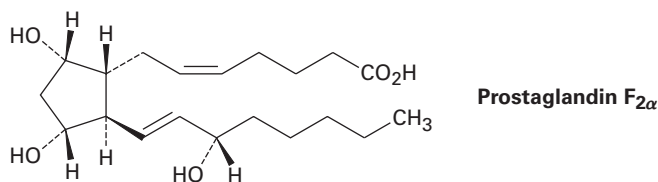
**Problem 4.5**

Draw the structures of the following molecules:

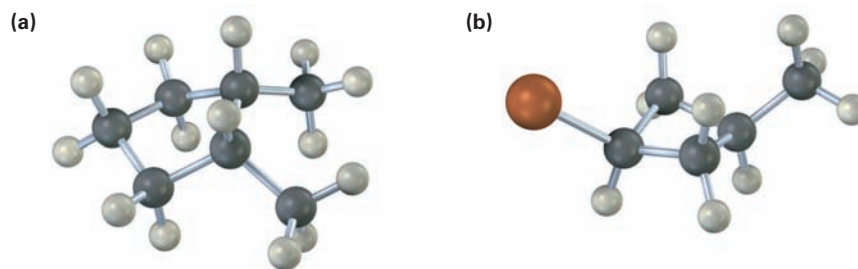
- (a) *trans*-1-Bromo-3-methylcyclohexane      (b) *cis*-1,2-Dimethylcyclobutane  
 (c) *trans*-1-*tert*-Butyl-2-ethylcyclohexane

**Problem 4.6**

Prostaglandin  $F_{2\alpha}$ , a hormone that causes uterine contraction during childbirth, has the following structure. Are the two hydroxyl groups ( $-\text{OH}$ ) on the cyclopentane ring *cis* or *trans* to each other? What about the two carbon chains attached to the ring?

**Problem 4.7**

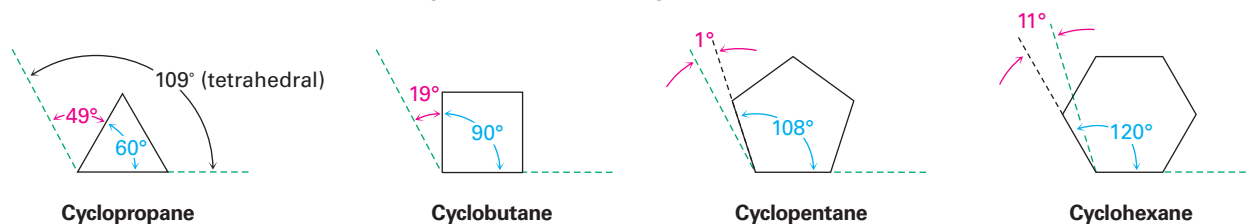
Name the following substances, including the *cis*- or *trans*- prefix (red-brown = Br):



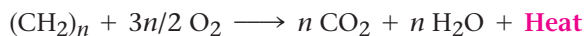
## 4.3 Stability of Cycloalkanes: Ring Strain

Chemists in the late 1800s knew that cyclic molecules existed, but the limitations on ring size were unclear. Although numerous compounds containing five-membered and six-membered rings were known, smaller and larger ring sizes had not been prepared, despite many efforts.

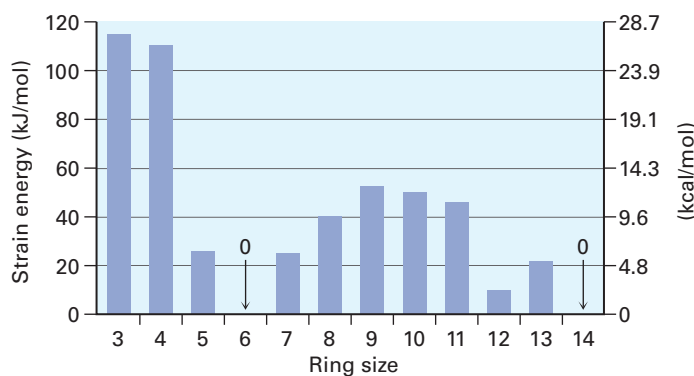
A theoretical interpretation of this observation was proposed in 1885 by Adolf von Baeyer, who suggested that small and large rings might be unstable due to **angle strain**—the strain induced in a molecule when bond angles are forced to deviate from the ideal  $109^\circ$  tetrahedral value. Baeyer based his suggestion on the simple geometric notion that a three-membered ring (cyclopropane) should be an equilateral triangle with bond angles of  $60^\circ$  rather than  $109^\circ$ , a four-membered ring (cyclobutane) should be a square with bond angles of  $90^\circ$ , a five-membered ring should be a regular pentagon with bond angles of  $108^\circ$ , and so on. Continuing this argument, large rings should be strained by having bond angles that are much greater than  $109^\circ$ .



What are the facts? To measure the amount of strain in a compound, we have to measure the total energy of the compound and then subtract the energy of a strain-free reference compound. The difference between the two values should represent the amount of extra energy in the molecule due to strain. The simplest experimental way to do this for a cycloalkane is to measure its *heat of combustion*, the amount of heat released when the compound burns completely with oxygen. The more energy (strain) the compound contains, the more energy (heat) is released on combustion.



Because the heat of combustion of a cycloalkane depends on size, we need to look at heats of combustion per  $\text{CH}_2$  unit. Subtracting a reference value derived from a strain-free acyclic alkane and then multiplying by the number of  $\text{CH}_2$  units in the ring gives the overall strain energy. **Figure 4.3** shows the results.



**Figure 4.3** Cycloalkane strain energies, calculated by taking the difference between cycloalkane heat of combustion per  $\text{CH}_2$  and acyclic alkane heat of combustion per  $\text{CH}_2$ , and multiplying by the number of  $\text{CH}_2$  units in a ring. Small and medium rings are strained, but cyclohexane rings and very large rings are strain-free.

The data in Figure 4.3 show that Baeyer's theory is only partially correct. Cyclopropane and cyclobutane are indeed strained, just as predicted, but cyclopentane is more strained than predicted, and cyclohexane is strain-free. Cycloalkanes of intermediate size have only modest strain, and rings of 14 carbons or more are strain-free. Why is Baeyer's theory wrong?

Baeyer's theory is wrong for the simple reason that he assumed all cycloalkanes to be flat. In fact, as we'll see in the next section, most cycloalkanes are *not* flat; they adopt puckered three-dimensional conformations that allow bond angles to be nearly tetrahedral. As a result, angle strain occurs only in three- and four-membered rings, which have little flexibility. For most ring sizes, particularly the medium-ring ( $\text{C}_7$ – $\text{C}_{11}$ ) cycloalkanes, torsional strain caused by  $\text{H}\leftrightarrow\text{H}$  eclipsing interactions on adjacent carbons (**Section 3.6**) and steric strain caused by the repulsion between nonbonded atoms that approach too closely (**Section 3.7**) are the most important factors. Thus, three kinds of strain contribute to the overall energy of a cycloalkane.

- **Angle strain**—the strain due to expansion or compression of bond angles
- **Torsional strain**—the strain due to eclipsing of bonds on neighboring atoms
- **Steric strain**—the strain due to repulsive interactions when atoms approach each other too closely

**Problem 4.8**

Each  $\text{H} \leftrightarrow \text{H}$  eclipsing interaction in ethane costs about 4.0 kJ/mol. How many such interactions are present in cyclopropane? What fraction of the overall 115 kJ/mol (27.5 kcal/mol) strain energy of cyclopropane is due to torsional strain?

**Problem 4.9**

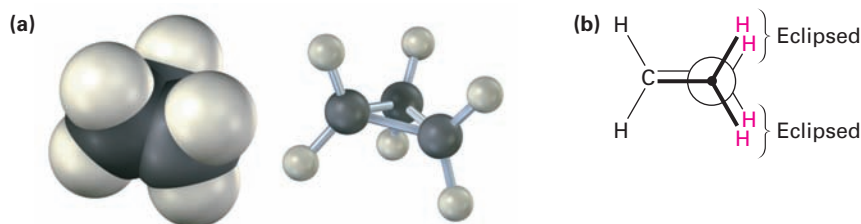
*cis*-1,2-Dimethylcyclopropane has more strain than *trans*-1,2-dimethylcyclopropane. How can you account for this difference? Which of the two compounds is more stable?

## 4.4 Conformations of Cycloalkanes

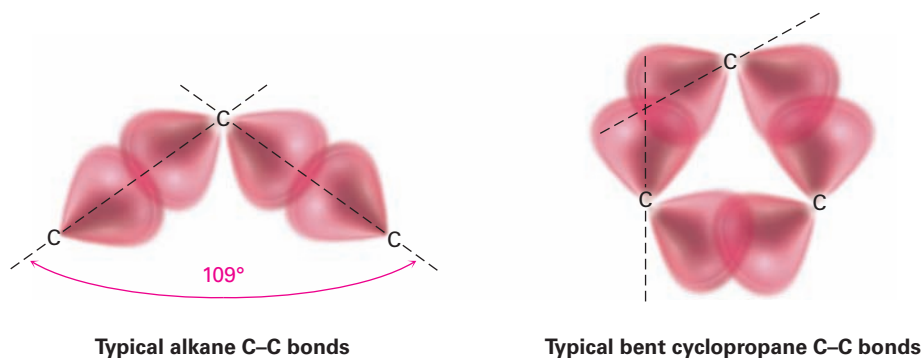
### Cyclopropane

Cyclopropane is the most strained of all rings, primarily because of the angle strain caused by its  $60^\circ$  C–C–C bond angles. In addition, cyclopropane has considerable torsional strain because the C–H bonds on neighboring carbon atoms are eclipsed (**Figure 4.4**).

**Figure 4.4** The structure of cyclopropane, showing the eclipsing of neighboring C–H bonds that gives rise to torsional strain. Part (b) is a Newman projection along a C–C bond.

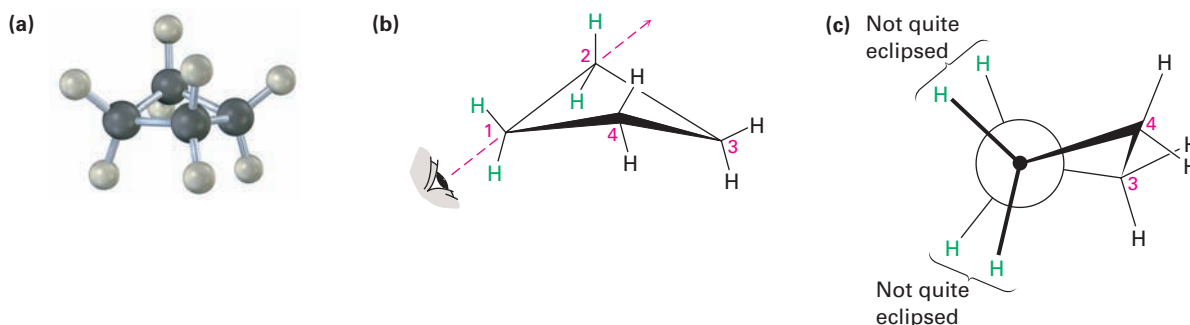


How can the hybrid-orbital model of bonding account for the large distortion of bond angles from the normal  $109^\circ$  tetrahedral value to  $60^\circ$  in cyclopropane? The answer is that cyclopropane has *bent bonds*. In an unstrained alkane, maximum bonding is achieved when two atoms have their overlapping orbitals pointing directly toward each other. In cyclopropane, though, the orbitals can't point directly toward each other; rather, they overlap at a slight angle. The result is that cyclopropane bonds are weaker and more reactive than typical alkane bonds—255 kJ/mol (61 kcal/mol) for a C–C bond in cyclopropane versus 370 kJ/mol (88 kcal/mol) for a C–C bond in open-chain propane.



## Cyclobutane

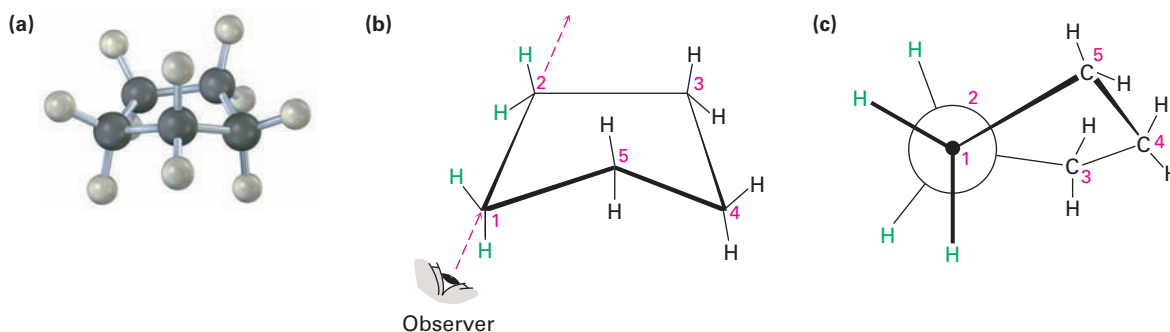
Cyclobutane has less angle strain than cyclopropane but has more torsional strain because of its larger number of ring hydrogens. As a result, the total strain for the two compounds is nearly the same—110 kJ/mol (26.4 kcal/mol) for cyclobutane versus 115 kJ/mol (27.5 kcal/mol) for cyclopropane. Cyclobutane is not quite flat but is slightly bent so that one carbon atom lies about  $25^\circ$  above the plane of the other three (**Figure 4.5**). The effect of this slight bend is to *increase* angle strain but to *decrease* torsional strain, until a minimum-energy balance between the two opposing effects is achieved.



**Figure 4.5** The conformation of cyclobutane. Part (c) is a Newman projection along a C–C bond, showing that neighboring C–H bonds are not quite eclipsed.

## Cyclopentane

Cyclopentane was predicted by Baeyer to be nearly strain-free, but it actually has a total strain energy of 26 kJ/mol (6.2 kcal/mol). Although planar cyclopentane has practically no angle strain, it has a large amount of torsional strain. Cyclopentane therefore twists to adopt a puckered, nonplanar conformation that strikes a balance between increased angle strain and decreased torsional strain. Four of the cyclopentane carbon atoms are in approximately the same plane, with the fifth carbon atom bent out of the plane. Most of the hydrogens are nearly staggered with respect to their neighbors (**Figure 4.6**).



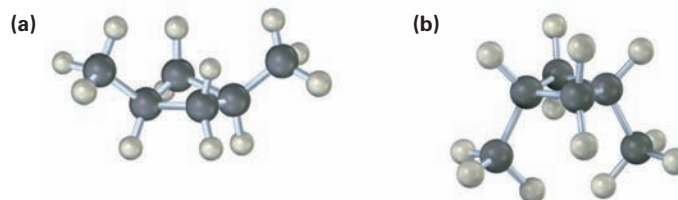
**Figure 4.6** The conformation of cyclopentane. Carbons 1, 2, 3, and 4 are nearly planar, but carbon 5 is out of the plane. Part (c) is a Newman projection along the C1–C2 bond, showing that neighboring C–H bonds are nearly staggered.

**Problem 4.10**

How many  $H \leftrightarrow H$  eclipsing interactions would be present if cyclopentane were planar? Assuming an energy cost of 4.0 kJ/mol for each eclipsing interaction, how much torsional strain would planar cyclopentane have? Since the measured total strain of cyclopentane is 26 kJ/mol, how much of the torsional strain is relieved by puckering?

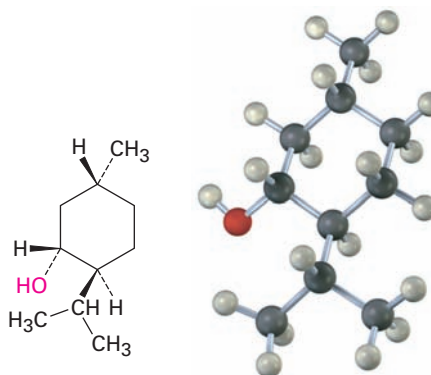
**Problem 4.11**

Two conformations of *cis*-1,3-dimethylcyclobutane are shown. What is the difference between them, and which do you think is likely to be more stable?



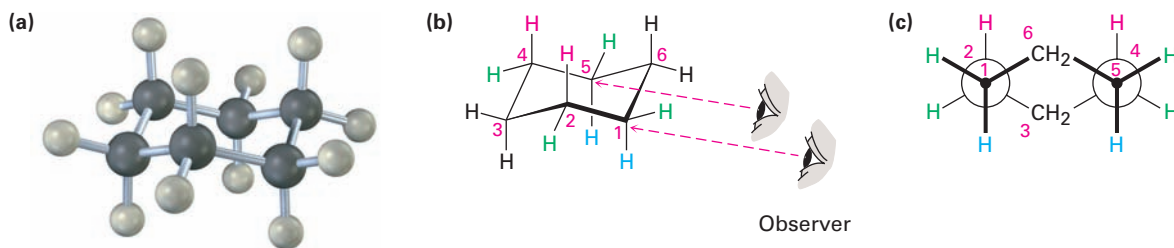
## 4.5 Conformations of Cyclohexane

Substituted cyclohexanes are the most common cycloalkanes and occur widely in nature. A large number of compounds, including steroids and many pharmaceutical agents, have cyclohexane rings. The flavoring agent menthol, for instance, has three substituents on a six-membered ring.



**Menthol**

Cyclohexane adopts a strain-free, three-dimensional shape that is called a **chair conformation** because of its similarity to a lounge chair, with a back, seat, and footrest (**Figure 4.7**). Chair cyclohexane has neither angle strain nor torsional strain—all C–C–C bond angles are near the  $109.5^\circ$  tetrahedral value, and all neighboring C–H bonds are staggered.



**Figure 4.7** The strain-free chair conformation of cyclohexane. All C—C—C bond angles are  $111.5^\circ$ , close to the ideal  $109.5^\circ$  tetrahedral angle, and all neighboring C—H bonds are staggered.

The easiest way to visualize chair cyclohexane is to build a molecular model. (In fact, do it now if you have access to a model kit.) Two-dimensional drawings like that in Figure 4.7 are useful, but there's no substitute for holding, twisting, and turning a three-dimensional model in your own hands.

The chair conformation of cyclohexane can be drawn in three steps.

#### STEP 1

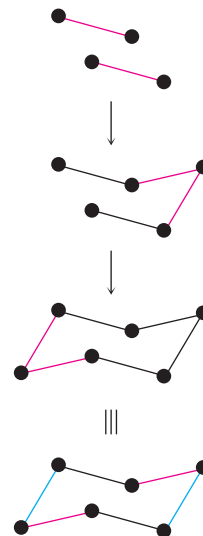
Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.

#### STEP 2

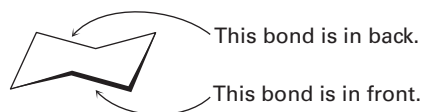
Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.

#### STEP 3

Place the bottommost carbon atom below and to the left of the plane of the middle four, and connect the bonds. Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.



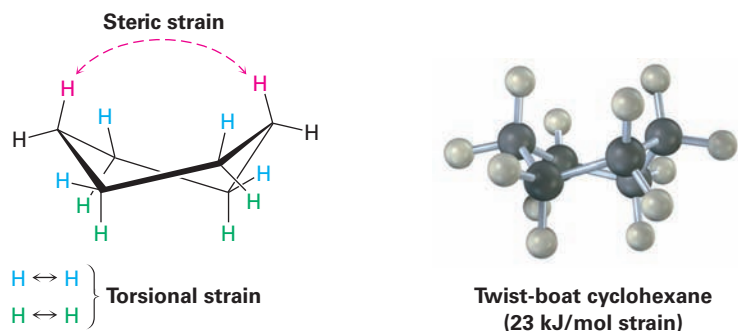
When viewing cyclohexane, it's helpful to remember that the lower bond is in front and the upper bond is in back. If this convention is not defined, an optical illusion can make it appear that the reverse is true. For clarity, all cyclohexane rings drawn in this book will have the front (lower) bond heavily shaded to indicate nearness to the viewer.



In addition to the chair conformation of cyclohexane, an alternative called the **twist-boat conformation** is also nearly free of angle strain. It does, however, have both steric strain and torsional strain and is about 23 kJ/mol

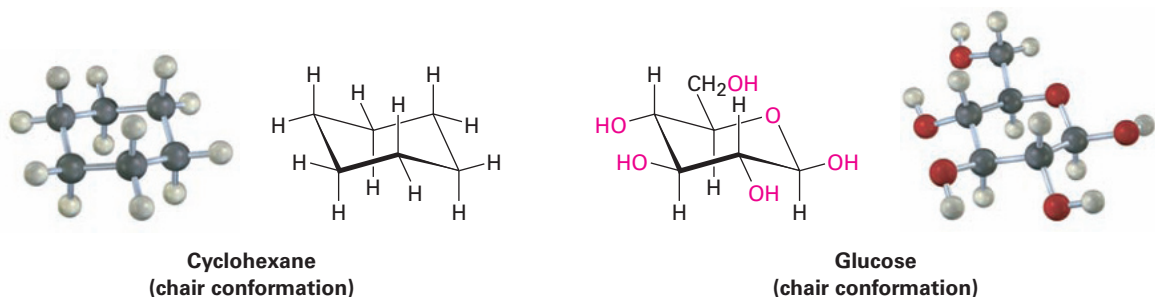


(5.5 kcal/mol) higher in energy than the chair conformation. As a result, molecules adopt the twist-boat geometry only under special circumstances.



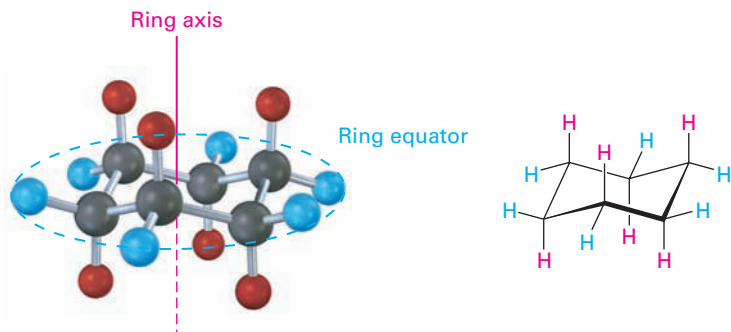
## 4.6 Axial and Equatorial Bonds in Cyclohexane

The chair conformation of cyclohexane leads to many consequences. We'll see in **Section 11.9**, for instance, that the chemical behavior of many substituted cyclohexanes is influenced by their conformation. In addition, we'll see in **Section 25.5** that simple carbohydrates, such as glucose, adopt a conformation based on the cyclohexane chair and that their chemistry is directly affected as a result.

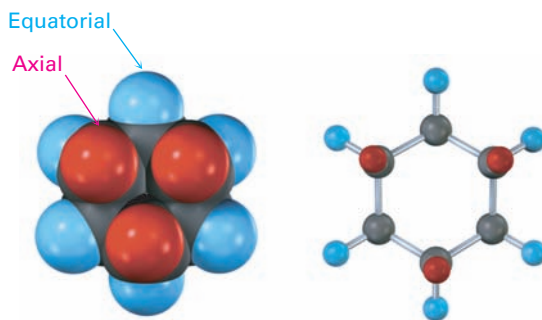


Another consequence of the chair conformation is that there are two kinds of positions for substituents on the cyclohexane ring: *axial* positions and *equatorial* positions (**Figure 4.8**). The six **axial** positions are perpendicular to the ring, parallel to the ring axis, and the six **equatorial** positions are in the rough plane of the ring, around the ring equator.

**Figure 4.8** Axial and equatorial positions in chair cyclohexane. The six axial hydrogens are parallel to the ring axis, and the six equatorial hydrogens are in a band around the ring equator.



As shown in Figure 4.8, each carbon atom in chair cyclohexane has one axial and one equatorial hydrogen. Furthermore, each face of the ring has three axial and three equatorial hydrogens in an alternating arrangement. For example, if the top face of the ring has axial hydrogens on carbons 1, 3, and 5, then it has equatorial hydrogens on carbons 2, 4, and 6. Exactly the reverse is true for the bottom face: carbons 1, 3, and 5 have equatorial hydrogens, but carbons 2, 4, and 6 have axial hydrogens (**Figure 4.9**).

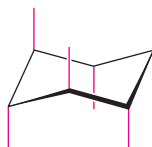


**Figure 4.9** Alternating **axial** and **equatorial** positions in chair cyclohexane, as shown in a view looking directly down the ring axis. Each carbon atom has one axial and one equatorial position, and each face has alternating axial and equatorial positions.

Note that we haven't used the words *cis* and *trans* in this discussion of cyclohexane conformation. Two hydrogens on the same face of the ring are always *cis*, regardless of whether they're axial or equatorial and regardless of whether they're adjacent. Similarly, two hydrogens on opposite faces of the ring are always *trans*.

Axial and equatorial bonds can be drawn following the procedure in **Figure 4.10**. Look at a molecular model as you practice.

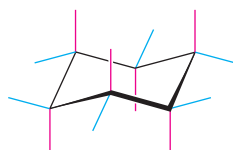
**Axial bonds:** The six axial bonds, one on each carbon, are parallel and alternate up–down.



**Equatorial bonds:** The six equatorial bonds, one on each carbon, come in three sets of two parallel lines. Each set is also parallel to two ring bonds. Equatorial bonds alternate between sides around the ring.



**Completed cyclohexane**



**Figure 4.10** A procedure for drawing axial and equatorial bonds in chair cyclohexane.

Because chair cyclohexane has two kinds of positions—axial and equatorial—we might expect to find two isomeric forms of a monosubstituted cyclohexane. In fact, we don't. There is only *one* methylcyclohexane, *one* bromocyclohexane,



## Drawing the Chair Conformation of a Substituted Cyclohexane

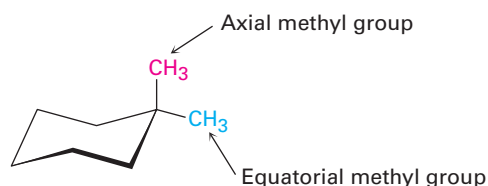
### Worked Example 4.2

Draw 1,1-dimethylcyclohexane in a chair conformation, indicating which methyl group in your drawing is axial and which is equatorial.

#### Strategy

Draw a chair cyclohexane ring using the procedure in Figure 4.10, and then put two methyl groups on the same carbon. The methyl group in the rough plane of the ring is equatorial, and the one directly above or below the ring is axial.

#### Solution



#### Problem 4.12

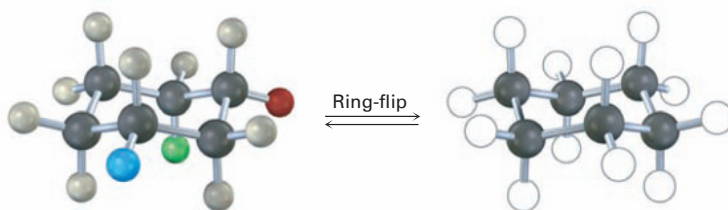
Draw two different chair conformations of cyclohexanol (hydroxycyclohexane), showing all hydrogen atoms. Identify each position as axial or equatorial.

#### Problem 4.13

Draw two different chair conformations of *trans*-1,4-dimethylcyclohexane, and label all positions as axial or equatorial.

#### Problem 4.14

Identify each of the colored positions—red, blue, and green—as axial or equatorial. Then carry out a ring-flip, and show the new positions occupied by each color.



## 4.7 Conformations of Monosubstituted Cyclohexanes

Even though cyclohexane rings flip rapidly between chair conformations at room temperature, the two conformations of a monosubstituted cyclohexane aren't equally stable. In methylcyclohexane, for instance, the equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol (1.8 kcal/mol). The same is true of other monosubstituted cyclohexanes: a substituent is almost always more stable in an equatorial position than in an axial position.

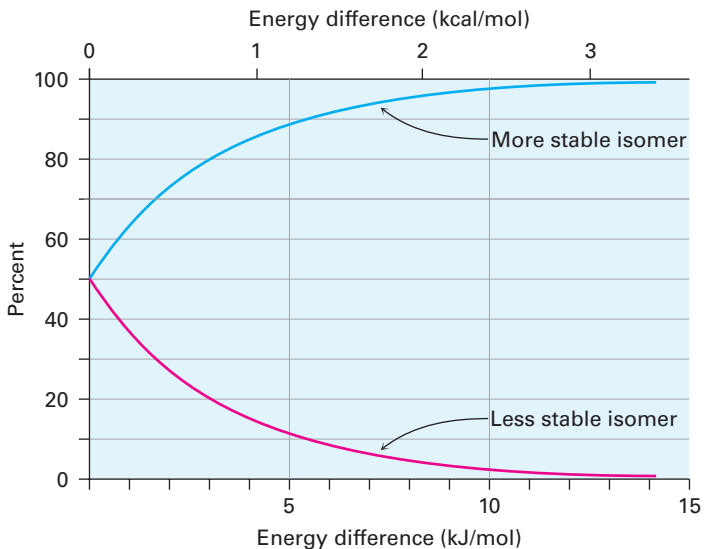
You might recall from your general chemistry course that it's possible to calculate the percentages of two isomers at equilibrium using the equation

#### Key IDEAS

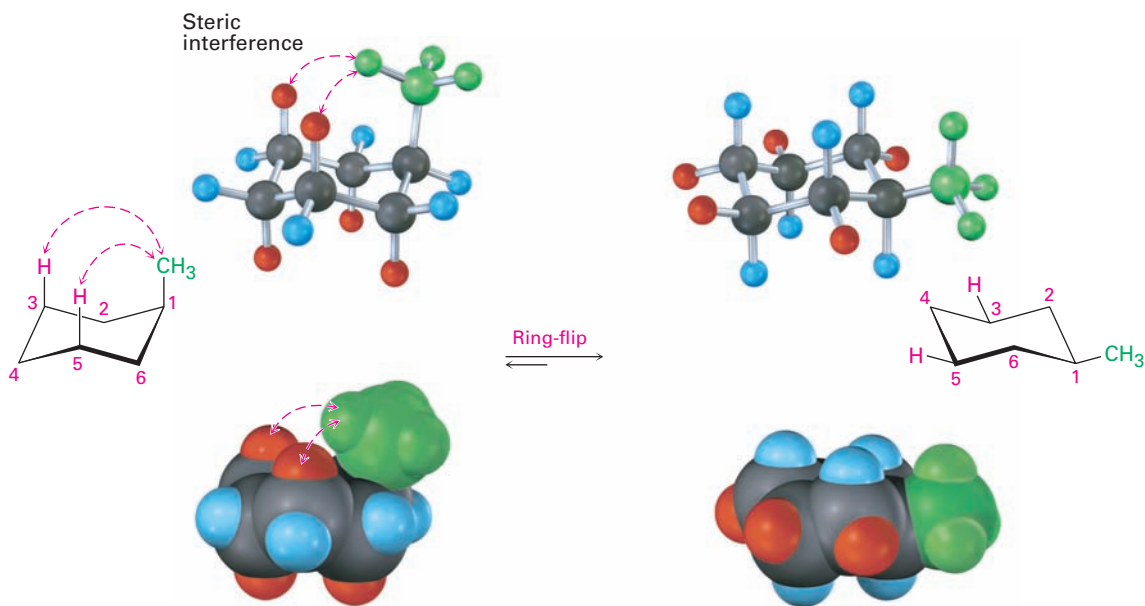
Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

$\Delta E = -RT \ln K$ , where  $\Delta E$  is the energy difference between isomers,  $R$  is the gas constant [8.315 J/(K·mol)],  $T$  is the Kelvin temperature, and  $K$  is the equilibrium constant between isomers. For example, an energy difference of 7.6 kJ/mol means that about 95% of methylcyclohexane molecules have the methyl group equatorial at any given instant and only 5% have the methyl group axial. **Figure 4.12** plots the relationship between energy and isomer percentages.

**Figure 4.12** A plot of the percentages of two isomers at equilibrium versus the energy difference between them. The curves are calculated using the equation  $\Delta E = -RT \ln K$ .

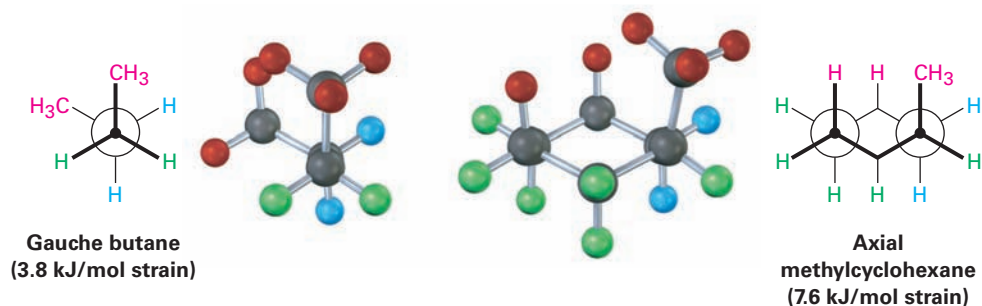


The energy difference between axial and equatorial conformations is due to steric strain caused by **1,3-diaxial interactions**. The axial methyl group on C1 is too close to the axial hydrogens three carbons away on C3 and C5, resulting in 7.6 kJ/mol of steric strain (**Figure 4.13**).



**Figure 4.13** Interconversion of axial and equatorial methylcyclohexane, as represented in several formats. The equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol.

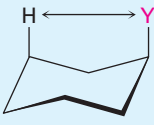
The 1,3-diaxial steric strain in substituted methylcyclohexane is already familiar—we saw it previously as the steric strain between methyl groups in gauche butane. Recall from **Section 3.7** that gauche butane is less stable than anti butane by 3.8 kJ/mol (0.9 kcal/mol) because of steric interference between hydrogen atoms on the two methyl groups. Comparing a four-carbon fragment of axial methylcyclohexane with gauche butane shows that the steric interaction is the same in both cases (**Figure 4.14**). Because axial methylcyclohexane has two such interactions, it has  $2 \times 3.8 = 7.6$  kJ/mol of steric strain. Equatorial methylcyclohexane has no such interactions and is therefore more stable.



**Figure 4.14** The origin of 1,3-diaxial interactions in methylcyclohexane. The steric strain between an **axial methyl group** and an **axial hydrogen atom** three carbons away is identical to the steric strain in gauche butane. Note that the  $-\text{CH}_3$  group in methylcyclohexane moves slightly away from a true axial position to minimize the strain.

The exact amount of 1,3-diaxial steric strain in a given substituted cyclohexane depends on the nature and size of the substituent, as indicated in Table 4.1. Not surprisingly, the amount of steric strain increases through the series  $\text{H}_3\text{C}- < \text{CH}_3\text{CH}_2- < (\text{CH}_3)_2\text{CH}- \ll (\text{CH}_3)_3\text{C}-$ , paralleling the increasing size of the alkyl groups. Note that the values in Table 4.1 refer to 1,3-diaxial interactions of the substituent with a single hydrogen atom. These values must be doubled to arrive at the amount of strain in a monosubstituted cyclohexane.

**Table 4.1** Steric Strain in Monosubstituted Cyclohexanes

Y	1,3-Diaxial strain		
	(kJ/mol)	(kcal/mol)	
F	0.5	0.12	
Cl, Br	1.0	0.25	
OH	2.1	0.5	
$\text{CH}_3$	3.8	0.9	
$\text{CH}_2\text{CH}_3$	4.0	0.95	
$\text{CH}(\text{CH}_3)_2$	4.6	1.1	
$\text{C}(\text{CH}_3)_3$	11.4	2.7	
$\text{C}_6\text{H}_5$	6.3	1.5	
$\text{CO}_2\text{H}$	2.9	0.7	
CN	0.4	0.1	

**Problem 4.15**

What is the energy difference between the axial and equatorial conformations of cyclohexanol (hydroxycyclohexane)?

**Problem 4.16**

Why do you suppose an axial cyano ( $-\text{CN}$ ) substituent causes practically no 1,3-diaxial steric strain (0.4 kJ/mol)? Use molecular models to help with your answer.

**Problem 4.17**

Look at Figure 4.12 on page 124, and estimate the percentages of axial and equatorial conformations present at equilibrium in bromocyclohexane.

## 4.8 Conformations of Disubstituted Cyclohexanes

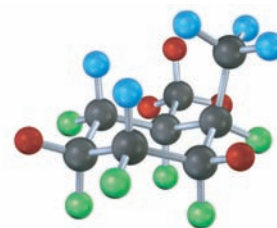
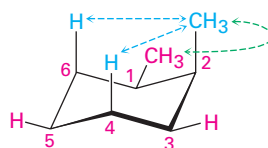
Monosubstituted cyclohexanes are always more stable with their substituent in an equatorial position, but the situation in disubstituted cyclohexanes is more complex because the steric effects of both substituents must be taken into account. All steric interactions in both possible chair conformations must be analyzed before deciding which conformation is favored.

Let's look at 1,2-dimethylcyclohexane as an example. There are two isomers, *cis*-1,2-dimethylcyclohexane and *trans*-1,2-dimethylcyclohexane, which must be considered separately. In the *cis* isomer, both methyl groups are on the same face of the ring and the compound can exist in either of the two chair conformations shown in **Figure 4.15**. (It may be easier for you to see whether a compound is *cis*- or *trans*-disubstituted by first drawing the ring as a flat representation and then converting to a chair conformation.)

***cis*-1,2-Dimethylcyclohexane**

One gauche interaction (3.8 kJ/mol)  
Two  $\text{CH}_3 \leftrightarrow \text{H}$  diaxial interactions (7.6 kJ/mol)

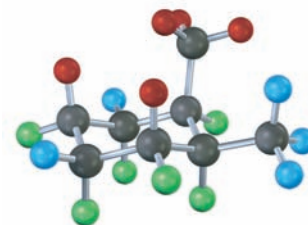
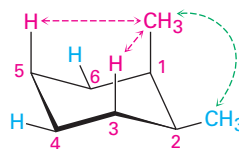
**Total strain:  $3.8 + 7.6 = 11.4$  kJ/mol**



Ring-flip

One gauche interaction (3.8 kJ/mol)  
Two  $\text{CH}_3 \leftrightarrow \text{H}$  diaxial interactions (7.6 kJ/mol)

**Total strain:  $3.8 + 7.6 = 11.4$  kJ/mol**



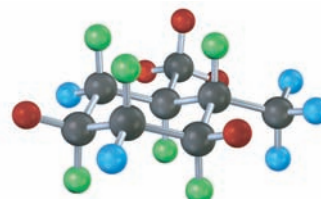
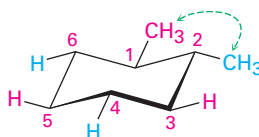
**Figure 4.15** Conformations of *cis*-1,2-dimethylcyclohexane. The two chair conformations are equal in energy because each has one axial methyl group and one equatorial methyl group.

Both chair conformations of *cis*-1,2-dimethylcyclohexane have one axial methyl group and one equatorial methyl group. The top conformation in Figure 4.15 has an axial methyl group at C2, which has 1,3-diaxial interactions with hydrogens on C4 and C6. The ring-flipped conformation has an axial methyl group at C1, which has 1,3-diaxial interactions with hydrogens on C3 and C5. In addition, both conformations have gauche butane interactions between the two methyl groups. The two conformations are equal in energy, with a total steric strain of  $3 \times 3.8 \text{ kJ/mol} = 11.4 \text{ kJ/mol}$  (2.7 kcal/mol).

In *trans*-1,2-dimethylcyclohexane, the two methyl groups are on opposite faces of the ring and the compound can exist in either of the two chair conformations shown in Figure 4.16. The situation here is quite different from that of the *cis* isomer. The top conformation in Figure 4.16 has both methyl groups equatorial and therefore has only a gauche butane interaction between them (3.8 kJ/mol) but no 1,3-diaxial interactions. The ring-flipped conformation, however, has both methyl groups axial. The axial methyl group at C1 interacts with axial hydrogens at C3 and C5, and the axial methyl group at C2 interacts with axial hydrogens at C4 and C6. These four 1,3-diaxial interactions produce a steric strain of  $4 \times 3.8 \text{ kJ/mol} = 15.2 \text{ kJ/mol}$  and make the diaxial conformation  $15.2 - 3.8 = 11.4 \text{ kJ/mol}$  less favorable than the diequatorial conformation. We therefore predict that *trans*-1,2-dimethylcyclohexane will exist almost exclusively in the diequatorial conformation.

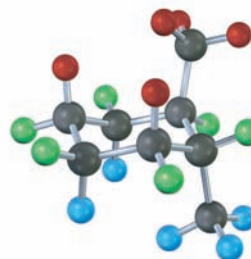
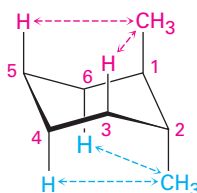
#### *trans*-1,2-Dimethylcyclohexane

One gauche  
interaction (3.8 kJ/mol)



Ring-flip  
↓

Four CH<sub>3</sub> ↔ H diaxial  
interactions (15.2 kJ/mol)

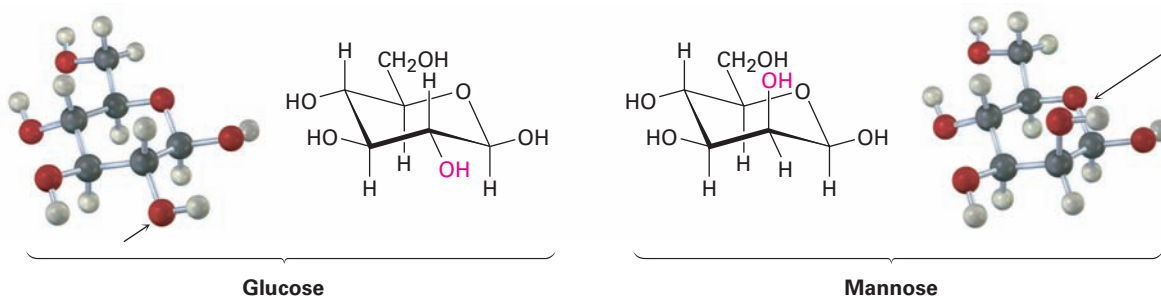


**Figure 4.16** Conformations of *trans*-1,2-dimethylcyclohexane. The conformation with both methyl groups equatorial (top) is favored by 11.4 kJ/mol (2.7 kcal/mol) over the conformation with both methyl groups axial (bottom).

The same kind of **conformational analysis** just carried out for *cis*- and *trans*-1,2-dimethylcyclohexane can be done for any substituted cyclohexane, such as *cis*-1-*tert*-butyl-4-chlorocyclohexane (see Worked Example 4.3). As you might imagine, though, the situation becomes more complex as the number of substituents increases. For instance, compare glucose with mannose, a carbohydrate present in seaweed. Which do you think is more strained? In glucose,



all substituents on the six-membered ring are equatorial, while in mannose, one of the  $-OH$  groups is axial, making mannose more strained.



A summary of the various axial and equatorial relationships among substituent groups in the different possible cis and trans substitution patterns for disubstituted cyclohexanes is given in Table 4.2.

**Table 4.2** Axial and Equatorial Relationships in Cis- and Trans-Disubstituted Cyclohexanes

Cis/trans substitution pattern	Axial/equatorial relationships		
1,2-Cis disubstituted	a,e	or	e,a
1,2-Trans disubstituted	a,a	or	e,e
1,3-Cis disubstituted	a,a	or	e,e
1,3-Trans disubstituted	a,e	or	e,a
1,4-Cis disubstituted	a,e	or	e,a
1,4-Trans disubstituted	a,a	or	e,e

### Worked Example 4.3

#### Drawing the Most Stable Conformation of a Substituted Cyclohexane

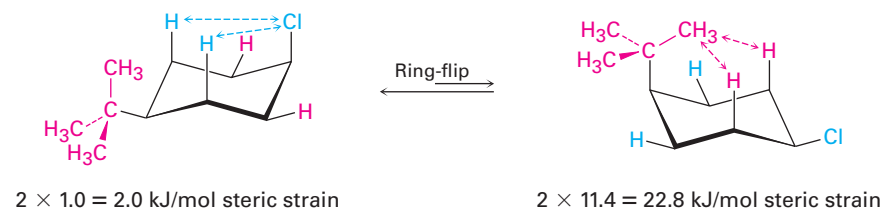
Draw the more stable chair conformation of *cis*-1-*tert*-butyl-4-chlorocyclohexane. By how much is it favored?

#### Strategy

Draw the two possible chair conformations, and calculate the strain energy in each. Remember that equatorial substituents cause less strain than axial substituents.

#### Solution

First draw the two chair conformations of the molecule:



In the conformation on the left, the *tert*-butyl group is equatorial and the chlorine is axial. In the conformation on the right, the *tert*-butyl group is axial and the chlorine is equatorial. These conformations aren't of equal energy because an axial *tert*-butyl substituent and an axial chloro substituent produce different amounts of steric strain. Table 4.1 shows that the 1,3-diaxial interaction between a hydrogen and a *tert*-butyl group costs 11.4 kJ/mol (2.7 kcal/mol), whereas the interaction between a hydrogen and a chlorine costs only 1.0 kJ/mol (0.25 kcal/mol). An axial *tert*-butyl group therefore produces  $(2 \times 11.4 \text{ kJ/mol}) - (2 \times 1.0 \text{ kJ/mol}) = 20.8 \text{ kJ/mol}$  (4.9 kcal/mol) more steric strain than does an axial chlorine, and the compound preferentially adopts the conformation with the chlorine axial and the *tert*-butyl equatorial.

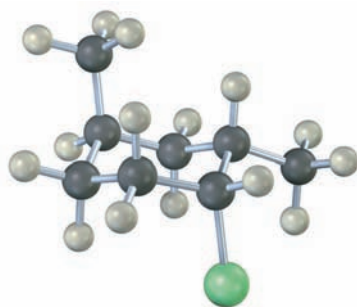
### Problem 4.18

Draw the more stable chair conformation of the following molecules, and estimate the amount of strain in each:

- (a) *trans*-1-Chloro-3-methylcyclohexane    (b) *cis*-1-Ethyl-2-methylcyclohexane  
 (c) *cis*-1-Bromo-4-ethylcyclohexane    (d) *cis*-1-*tert*-Butyl-4-ethylcyclohexane

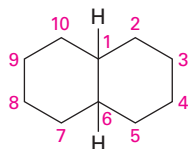
### Problem 4.19

Identify each substituent in the following compound as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



## 4.9 Conformations of Polycyclic Molecules

The final point we'll consider about cycloalkane stereochemistry is to see what happens when two or more cycloalkane rings are fused together along a common bond to construct a **polycyclic** molecule—for example, decalin.

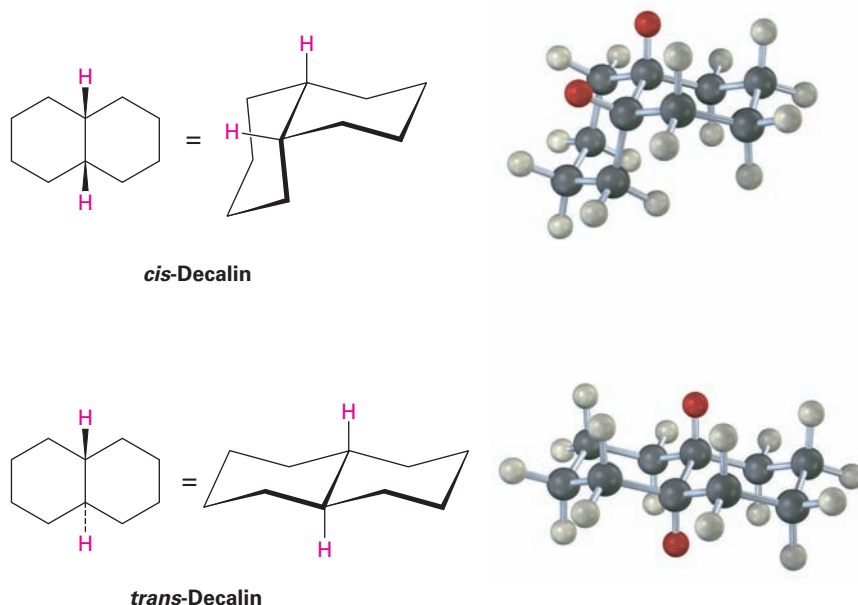


Decalin—two fused cyclohexane rings

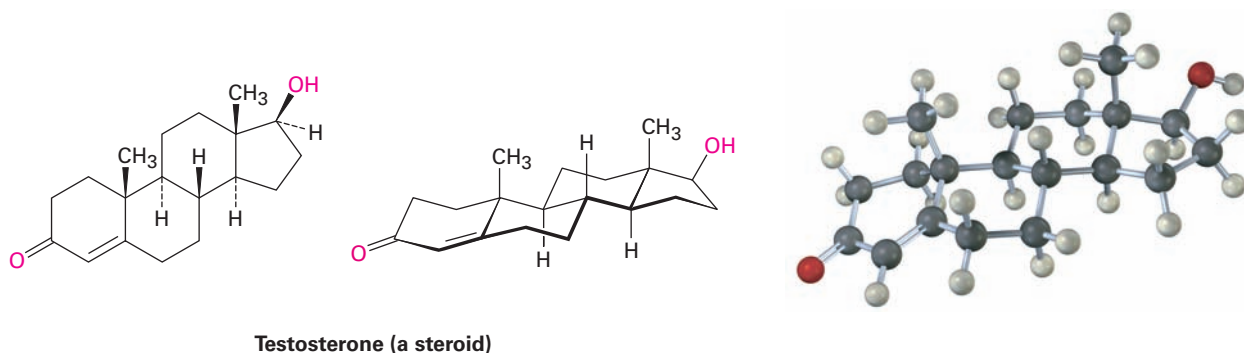
Decalin consists of two cyclohexane rings joined to share two carbon atoms (the *bridgehead* carbons, C1 and C6) and a common bond. Decalin can exist in either of two isomeric forms, depending on whether the rings are *trans* fused or *cis* fused. In *cis*-decalin, the hydrogen atoms at the bridgehead carbons are on the same face of the rings; in *trans*-decalin, the bridgehead hydrogens are on

opposite faces. **Figure 4.17** shows how both compounds can be represented using chair cyclohexane conformations. Note that *cis*- and *trans*-decalin are not interconvertible by ring-flips or other rotations. They are *cis*-*trans* stereoisomers and have the same relationship to each other that *cis*- and *trans*-1,2-dimethylcyclohexane have.

**Figure 4.17** Representations of *cis*- and *trans*-decalin. The **hydrogen atoms** at the bridgehead carbons are on the same face of the rings in the *cis* isomer but on opposite faces in the *trans* isomer.

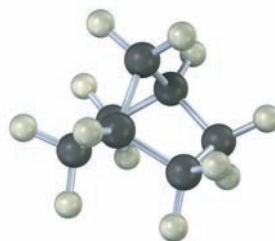
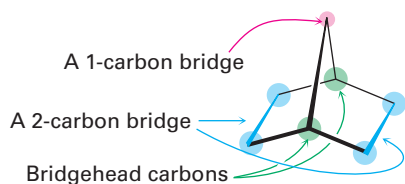


Polycyclic compounds are common in nature, and many valuable substances have fused-ring structures. For example, steroids, such as the male hormone testosterone, have 3 six-membered rings and 1 five-membered ring fused together. Although steroids look complicated compared with cyclohexane or decalin, the same principles that apply to the conformational analysis of simple cyclohexane rings apply equally well (and often better) to steroids.



Another common ring system is the norbornane, or bicyclo[2.2.1]heptane, structure. Like decalin, norbornane is a *bicycloalkane*, so called because *two* rings would have to be broken open to generate an acyclic structure. Its systematic name, bicyclo[2.2.1]heptane, reflects the fact that the molecule has seven

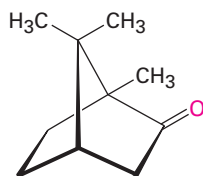
carbons, is bicyclic, and has three “bridges” of 2, 2, and 1 carbon atoms connecting the two bridgehead carbons.



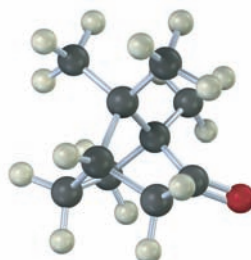
**Norbornane**  
(bicyclo[2.2.1]heptane)

Norbornane has a conformationally locked boat cyclohexane ring (**Section 4.5**) in which carbons 1 and 4 are joined by an additional  $\text{CH}_2$  group. Note how, in drawing this structure, a break in the rear bond indicates that the vertical bond crosses in front of it. Making a molecular model is particularly helpful when trying to see the three-dimensionality of norbornane.

Substituted norbornanes, such as camphor, are found widely in nature, and many have been important historically in developing organic structural theories.



**Camphor**

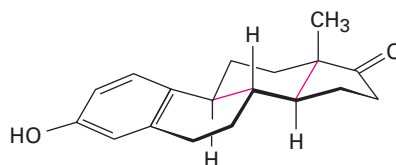
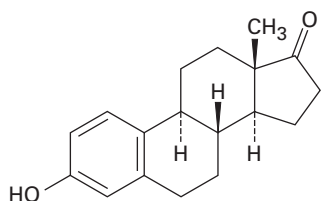


#### Problem 4.20

Which isomer is more stable, *cis*-decalin or *trans*-decalin? Explain.

#### Problem 4.21

Look at the following structure of the female hormone estrone, and tell whether each of the two indicated ring-fusions is *cis* or *trans*.



**Estrone**

## Molecular Mechanics

## A DEEPER LOOK

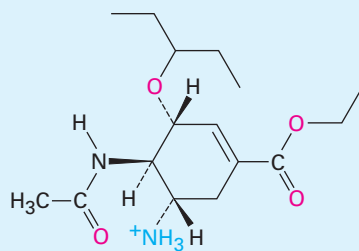
All the structural models in this book are computer-drawn. To make sure they accurately portray bond angles, bond lengths, torsional interactions, and steric interactions, the most stable geometry of each molecule has been calculated on a desktop computer using a commercially available *molecular mechanics* program based on work by N. L. Allinger of the University of Georgia.

The idea behind molecular mechanics is to begin with a rough geometry for a molecule and then calculate a total strain energy for that starting geometry, using mathematical equations that assign values to specific kinds of molecular interactions. Bond angles that are too large or too small cause angle strain; bond lengths that are too short or too long cause stretching or compressing strain; unfavorable eclipsing interactions around single bonds cause torsional strain; and nonbonded atoms that approach each other too closely cause steric, or *van der Waals*, strain.

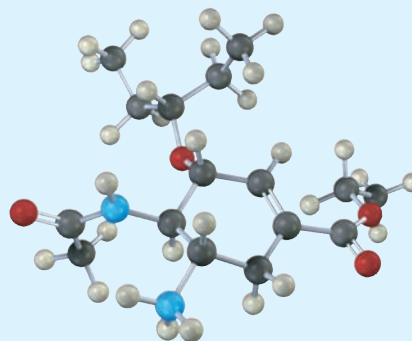
$$E_{\text{total}} = E_{\text{bond stretching}} + E_{\text{angle strain}} + E_{\text{torsional strain}} + E_{\text{van der Waals}}$$

After calculating a total strain energy for the starting geometry, the program automatically changes the geometry slightly in an attempt to lower strain—perhaps by lengthening a bond that is too short or decreasing an angle that is too large. Strain is recalculated for the new geometry, more changes are made, and more calculations are done. After dozens or hundreds of iterations, the calculation ultimately converges on a minimum energy that corresponds to the most favorable, least strained conformation of the molecule.

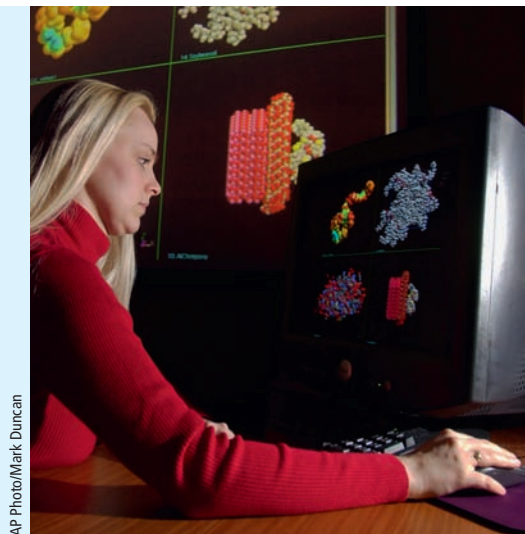
Molecular mechanics calculations have proven to be particularly useful in pharmaceutical research, where the complementary fit between a drug molecule and a receptor molecule in the body is often a key to designing new pharmaceutical agents (Figure 4.18).



**Tamiflu (oseltamivir phosphate)**



**Figure 4.18** The structure of Tamiflu (oseltamivir phosphate), an antiviral agent active against type A influenza, and a molecular model of its minimum-energy conformation as calculated by molecular mechanics.



AP Photo/Mark Duncan

Computer programs make it possible to portray accurate representations of molecular geometry.

## Summary

Cyclic molecules are so commonly encountered throughout organic and biological chemistry that it's important to understand the consequences of their cyclic structures. Thus, we've taken a close look at cyclic structures in this chapter.

A **cycloalkane** is a saturated cyclic hydrocarbon with the general formula  $C_nH_{2n}$ . In contrast to open-chain alkanes, where nearly free rotation occurs around C–C bonds, rotation is greatly reduced in cycloalkanes. Disubstituted cycloalkanes can therefore exist as **cis–trans isomers**. The cis isomer has both substituents on the same face of the ring; the trans isomer has substituents on opposite faces. Cis–trans isomers are just one kind of **stereoisomers**—compounds that have the same connections between atoms but different three-dimensional arrangements.

Not all cycloalkanes are equally stable. Three kinds of strain contribute to the overall energy of a cycloalkane: (1) **angle strain** is the resistance of a bond angle to compression or expansion from the normal  $109^\circ$  tetrahedral value, (2) torsional strain is the energy cost of having neighboring C–H bonds eclipsed rather than staggered, and (3) steric strain is the repulsive interaction that arises when two groups attempt to occupy the same space.

Cyclopropane (115 kJ/mol strain) and cyclobutane (110.4 kJ/mol strain) have both angle strain and torsional strain. Cyclopentane is free of angle strain but has a substantial torsional strain due to its large number of eclipsing interactions. Both cyclobutane and cyclopentane pucker slightly away from planarity to relieve torsional strain.

Cyclohexane is strain-free because it adopts a puckered **chair conformation**, in which all bond angles are near  $109^\circ$  and all neighboring C–H bonds are staggered. Chair cyclohexane has two kinds of positions: **axial** and **equatorial**. Axial positions are oriented up and down, parallel to the ring axis, while equatorial positions lie in a belt around the equator of the ring. Each carbon atom has one axial and one equatorial position.

Chair cyclohexanes are conformationally mobile and can undergo a **ring-flip**, which interconverts axial and equatorial positions. Substituents on the ring are more stable in the equatorial position because axial substituents cause **1,3-diaxial interactions**. The amount of 1,3-diaxial steric strain caused by an axial substituent depends on its size.

### Key words

alicyclic, 109  
 angle strain, 114  
 axial position, 120  
 chair conformation, 118  
 cis–trans isomers, 113  
 conformational analysis, 127  
 cycloalkane, 109  
 1,3-diaxial interaction, 124  
 equatorial position, 120  
 polycyclic compound, 129  
 ring-flip (cyclohexane), 122  
 stereochemistry, 112  
 stereoisomers, 112  
 twist–boat conformation, 119

## Exercises

**OWL** Interactive versions of these problems are assignable in OWL for Organic Chemistry.

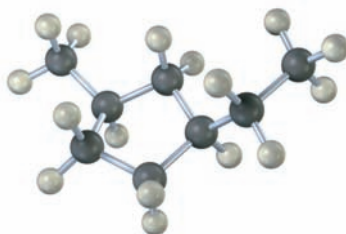
▲ denotes problems linked to the Key Ideas in this chapter.

## Visualizing Chemistry

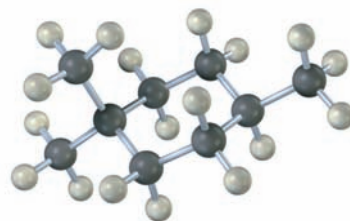
(Problems 4.1–4.21 appear within the chapter.)

4.22 Name the following cycloalkanes:

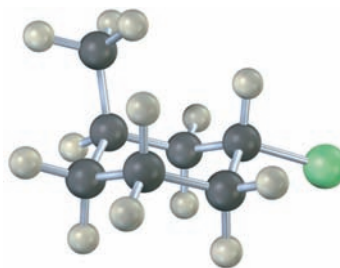
(a)



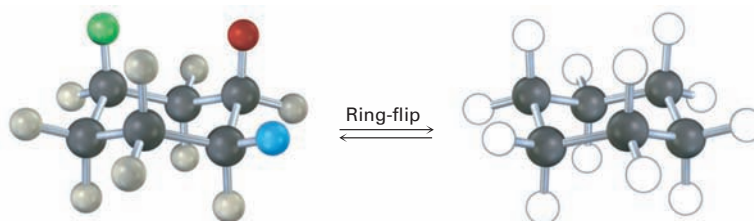
(b)



4.23 Name the following compound, identify each substituent as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):

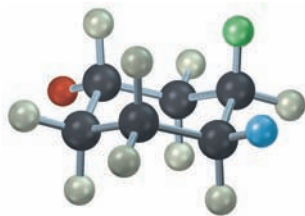


4.24 ▲ A trisubstituted cyclohexane with three substituents—red, green, and blue—undergoes a ring-flip to its alternative chair conformation. Identify each substituent as axial or equatorial, and show the positions occupied by the three substituents in the ring-flipped form.

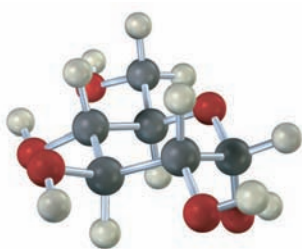
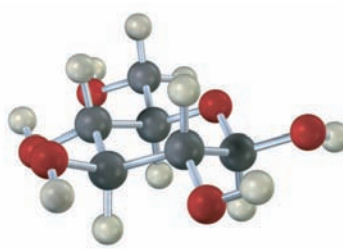


▲ Problems linked to Key Ideas in this chapter

- 4.25 The following cyclohexane derivative has three substituents—red, green, and blue. Identify each substituent as axial or equatorial, and identify each pair of relationships (red–blue, red–green, and blue–green) as cis or trans.



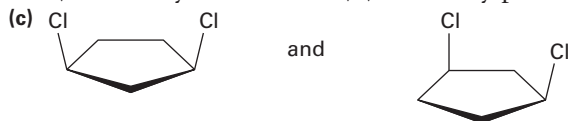
- 4.26 Glucose exists in two forms having a 36:64 ratio at equilibrium. Draw a skeletal structure of each, describe the difference between them, and tell which of the two you think is more stable (red = O).

 $\alpha$ -Glucose $\beta$ -Glucose

## Additional Problems

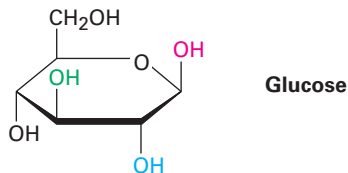
### Cycloalkane Isomers

- 4.27 Draw the five cycloalkanes with the formula  $C_5H_{10}$ .
- 4.28 Draw two constitutional isomers of *cis*-1,2-dibromocyclopentane.
- 4.29 Draw a stereoisomer of *trans*-1,3-dimethylcyclobutane.
- 4.30 Tell whether the following pairs of compounds are identical, constitutional isomers, stereoisomers, or unrelated.
- (a) *cis*-1,3-Dibromocyclohexane and *trans*-1,4-dibromocyclohexane
- (b) 2,3-Dimethylhexane and 2,3,3-trimethylpentane





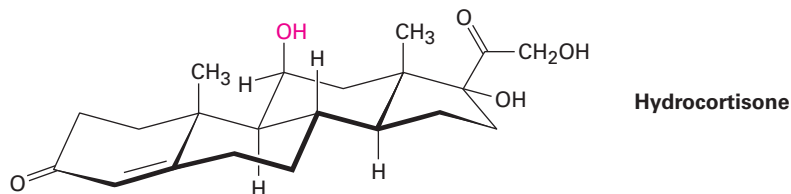
- 4.31 Draw three isomers of *trans*-1,2-dichlorocyclobutane, and label them as either constitutional isomers or stereoisomers.
- 4.32 Identify each pair of relationships among the –OH groups in glucose (red–blue, red–green, red–black, blue–green, blue–black, green–black) as *cis* or *trans*.



- 4.33 ▲ Draw 1,3,5-trimethylcyclohexane using a hexagon to represent the ring. How many *cis*–*trans* stereoisomers are possible?

### Cycloalkane Conformation and Stability

- 4.34 Hydrocortisone, a naturally occurring hormone produced in the adrenal glands, is often used to treat inflammation, severe allergies, and numerous other conditions. Is the indicated –OH group in the molecule axial or equatorial?



- 4.35 A 1,2-*cis* disubstituted cyclohexane, such as *cis*-1,2-dichlorocyclohexane, must have one group axial and one group equatorial. Explain.
- 4.36 A 1,2-*trans* disubstituted cyclohexane must have either both groups axial or both groups equatorial. Explain.
- 4.37 Why is a 1,3-*cis* disubstituted cyclohexane more stable than its *trans* isomer?
- 4.38 Which is more stable, a 1,4-*trans* disubstituted cyclohexane or its *cis* isomer?
- 4.39 *cis*-1,2-Dimethylcyclobutane is less stable than its *trans* isomer, but *cis*-1,3-dimethylcyclobutane is more stable than its *trans* isomer. Draw the most stable conformations of both, and explain.
- 4.40 From the data in Figure 4.12 and Table 4.1, estimate the percentages of molecules that have their substituents in an axial orientation for the following compounds:
- Isopropylcyclohexane
  - Fluorocyclohexane
  - Cyclohexanecarbonitrile, C<sub>6</sub>H<sub>11</sub>CN

▲ Problems linked to Key Ideas in this chapter

**4.41** ▲ Assume that you have a variety of cyclohexanes substituted in the positions indicated. Identify the substituents as either axial or equatorial. For example, a 1,2-cis relationship means that one substituent must be axial and one equatorial, whereas a 1,2-trans relationship means that both substituents are axial or both are equatorial.

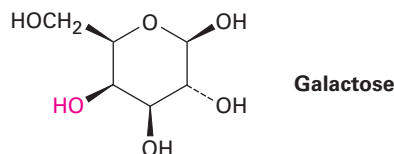
- (a) 1,3-Trans disubstituted      (b) 1,4-Cis disubstituted  
 (c) 1,3-Cis disubstituted      (d) 1,5-Trans disubstituted  
 (e) 1,5-Cis disubstituted      (f) 1,6-Trans disubstituted

### Cyclohexane Conformational Analysis

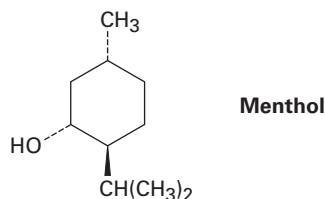
**4.42** Draw the two chair conformations of *cis*-1-chloro-2-methylcyclohexane. Which is more stable, and by how much?

**4.43** Draw the two chair conformations of *trans*-1-chloro-2-methylcyclohexane. Which is more stable?

**4.44** Galactose, a sugar related to glucose, contains a six-membered ring in which all the substituents except the  $-OH$  group indicated below in red are equatorial. Draw galactose in its more stable chair conformation.



**4.45** Draw the two chair conformations of menthol, and tell which is more stable.



**4.46** There are four *cis*-*trans* isomers of menthol (Problem 4.45), including the one shown. Draw the other three.

**4.47** ▲ The diaxial conformation of *cis*-1,3-dimethylcyclohexane is approximately 23 kJ/mol (5.4 kcal/mol) less stable than the diequatorial conformation. Draw the two possible chair conformations, and suggest a reason for the large energy difference.

**4.48** Approximately how much steric strain does the 1,3-diaxial interaction between the two methyl groups introduce into the diaxial conformation of *cis*-1,3-dimethylcyclohexane? (See Problem 4.47.)

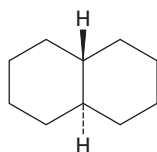
**4.49** In light of your answer to Problem 4.48, draw the two chair conformations of 1,1,3-trimethylcyclohexane and estimate the amount of strain energy in each. Which conformation is favored?

▲ Problems linked to Key Ideas in this chapter

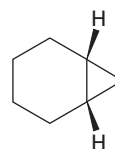
- 4.50 One of the two chair structures of *cis*-1-chloro-3-methylcyclohexane is more stable than the other by 15.5 kJ/mol (3.7 kcal/mol). Which is it? What is the energy cost of a 1,3-diaxial interaction between a chlorine and a methyl group?

### General Problems

- 4.51 We saw in Problem 4.20 that *cis*-decalin is less stable than *trans*-decalin. Assume that the 1,3-diaxial interactions in *cis*-decalin are similar to those in axial methylcyclohexane [that is, one  $\text{CH}_2 \leftrightarrow \text{H}$  interaction costs 3.8 kJ/mol (0.9 kcal/mol)], and calculate the magnitude of the energy difference between *cis*- and *trans*-decalin.
- 4.52 Using molecular models as well as structural drawings, explain why *trans*-decalin is rigid and cannot ring-flip whereas *cis*-decalin can easily ring-flip.
- 4.53 *trans*-Decalin is more stable than its *cis* isomer, but *cis*-bicyclo[4.1.0]heptane is more stable than its *trans* isomer. Explain.

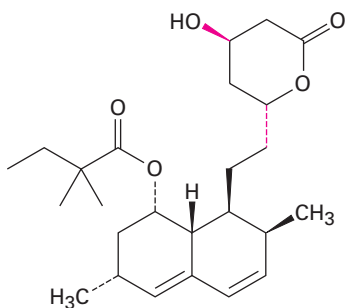


*trans*-Decalin

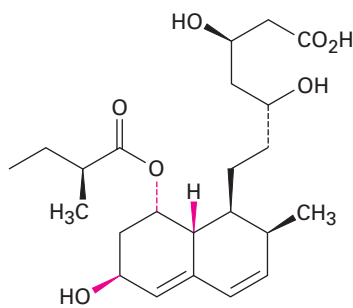


*cis*-Bicyclo[4.1.0]heptane

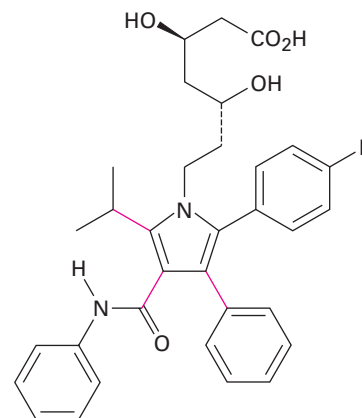
- 4.54 As mentioned in Problem 3.53, the statin drugs, such as simvastatin (Zocor), pravastatin (Pravachol), and atorvastatin (Lipitor) are the most widely prescribed drugs in the world.



Simvastatin  
(Zocor)



Pravastatin  
(Pravachol)

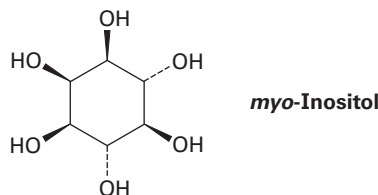


Atorvastatin  
(Lipitor)

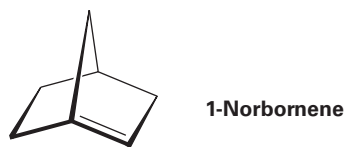
- (a) Are the two indicated bonds on simvastatin *cis* or *trans*?  
 (b) What are the *cis/trans* relationships among the three indicated bonds on pravastatin?  
 (c) Why can't the three indicated bonds on atorvastatin be identified as *cis* or *trans*?

▲ Problems linked to Key Ideas in this chapter

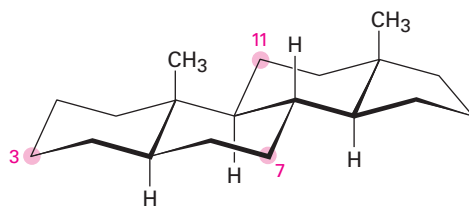
- 4.55 ▲ *myo*-Inositol, one of the isomers of 1,2,3,4,5,6-hexahydroxycyclohexane, acts as a growth factor in both animals and microorganisms. Draw the most stable chair conformation of *myo*-inositol.



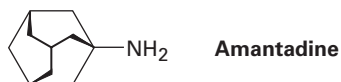
- 4.56 How many *cis*-*trans* stereoisomers of *myo*-inositol (Problem 4.55) are there? Draw the structure of the most stable isomer.
- 4.57 The German chemist J. Brecht proposed in 1935 that bicycloalkenes such as 1-norbornene, which have a double bond to the bridgehead carbon, are too strained to exist. Explain. (Making a molecular model will be helpful.)



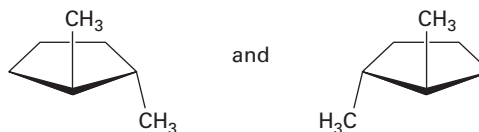
- 4.58 Tell whether each of the following substituents on a steroid is axial or equatorial. (A substituent that is “up” is on the top face of the molecule as drawn, and a substituent that is “down” is on the bottom face.)
- Substituent up at C3
  - Substituent down at C7
  - Substituent down at C11



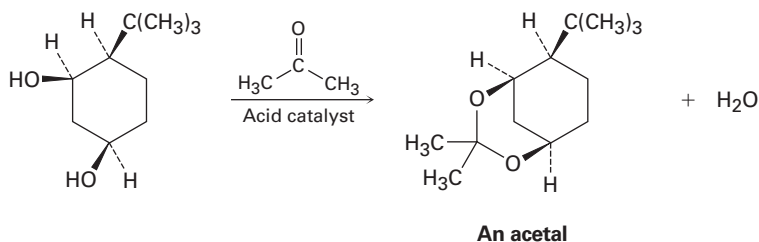
- 4.59 Amantadine is an antiviral agent that is active against influenza type A infection. Draw a three-dimensional representation of amantadine, showing the chair cyclohexane rings.



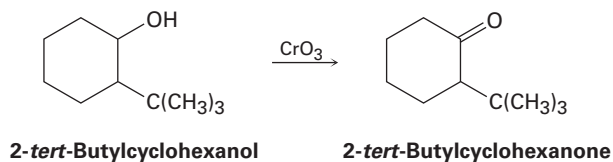
- 4.60** Here's a difficult one. There are two different substances named *trans*-1,2-dimethylcyclopentane. What is the relationship between them? (We'll explore this kind of isomerism in the next chapter.)



- 4.61** Ketones react with alcohols to yield products called *acetals*. Why does the all-*cis* isomer of 4-*tert*-butyl-1,3-cyclohexanediol react readily with acetone and an acid catalyst to form an acetal, but other stereoisomers do not react? In formulating your answer, draw the more stable chair conformations of all four stereoisomers and the product acetal from each.



**4.62** Alcohols undergo an *oxidation* reaction to yield carbonyl compounds on treatment with  $\text{CrO}_3$ . For example, 2-*tert*-butylcyclohexanol gives 2-*tert*-butylcyclohexanone. If axial  $-\text{OH}$  groups are generally more reactive than their equatorial isomers, which do you think reacts faster, the *cis* isomer of 2-*tert*-butylcyclohexanol or the *trans* isomer? Explain.



# 5

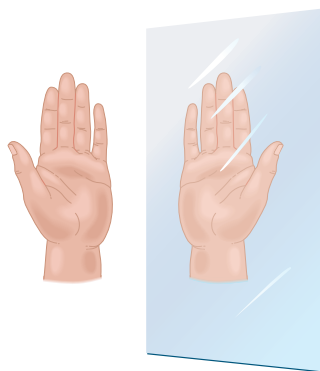


Like the mountain whose image is reflected in a lake, many organic molecules also have mirror-image counterparts.  
Image copyright Tischenko Irina, 2010. Used under license from Shutterstock.com

## Stereochemistry at Tetrahedral Centers

- 5.1 Enantiomers and the Tetrahedral Carbon
- 5.2 The Reason for Handedness in Molecules: Chirality
- 5.3 Optical Activity
- 5.4 Pasteur's Discovery of Enantiomers
- 5.5 Sequence Rules for Specifying Configuration
- 5.6 Diastereomers
- 5.7 Meso Compounds
- 5.8 Racemic Mixtures and the Resolution of Enantiomers
- 5.9 A Review of Isomerism
- 5.10 Chirality at Nitrogen, Phosphorus, and Sulfur
- 5.11 Prochirality
- 5.12 Chirality in Nature and Chiral Environments  
A Deeper Look—  
Chiral Drugs

Are you right-handed or left-handed? You may not spend much time thinking about it, but handedness plays a surprisingly large role in your daily activities. Many musical instruments, such as oboes and clarinets, have a handedness to them; the last available softball glove always fits the wrong hand; left-handed people write in a “funny” way. The reason for these difficulties is that our hands aren't identical; rather, they're *mirror images*. When you hold a *left* hand up to a mirror, the image you see looks like a *right* hand. Try it.



Left hand

Right hand

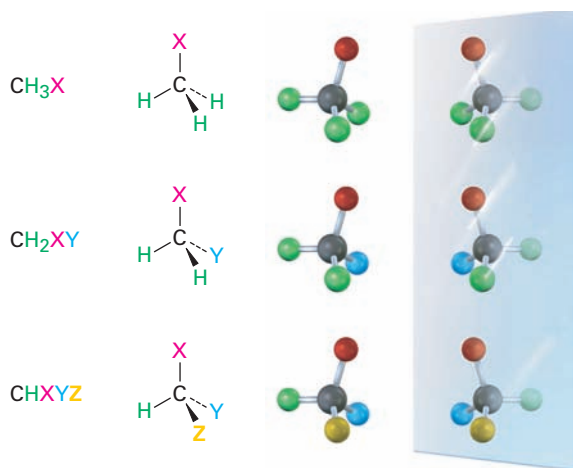
Handedness is also important in organic and biological chemistry, where it arises primarily as a consequence of the tetrahedral stereochemistry of  $sp^3$ -hybridized carbon atoms. Many drugs and almost all the molecules in our bodies—amino acids, carbohydrates, nucleic acids, and many more—are handed. Furthermore, molecular handedness makes possible the precise interactions between enzymes and their substrates that are involved in the hundreds of thousands of chemical reactions on which life is based.

**Why This Chapter?** Understanding the causes and consequences of molecular handedness is crucial to understanding organic and biological chemistry. The subject can be a bit complex at first, but the material covered in this chapter nevertheless forms the basis for much of the remainder of the book.

**OWL** Sign in to OWL for Organic Chemistry at [www.cengage.com/owl](http://www.cengage.com/owl) to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

## 5.1 Enantiomers and the Tetrahedral Carbon

What causes molecular handedness? Look at generalized molecules of the type  $\text{CH}_3\text{X}$ ,  $\text{CH}_2\text{XY}$ , and  $\text{CHXYZ}$  shown in **Figure 5.1**. On the left are three molecules, and on the right are their images reflected in a mirror. The  $\text{CH}_3\text{X}$  and  $\text{CH}_2\text{XY}$  molecules are identical to their mirror images and thus are not handed. If you make a molecular model of each molecule and its mirror image, you find that you can superimpose one on the other so that all atoms coincide. The  $\text{CHXYZ}$  molecule, by contrast, is *not* identical to its mirror image. You can't superimpose a model of the molecule on a model of its mirror image for the same reason that you can't superimpose a left hand on a right hand: they simply aren't the same.

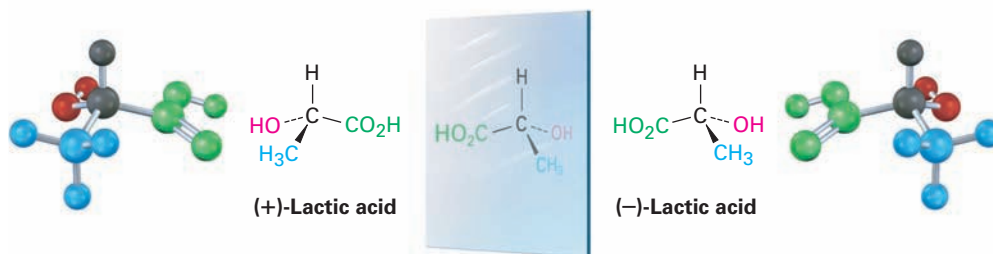


**Figure 5.1** Tetrahedral carbon atoms and their mirror images. Molecules of the type  $\text{CH}_3\text{X}$  and  $\text{CH}_2\text{XY}$  are identical to their mirror images, but a molecule of the type  $\text{CHXYZ}$  is not. A  $\text{CHXYZ}$  molecule is related to its mirror image in the same way that a right hand is related to a left hand.

Molecules that are not identical to their mirror images are kinds of stereoisomers called **enantiomers** (Greek *enantio*, meaning “opposite”). Enantiomers are related to each other as a right hand is related to a left hand and result whenever a tetrahedral carbon is bonded to four different substituents (one need not be H). For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups ( $-\text{H}$ ,  $-\text{OH}$ ,  $-\text{CH}_3$ ,  $-\text{CO}_2\text{H}$ ) bonded to the central carbon atom. The enantiomers are called (+)-lactic acid and (–)-lactic acid. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.

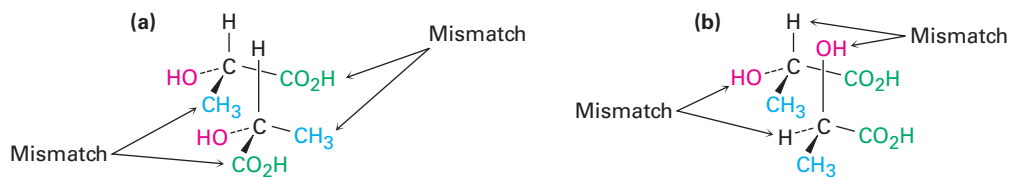


**Lactic acid: a molecule of general formula  $\text{CHXYZ}$**





No matter how hard you try, you can't superimpose a molecule of (+)-lactic acid on a molecule of (–)-lactic acid. If any two groups match up, say –H and –CO<sub>2</sub>H, the remaining two groups don't match (**Figure 5.2**).



**Figure 5.2** Attempts at superimposing the mirror-image forms of lactic acid. **(a)** When the –H and –OH substituents match up, the –CO<sub>2</sub>H and –CH<sub>3</sub> substituents don't; **(b)** when –CO<sub>2</sub>H and –CH<sub>3</sub> match up, –H and –OH don't. Regardless of how the molecules are oriented, they aren't identical.

## 5.2 The Reason for Handedness in Molecules: Chirality

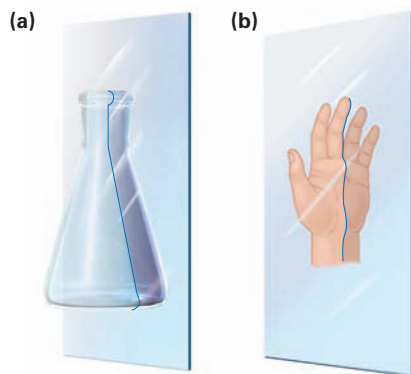
### Key IDEAS

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

A molecule that is not identical to its mirror image is said to be **chiral** (ky-ral, from the Greek *cheir*, meaning “hand”). You can't take a chiral molecule and its enantiomer and place one on the other so that all atoms coincide.

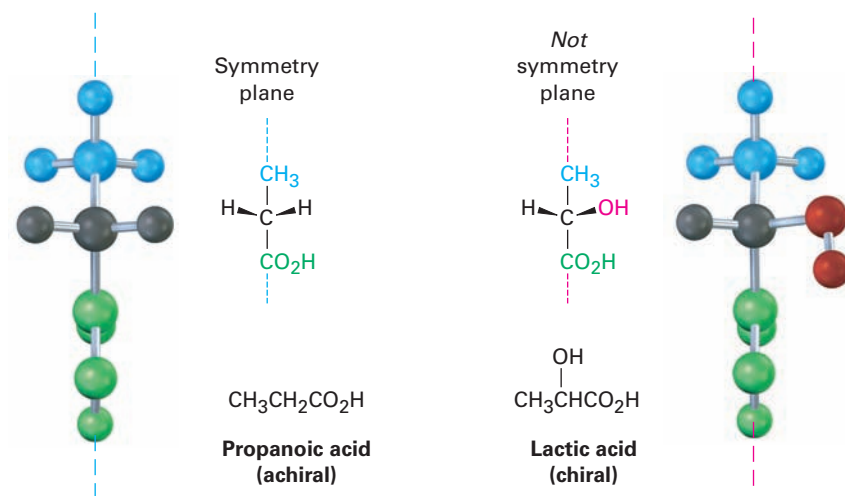
How can you predict whether a given molecule is or is not chiral? *A molecule is not chiral if it has a plane of symmetry.* A plane of symmetry is a plane that cuts through the middle of a molecule (or any object) in such a way that one half of the molecule or object is a mirror image of the other half. A laboratory flask, for example, has a plane of symmetry. If you were to cut the flask in half, one half would be a mirror image of the other half. A hand, however, does not have a plane of symmetry. One “half” of a hand is not a mirror image of the other half (**Figure 5.3**).

**Figure 5.3** The meaning of *symmetry plane*. **(a)** An object like the flask has a symmetry plane cutting through it so that right and left halves are mirror images. **(b)** An object like a hand has no symmetry plane; the right “half” of a hand is not a mirror image of the left half.



A molecule that has a plane of symmetry in any conformation must be identical to its mirror image and hence must be nonchiral, or **achiral**. Thus, propanoic acid, CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>H, has a plane of symmetry when lined up as shown in

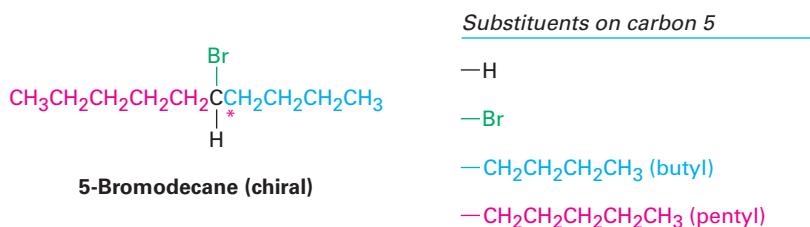
**Figure 5.4** and is achiral, while lactic acid,  $\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H}$ , has no plane of symmetry in any conformation and is chiral.



**Figure 5.4** The achiral propanoic acid molecule versus the chiral lactic acid molecule. Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other side. Lactic acid has no such symmetry plane.

The most common, although not the only, cause of chirality in an organic molecule is the presence of a tetrahedral carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are referred to as **chirality centers**, although other terms such as *stereocenter*, *asymmetric center*, and *stereogenic center* have also been used. Note that *chirality* is a property of the entire molecule, whereas a *chirality center* is the *cause* of chirality.

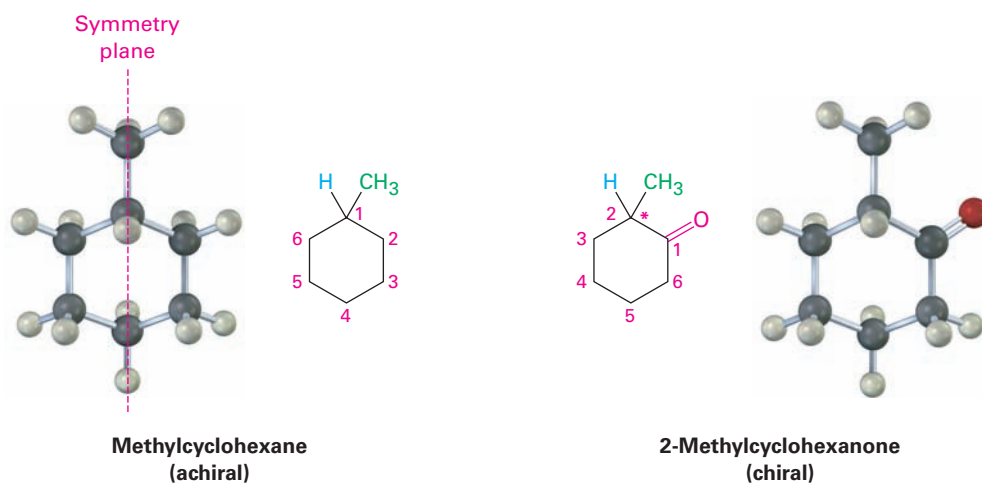
Detecting a chirality center in a complex molecule takes practice because it's not always immediately apparent that four different groups are bonded to a given carbon. The differences don't necessarily appear right next to the chirality center. For example, 5-bromodecane is a chiral molecule because four different groups are bonded to C5, the chirality center (marked with an asterisk). A butyl substituent is similar to a pentyl substituent, but it isn't identical. The difference isn't apparent until four carbon atoms away from the chirality center, but there's still a difference.



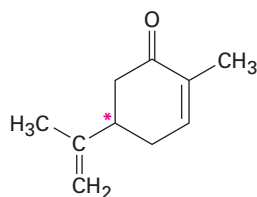
As other possible examples, look at methylcyclohexane and 2-methylcyclohexanone. Methylcyclohexane is achiral because no carbon atom in the molecule is bonded to four different groups. You can immediately eliminate all  $-\text{CH}_2-$  carbons and the  $-\text{CH}_3$  carbon from consideration, but what about C1 on the ring? The C1 carbon atom is bonded to a  $-\text{CH}_3$  group, to an  $-\text{H}$  atom, and to C2 and C6 of the ring. Carbons 2 and 6 are equivalent, however, as are carbons

3 and 5. Thus, the C6–C5–C4 “substituent” is equivalent to the C2–C3–C4 substituent, and methylcyclohexane is achiral. Another way of reaching the same conclusion is to realize that methylcyclohexane has a symmetry plane, which passes through the methyl group and through C1 and C4 of the ring.

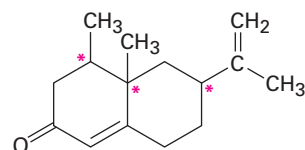
The situation is different for 2-methylcyclohexanone. 2-Methylcyclohexanone has no symmetry plane and is chiral because C2 is bonded to four different groups: a  $-\text{CH}_3$  group, an  $-\text{H}$  atom, a  $-\text{COCH}_2-$  ring bond (C1), and a  $-\text{CH}_2\text{CH}_2-$  ring bond (C3).



Several more examples of chiral molecules are shown below. Check for yourself that the labeled carbons are chirality centers. You might note that carbons in  $-\text{CH}_2-$ ,  $-\text{CH}_3$ ,  $\text{C}=\text{O}$ ,  $\text{C}=\text{C}$ , and  $\text{C}\equiv\text{C}$  groups can't be chirality centers. (Why not?)



Carvone (spearmint oil)



Nootkatone (grapefruit oil)

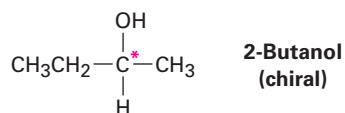
### Worked Example 5.1

#### Drawing the Three-Dimensional Structure of a Chiral Molecule

Draw the structure of a chiral alcohol.

#### Strategy

An alcohol is a compound that contains the  $-\text{OH}$  functional group. To make an alcohol chiral, we need to have four different groups bonded to a single carbon atom, say  $-\text{H}$ ,  $-\text{OH}$ ,  $-\text{CH}_3$ , and  $-\text{CH}_2\text{CH}_3$ .

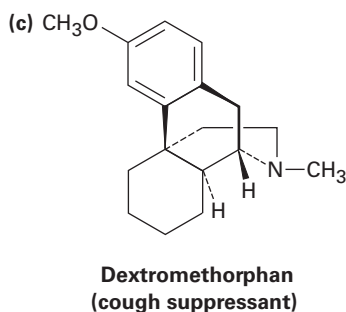
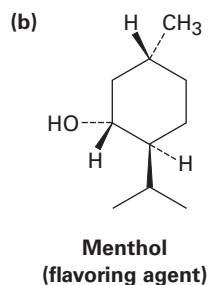
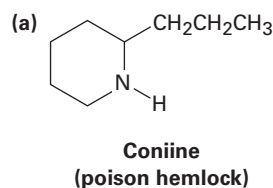
**Solution****Problem 5.1**

Which of the following objects are chiral?

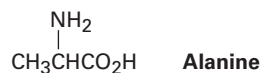
- (a) Soda can (b) Screwdriver (c) Screw (d) Shoe

**Problem 5.2**

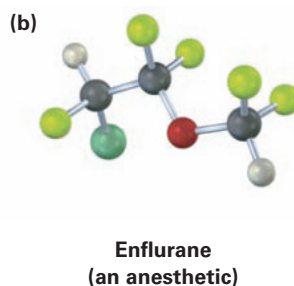
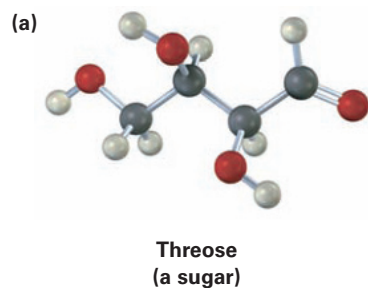
Which of the following molecules are chiral? Identify the chirality center(s) in each.

**Problem 5.3**

Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.

**Problem 5.4**

Identify the chirality centers in the following molecules (green = Cl, yellow-green = F):



## 5.3 Optical Activity

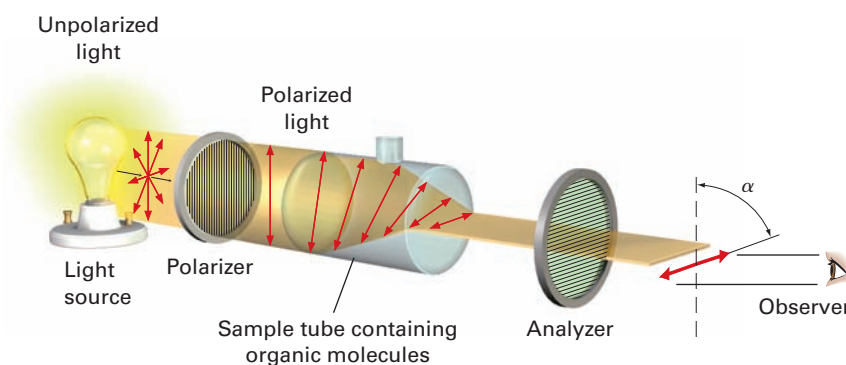
The study of chirality originated in the early 19th century during investigations by the French physicist Jean-Baptiste Biot into the nature of *plane-polarized light*. A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a

beam of ordinary light passes through a device called a *polarizer*, however, only the light waves oscillating in a single plane pass through and the light is said to be plane-polarized. Light waves in all other planes are blocked out.

Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is *rotated* through an angle,  $\alpha$ . Not all organic substances exhibit this property, but those that do are said to be **optically active**.

The angle of rotation can be measured with an instrument called a *polarimeter*, represented in **Figure 5.5**. A solution of optically active organic molecules is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the polarization plane occurs. The light then goes through a second polarizer called the *analyzer*. By rotating the analyzer until the light passes through *it*, we can find the new plane of polarization and can tell to what extent rotation has occurred.

**Figure 5.5** Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.



In addition to determining the extent of rotation, we can also find the direction. From the vantage point of the observer looking directly at the analyzer, some optically active molecules rotate polarized light to the left (counterclockwise) and are said to be **levorotatory**, whereas others rotate polarized light to the right (clockwise) and are said to be **dextrorotatory**. By convention, rotation to the left is given a minus sign ( $-$ ) and rotation to the right is given a plus sign ( $+$ ). ( $-$ )-Morphine, for example, is levorotatory, and ( $+$ )-sucrose is dextrorotatory.

The extent of rotation observed in a polarimetry experiment depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample pathlength. If the concentration of sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation doubles. It also happens that the angle of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The **specific rotation**,  $[\alpha]_D$ , of a compound is defined as the observed rotation when light of 589.6 nanometer (nm;  $1 \text{ nm} = 10^{-9} \text{ m}$ ) wavelength is used with a sample pathlength  $l$  of 1 decimeter (dm;  $1 \text{ dm} = 10 \text{ cm}$ ) and a sample concentration  $c$  of  $1 \text{ g/cm}^3$ . (Light of 589.6 nm, the so-called sodium D line, is the yellow light emitted from common sodium street lamps.)

$$[\alpha]_D \times \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

**Table 5.1** Specific Rotation of Some Organic Molecules

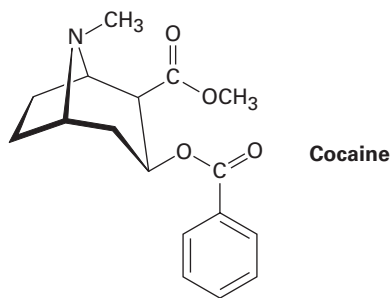
Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	+233	Cholesterol	-31.5
Sucrose	+66.47	Morphine	-132
Camphor	+44.26	Cocaine	-16
Chloroform	0	Acetic acid	0

When optical rotation data are expressed in this standard way, the specific rotation,  $[\alpha]_D$ , is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has  $[\alpha]_D = +3.82$ , and (-)-lactic acid has  $[\alpha]_D = -3.82$ . That is, the two enantiomers rotate plane-polarized light to exactly the same extent but in opposite directions. Note that the units of specific rotation are  $[(\text{deg} \cdot \text{cm}^2)/\text{g}]$  but that values are usually expressed without the units. Some additional examples are listed in Table 5.1.

### Calculating an Optical Rotation

### Worked Example 5.2

A 1.20 g sample of cocaine,  $[\alpha]_D = -16$ , was dissolved in 7.50 mL of chloroform and placed in a sample tube having a pathlength of 5.00 cm. What was the observed rotation?



#### Strategy

$$\text{Since } [\alpha]_D = \frac{\alpha}{l \times c}$$

$$\text{Then } \alpha = l \times c \times [\alpha]_D$$

$$\text{where } [\alpha]_D = -16; l = 5.00 \text{ cm} = 0.500 \text{ dm}; c = 1.20 \text{ g}/7.50 \text{ cm}^3 = 0.160 \text{ g/cm}^3$$

#### Solution

$$\alpha = (-16)(0.500)(0.160) = -1.3^\circ$$

#### Problem 5.5

Is cocaine (Worked Example 5.2) dextrorotatory or levorotatory?

#### Problem 5.6

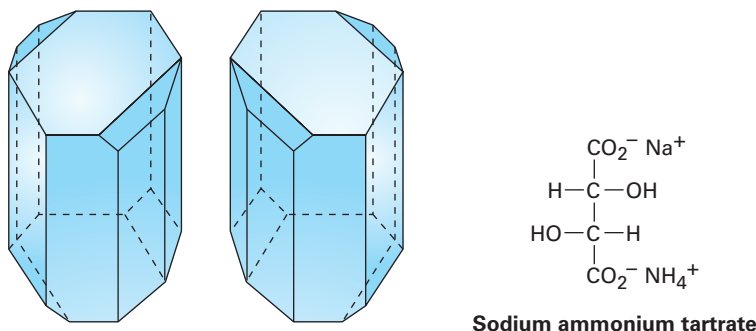
A 1.50 g sample of coniine, the toxic extract of poison hemlock, was dissolved in 10.0 mL of ethanol and placed in a sample cell with a 5.00 cm pathlength. The observed rotation at the sodium D line was  $+1.21^\circ$ . Calculate  $[\alpha]_D$  for coniine.

## 5.4 Pasteur's Discovery of Enantiomers

Little was done after Biot's discovery of optical activity until 1848, when Louis Pasteur began work on a study of crystalline tartaric acid salts derived from wine. On crystallizing a concentrated solution of sodium ammonium tartrate below 28 °C, Pasteur made the surprising observation that two distinct kinds of crystals precipitated. Furthermore, the two kinds of crystals were nonsuperimposable mirror images and were related in the same way that a right hand is related to a left hand.

Working carefully with tweezers, Pasteur was able to separate the crystals into two piles, one of "right-handed" crystals and one of "left-handed" crystals, like those shown in **Figure 5.6**. Although the original sample, a 50:50 mixture of right and left, was optically inactive, solutions of the crystals from each of the sorted piles were optically active and their specific rotations were equal in amount but opposite in sign.

**Figure 5.6** Drawings of sodium ammonium tartrate crystals taken from Pasteur's original sketches. One of the crystals is dextrorotatory in solution, and the other is levorotatory.



Pasteur was far ahead of his time. Although the structural theory of Kekulé had not yet been proposed, Pasteur explained his results by speaking of the molecules themselves, saying, "There is no doubt that [in the *dextro* tartaric acid] there exists an asymmetric arrangement having a nonsuperimposable image. It is no less certain that the atoms of the *levo* acid have precisely the inverse asymmetric arrangement." Pasteur's vision was extraordinary, for it was not until 25 years later that his ideas regarding the asymmetric carbon atom were confirmed.

Today, we would describe Pasteur's work by saying that he had discovered enantiomers. Enantiomers, also called *optical isomers*, have identical physical properties, such as melting point and boiling point, but differ in the direction in which their solutions rotate plane-polarized light.

## 5.5 Sequence Rules for Specifying Configuration

### Key IDEAS

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

Structural drawings provide a visual representation of stereochemistry, but a written method for indicating the three-dimensional arrangement, or **configuration**, of substituents at a chirality center is also needed. The method used employs a set of *sequence rules* to rank the four groups attached to the chirality center and then looks at the handedness with which those groups are attached.

Called the **Cahn–Ingold–Prelog rules** after the chemists who proposed them, the sequence rules are as follows:

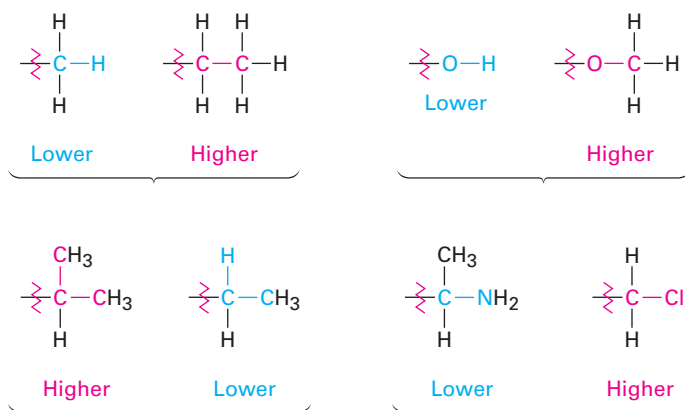
**RULE 1**

**Look at the four atoms directly attached to the chirality center, and rank them according to atomic number.** The atom with the highest atomic number has the highest ranking (first), and the atom with the lowest atomic number (usually hydrogen) has the lowest ranking (fourth). When different isotopes of the same element are compared, such as deuterium ( $^2\text{H}$ ) and protium ( $^1\text{H}$ ), the heavier isotope ranks higher than the lighter isotope. Thus, atoms commonly found in organic compounds have the following order.

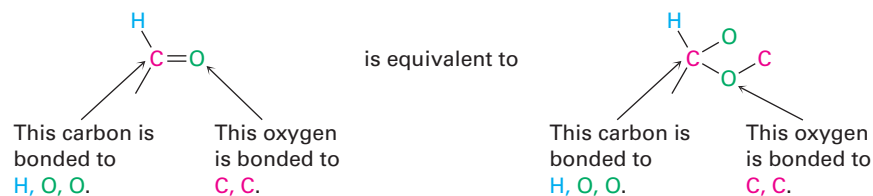
**Atomic number** 35 17 16 15 8 7 6 (2) (1)  
**Higher ranking** Br > Cl > S > P > O > N > C >  $^2\text{H}$  >  $^1\text{H}$  **Lower ranking**

**RULE 2**

**If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found.** A  $-\text{CH}_2\text{CH}_3$  substituent and a  $-\text{CH}_3$  substituent are equivalent by rule 1 because both have carbon as the first atom. By rule 2, however, ethyl ranks higher than methyl because ethyl has a *carbon* as its highest second atom, while methyl has only *hydrogen* as its second atom. Look at the following pairs of examples to see how the rule works:

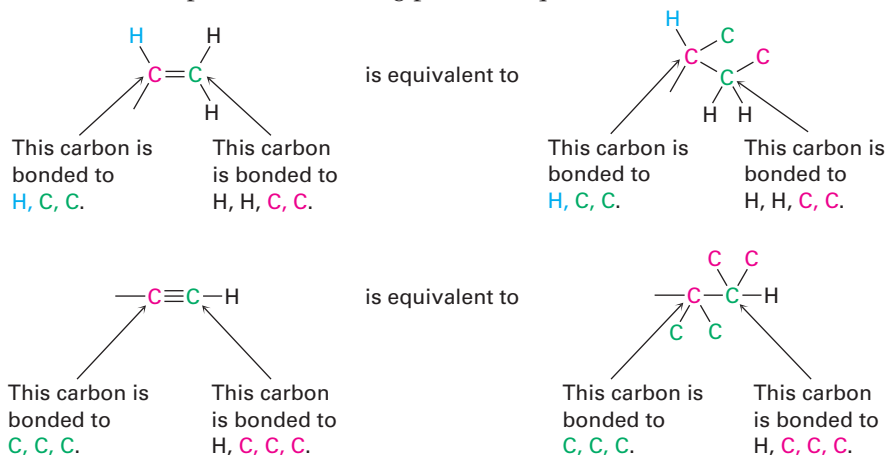
**RULE 3**

**Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.** For example, an aldehyde substituent ( $-\text{CH}=\text{O}$ ), which has a carbon atom *doubly* bonded to *one* oxygen, is equivalent to a substituent having a carbon atom *singly* bonded to *two* oxygens:

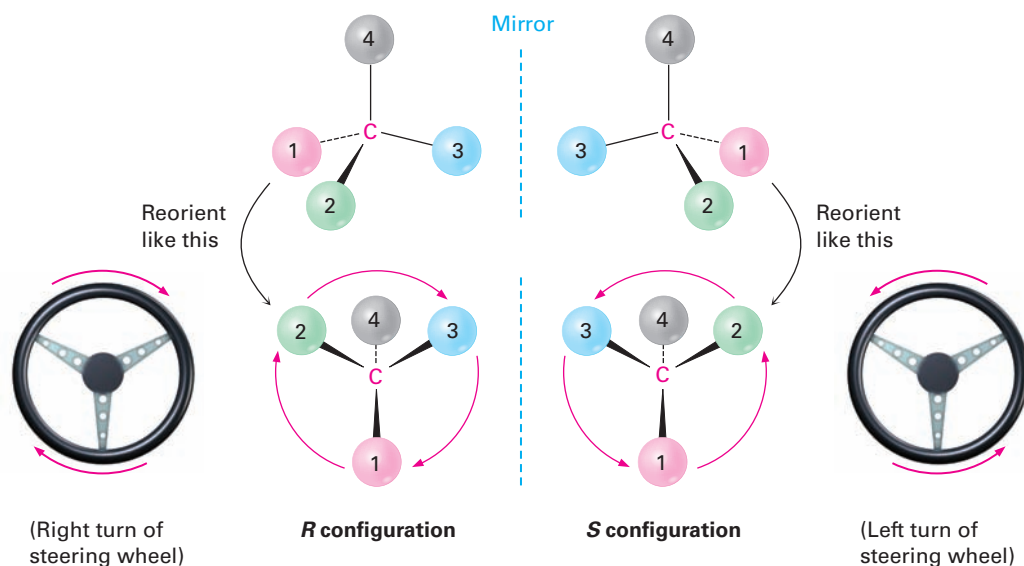




As further examples, the following pairs are equivalent:

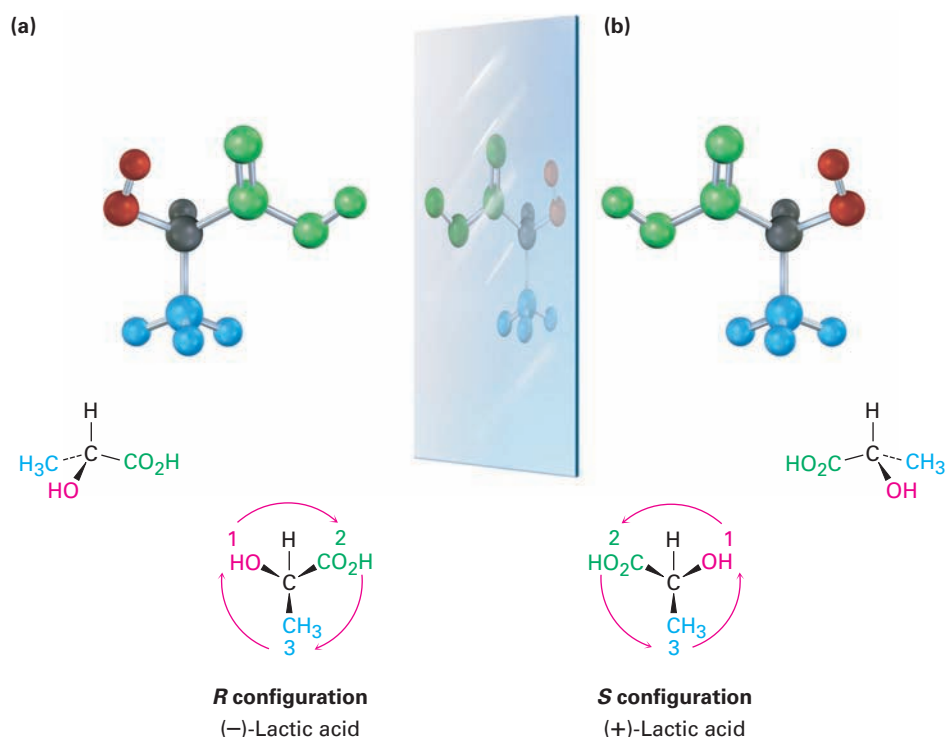


Having ranked the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) points directly back, away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel (**Figure 5.7**). If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent ( $1 \rightarrow 2 \rightarrow 3$ ) is clockwise, we say that the chirality center has the **R configuration** (Latin *rectus*, meaning “right”). If an arrow from  $1 \rightarrow 2 \rightarrow 3$  is counterclockwise, the chirality center has the **S configuration** (Latin *sinister*, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a Right (clockwise) turn.



**Figure 5.7** Assigning configuration to a chirality center. When the molecule is oriented so that the lowest-ranked group (4) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel  $1 \rightarrow 2 \rightarrow 3$  is clockwise (right turn), the center has the R configuration. If the direction of travel  $1 \rightarrow 2 \rightarrow 3$  is counterclockwise (left turn), the center is S.

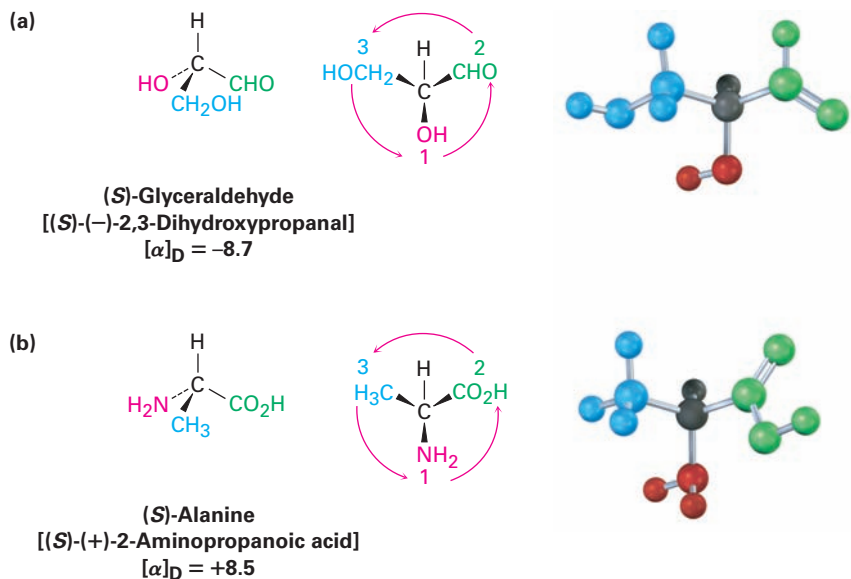
Look at (–)-lactic acid in **Figure 5.8** for an example of how to assign configuration. Sequence rule 1 says that –OH is ranked 1 and –H is ranked 4, but it doesn't allow us to distinguish between –CH<sub>3</sub> and –CO<sub>2</sub>H because both groups have carbon as their first atom. Sequence rule 2, however, says that –CO<sub>2</sub>H ranks higher than –CH<sub>3</sub> because O (the highest second atom in –CO<sub>2</sub>H) outranks H (the highest second atom in –CH<sub>3</sub>). Now, turn the molecule so that the fourth-ranked group (–H) is oriented toward the rear, away from the observer. Since a curved arrow from 1 (–OH) to 2 (–CO<sub>2</sub>H) to 3 (–CH<sub>3</sub>) is clockwise (right turn of the steering wheel), (–)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.



**Figure 5.8** Assigning configuration to **(a)** *R*-(–)-lactic acid and **(b)** *S*-(+)-lactic acid.

Further examples are provided by naturally occurring (–)-glyceraldehyde and (+)-alanine, which both have the *S* configuration as shown in **Figure 5.9**. Note that the sign of optical rotation, (+) or (–), is not related to the *R,S* designation. (*S*)-Glyceraldehyde happens to be levorotatory (–), and (*S*)-alanine happens to be dextrorotatory (+). There is no simple correlation between *R,S* configuration and direction or magnitude of optical rotation.

**Figure 5.9** Assigning configuration to (a) (–)-glyceraldehyde. (b) (+)-alanine. Both happen to have the *S* configuration, although one is levorotatory and the other is dextrorotatory.

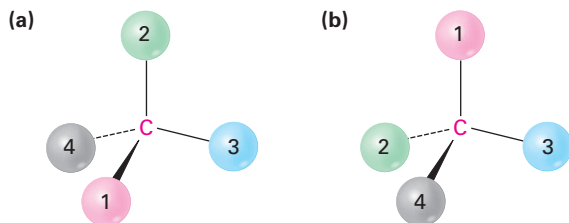


One additional point needs to be mentioned—the matter of **absolute configuration**. How do we know that the assignments of *R* and *S* configuration are correct in an *absolute*, rather than a relative, sense? Since we can't see the molecules themselves, how do we know that the *R* configuration belongs to the levorotatory enantiomer of lactic acid? This difficult question was finally solved in 1951, when an X-ray diffraction method for determining the absolute spatial arrangement of atoms in a molecule was found. Based on those results, we can say with certainty that the *R,S* conventions are correct.

### Worked Example 5.3

#### Assigning Configuration to Chirality Centers

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

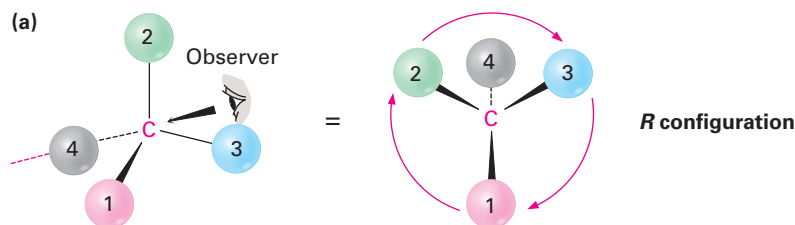


#### Strategy

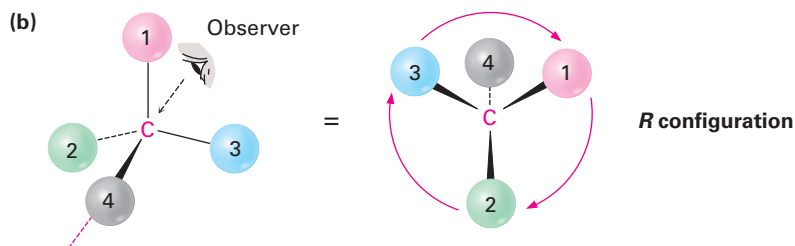
It takes practice to be able to visualize and orient a chirality center in three dimensions. You might start by indicating where the observer must be located—180° opposite the lowest-ranked group. Then imagine yourself in the position of the observer, and redraw what you would see.

#### Solution

In (a), you would be located in front of the page toward the top right of the molecule, and you would see group 2 to your left, group 3 to your right, and group 1 below you. This corresponds to an *R* configuration.



In (b), you would be located behind the page toward the top left of the molecule from your point of view, and you would see group 3 to your left, group 1 to your right, and group 2 below you. This also corresponds to an *R* configuration.



## Drawing the Three-Dimensional Structure of a Specific Enantiomer

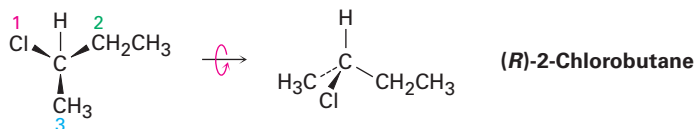
### Worked Example 5.4

Draw a tetrahedral representation of (*R*)-2-chlorobutane.

#### Strategy

Begin by ranking the four substituents bonded to the chirality center: (1)  $-\text{Cl}$ , (2)  $-\text{CH}_2\text{CH}_3$ , (3)  $-\text{CH}_3$ , (4)  $-\text{H}$ . To draw a tetrahedral representation of the molecule, orient the lowest-ranked group ( $-\text{H}$ ) away from you and imagine that the other three groups are coming out of the page toward you. Then place the remaining three substituents such that the direction of travel  $1 \rightarrow 2 \rightarrow 3$  is clockwise (right turn), and tilt the molecule toward you to bring the rear hydrogen into view. Using molecular models is a great help in working problems of this sort.

#### Solution



#### Problem 5.7

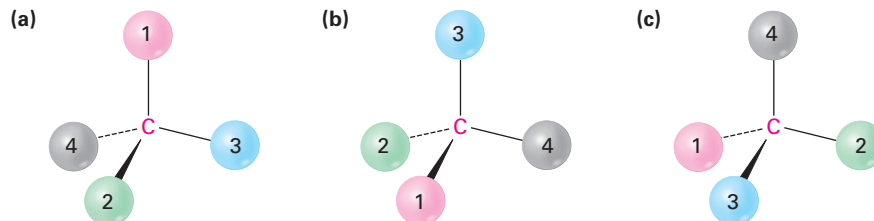
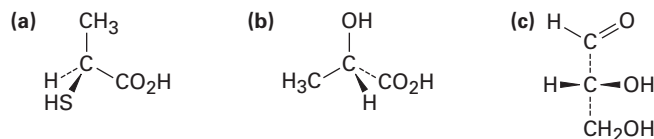
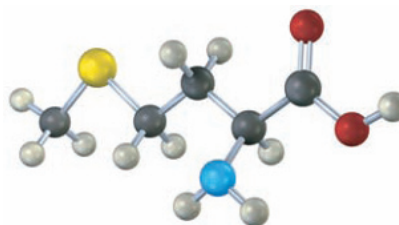
Which member in each of the following sets ranks higher?

- $-\text{H}$  or  $-\text{Br}$
- $-\text{Cl}$  or  $-\text{Br}$
- $-\text{CH}_3$  or  $-\text{CH}_2\text{CH}_3$
- $-\text{NH}_2$  or  $-\text{OH}$
- $-\text{CH}_2\text{OH}$  or  $-\text{CH}_3$
- $-\text{CH}_2\text{OH}$  or  $-\text{CH}=\text{O}$

**Problem 5.8**

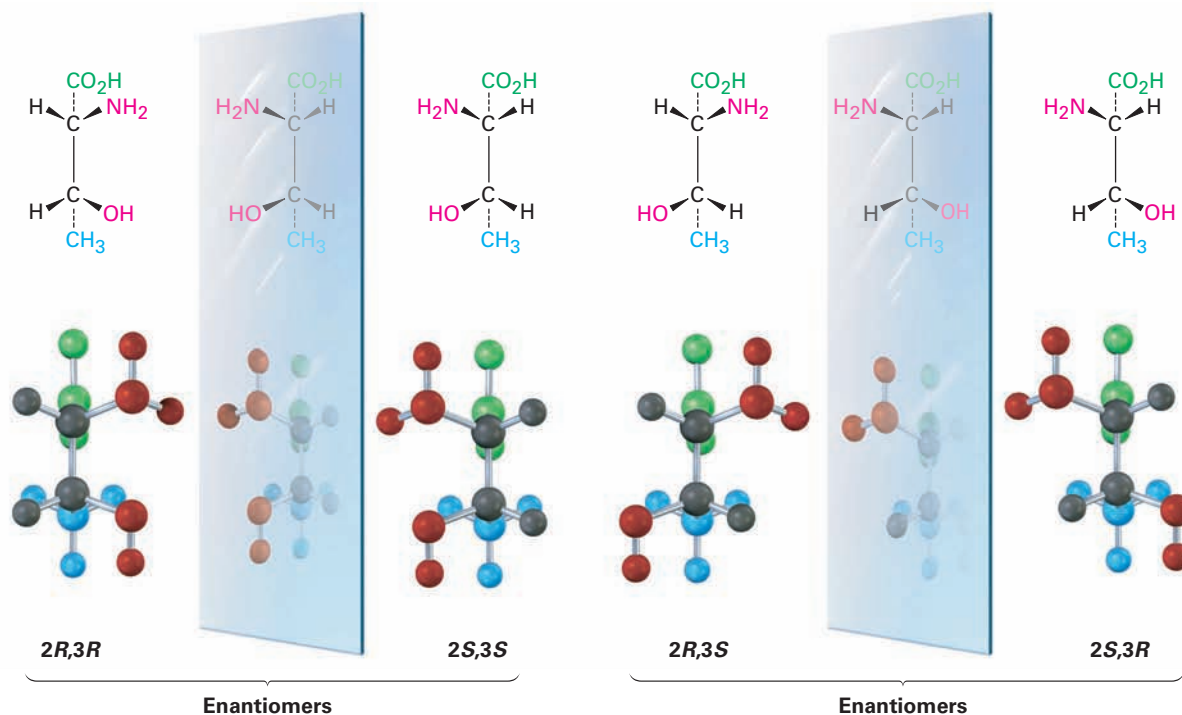
Rank the following sets of substituents:

- (a)  $-\text{H}$ ,  $-\text{OH}$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$   
 (b)  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{OH}$   
 (c)  $-\text{CN}$ ,  $-\text{CH}_2\text{NH}_2$ ,  $-\text{CH}_2\text{NHCH}_3$ ,  $-\text{NH}_2$   
 (d)  $-\text{SH}$ ,  $-\text{CH}_2\text{SCH}_3$ ,  $-\text{CH}_3$ ,  $-\text{SSCH}_3$

**Problem 5.9**Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:**Problem 5.10**Assign *R* or *S* configuration to the chirality center in each of the following molecules:**Problem 5.11**Draw a tetrahedral representation of (*S*)-2-pentanol (2-hydroxypentane).**Problem 5.12**Assign *R* or *S* configuration to the chirality center in the following molecular model of the amino acid methionine (blue = N, yellow = S):

## 5.6 Diastereomers

Molecules like lactic acid, alanine, and glyceraldehyde are relatively simple because each has only one chirality center and only two stereoisomers. The situation becomes more complex, however, with molecules that have more than one chirality center. As a general rule, a molecule with  $n$  chirality centers can have up to  $2^n$  stereoisomers (although it may have fewer, as we'll see below). Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for example. Since threonine has two chirality centers (C2 and C3), there are four possible stereoisomers, as shown in **Figure 5.10**. Check for yourself that the *R,S* configurations are correct.



**Figure 5.10** The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The  $2R,3R$  stereoisomer is the mirror image of  $2S,3S$ , and the  $2R,3S$  stereoisomer is the mirror image of  $2S,3R$ . But what is the relationship between any two molecules that are not mirror images? What, for instance, is the relationship between the  $2R,3R$  isomer and the  $2R,3S$  isomer? They are stereoisomers, yet they aren't enantiomers. To describe such a relationship, we need a new term—*diastereomer*.

**Diastereomers** are stereoisomers that are not mirror images. Since we used the right-hand/left-hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and your friend's hand look *similar*, but they aren't identical and they aren't mirror images. The same is true of diastereomers: they're similar, but they aren't identical and they aren't mirror images.

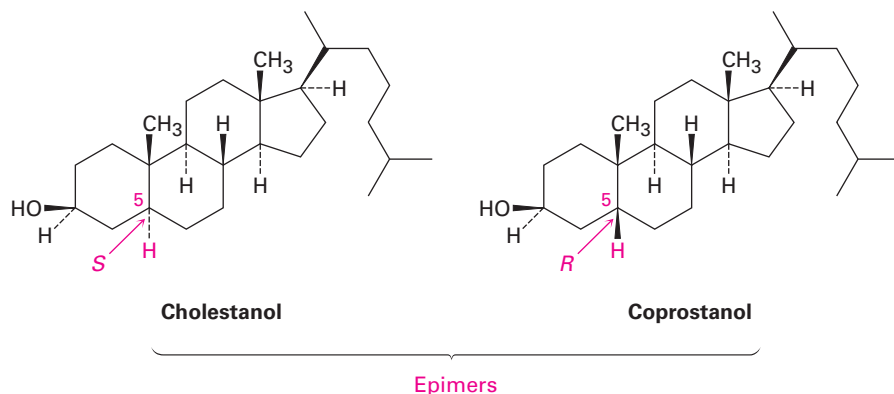
Note carefully the difference between enantiomers and diastereomers: enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. A full description of the four stereoisomers of threonine is given in Table 5.2. Of the four, only the  $2S,3R$  isomer,  $[\alpha]_D = -28.3$ , occurs naturally in plants and animals and is an essential human nutrient. This result is typical: most biological molecules are chiral, and usually only one stereoisomer is found in nature.

In the special case where two diastereomers differ at only one chirality center but are the same at all others, we say that the compounds are **epimers**.

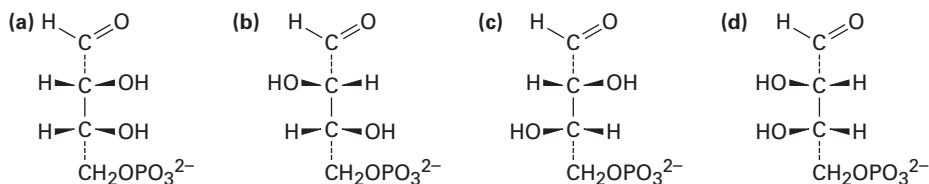
**Table 5.2** Relationships among the Four Stereoisomers of Threonine

Stereoisomer	Enantiomer	Diastereomer
2 <i>R</i> ,3 <i>R</i>	2 <i>S</i> ,3 <i>S</i>	2 <i>R</i> ,3 <i>S</i> and 2 <i>S</i> ,3 <i>R</i>
2 <i>S</i> ,3 <i>S</i>	2 <i>R</i> ,3 <i>R</i>	2 <i>R</i> ,3 <i>S</i> and 2 <i>S</i> ,3 <i>R</i>
2 <i>R</i> ,3 <i>S</i>	2 <i>S</i> ,3 <i>R</i>	2 <i>R</i> ,3 <i>R</i> and 2 <i>S</i> ,3 <i>S</i>
2 <i>S</i> ,3 <i>R</i>	2 <i>R</i> ,3 <i>S</i>	2 <i>R</i> ,3 <i>R</i> and 2 <i>S</i> ,3 <i>S</i>

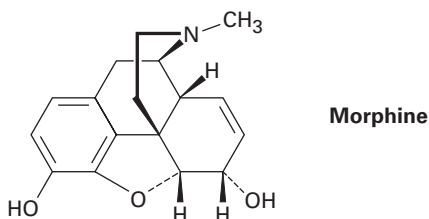
Cholestanol and coprostanol, for instance, are both found in human feces, and both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric* at C5.

**Problem 5.13**

One of the following molecules (a)–(d) is D-erythrose 4-phosphate, an intermediate in the Calvin photosynthetic cycle by which plants incorporate CO<sub>2</sub> into carbohydrates. If D-erythrose 4-phosphate has *R* stereochemistry at both chirality centers, which of the structures is it? Which of the remaining three structures is the enantiomer of D-erythrose 4-phosphate, and which are diastereomers?

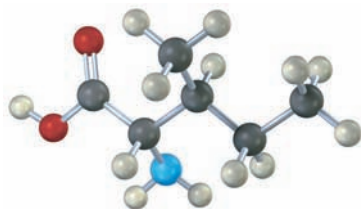
**Problem 5.14**

How many chirality centers does morphine have? How many stereoisomers of morphine are possible in principle?



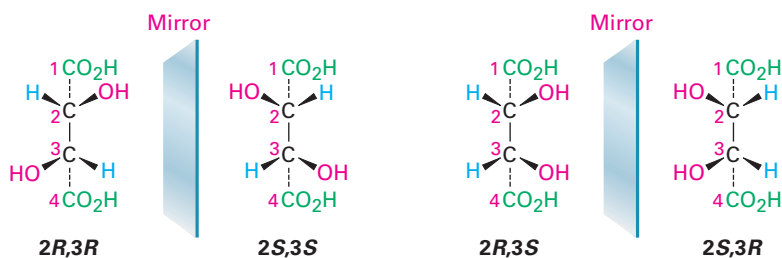
**Problem 5.15**

Assign *R,S* configuration to each chirality center in the following molecular model of the amino acid isoleucine (blue = N):

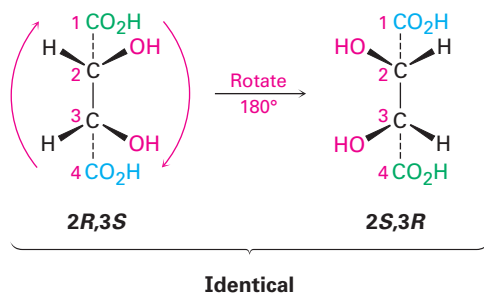


## 5.7 Meso Compounds

Let's look at another example of a compound with more than one chirality center: the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The *2R,3R* and *2S,3S* structures are nonsuperimposable mirror images and therefore represent a pair of enantiomers. A close look at the *2R,3S* and *2S,3R* structures, however, shows that they *are* superimposable, and thus identical, as can be seen by rotating one structure  $180^\circ$ .

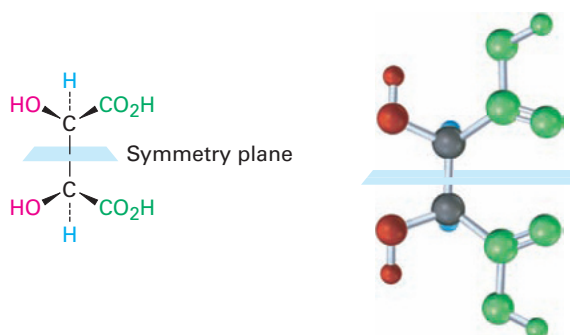


The *2R,3S* and *2S,3R* structures are identical because the molecule has a plane of symmetry and is therefore achiral. The symmetry plane cuts through the C2–C3 bond, making one half of the molecule a mirror image of the other half (**Figure 5.11**). Because of the plane of symmetry, the molecule is achiral, despite the fact that it has two chirality centers. Compounds that are achiral, yet contain chirality centers, are called **meso compounds (me-zo)**. Thus,



tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

**Figure 5.11** A symmetry plane through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral.



Some physical properties of the three stereoisomers are listed in Table 5.3. The (+)- and (–)-tartaric acids have identical melting points, solubilities, and densities, but they differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (–) forms. It has no mirror-image relationship to (+)- and (–)-tartaric acids, is a different compound altogether, and has different physical properties.

**Table 5.3** Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm <sup>3</sup> )	Solubility at 20 °C (g/100 mL H <sub>2</sub> O)
(+)	168–170	+12	1.7598	139.0
(–)	168–170	–12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

## Worked Example 5.5

### Distinguishing Chiral Compounds from Meso Compounds

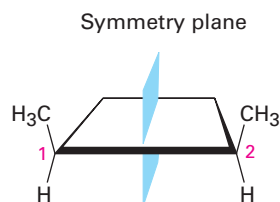
Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

#### Strategy

To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for the presence or absence of a symmetry plane. Not all molecules with chirality centers are chiral overall—meso compounds are an exception.

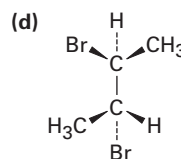
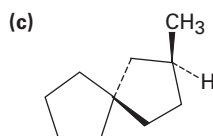
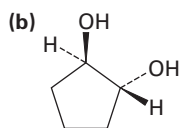
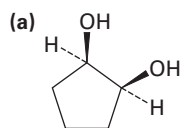
#### Solution

A look at the structure of *cis*-1,2-dimethylcyclobutane shows that both methyl-bearing ring carbons (C1 and C2) are chirality centers. Overall, though, the compound is achiral because there is a symmetry plane bisecting the ring between C1 and C2. Thus, the molecule is a meso compound.



**Problem 5.16**

Which of the following structures represent meso compounds?

**Problem 5.17**

Which of the following have a meso form? (Recall that the *-ol* suffix refers to an alcohol, ROH.)

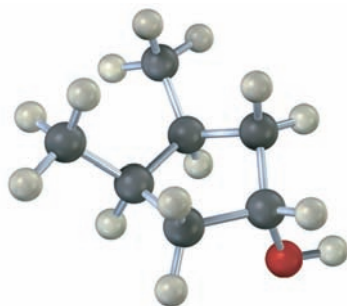
(a) 2,3-Butanediol

(b) 2,3-Pentanediol

(c) 2,4-Pentanediol

**Problem 5.18**

Does the following structure represent a meso compound? If so, indicate the symmetry plane.

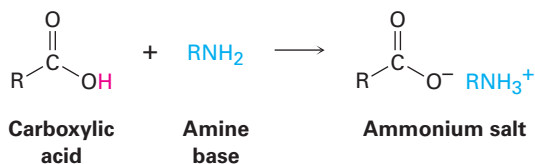


## 5.8 Racemic Mixtures and the Resolution of Enantiomers

To end this discussion of stereoisomerism, let's return for a last look at Pasteur's pioneering work, described in **Section 5.4**. Pasteur took an optically inactive tartaric acid salt and found that he could crystallize from it two optically active forms having what we would now call the *2R,3R* and *2S,3S* configurations. But what was the optically inactive form he started with? It couldn't have been *meso*-tartaric acid, because *meso*-tartaric acid is a different chemical compound and can't interconvert with the two chiral enantiomers without breaking and re-forming chemical bonds.

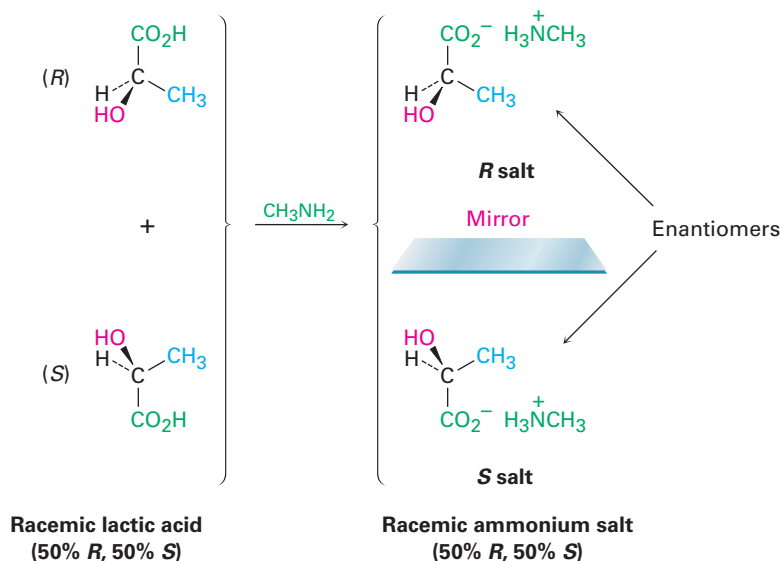
The answer is that Pasteur started with a 50:50 *mixture* of the two chiral tartaric acid enantiomers. Such a mixture is called a **racemate** (*raa*-suh-mate), or *racemic mixture*, and is denoted by either the symbol ( $\pm$ ) or the prefix *d,l* to indicate an equal mixture of dextrorotatory and levorotatory forms. Racemates show no optical rotation because the (+) rotation from one enantiomer exactly cancels the (–) rotation from the other. Through luck, Pasteur was able to separate, or **resolve**, racemic tartaric acid into its (+) and (–) enantiomers. Unfortunately, the fractional crystallization technique he used doesn't work for most racemates, so other methods are needed.

The most common method of resolution uses an acid–base reaction between the racemate of a chiral carboxylic acid ( $\text{RCO}_2\text{H}$ ) and an amine base ( $\text{RNH}_2$ ) to yield an ammonium salt:



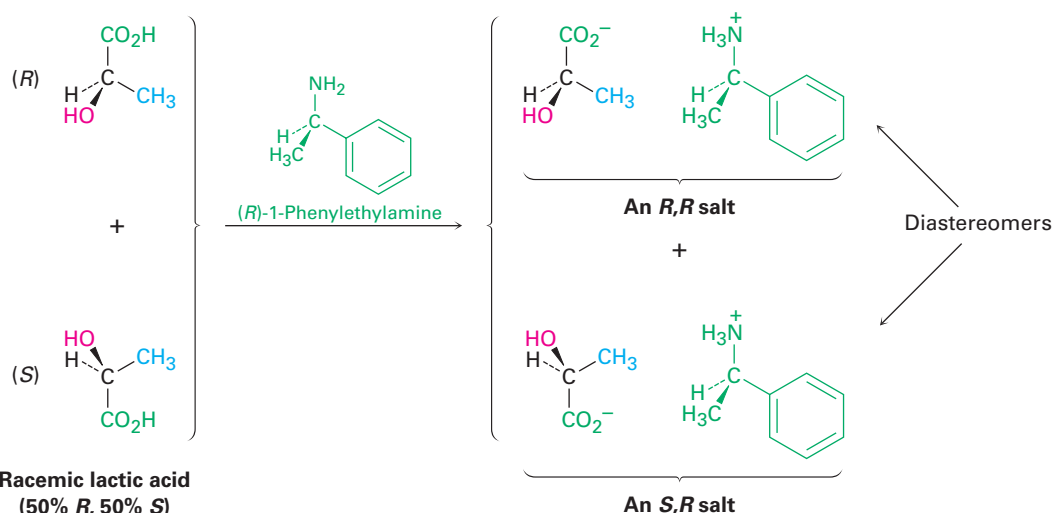
To understand how this method of resolution works, let's see what happens when a racemic mixture of chiral acids, such as (+)- and (–)-lactic acids, reacts with an achiral amine base, such as methylamine,  $\text{CH}_3\text{NH}_2$ . Stereochemically, the situation is analogous to what happens when left and right hands (chiral) pick up a ball (achiral). Both left and right hands pick up the ball equally well, and the products—ball in right hand versus ball in left hand—are mirror images. In the same way, both (+)- and (–)-lactic acid react with methylamine equally well, and the product is a racemic mixture of the two enantiomers methylammonium (+)-lactate and methylammonium (–)-lactate (**Figure 5.12**).

**Figure 5.12** Reaction of racemic lactic acid with achiral methylamine leads to a racemic mixture of ammonium salts.



Now let's see what happens when the racemic mixture of (+)- and (–)-lactic acids reacts with a single enantiomer of a chiral amine base, such as (*R*)-1-phenylethylamine. Stereochemically, the situation is analogous to what happens when left and right hands (chiral) put on a right-handed glove (*also chiral*). Left and right hands don't put on the right-handed glove in the same way, so the products—right hand in right glove versus left hand in right glove—are not mirror images; they're similar but different.

In the same way, (+)- and (–)-lactic acids react with (*R*)-1-phenylethylamine to give two different products (**Figure 5.13**). (*R*)-Lactic acid reacts with (*R*)-1-phenylethylamine to give the *R,R* salt, and (*S*)-lactic acid reacts with the *R* amine to give the *S,R* salt. *The two salts are diastereomers*. They have different chemical and physical properties, and it may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with a strong acid then allows us to isolate the two pure enantiomers of lactic acid and to recover the chiral amine for reuse.

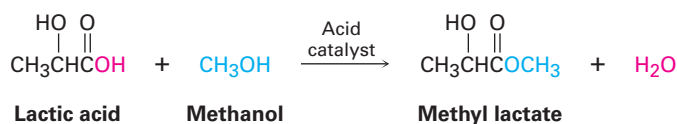


**Figure 5.13** Reaction of racemic lactic acid with (*R*)-1-phenylethylamine yields a mixture of diastereomeric ammonium salts, which have different properties and can be separated.

## Predicting the Chirality of a Reaction Product

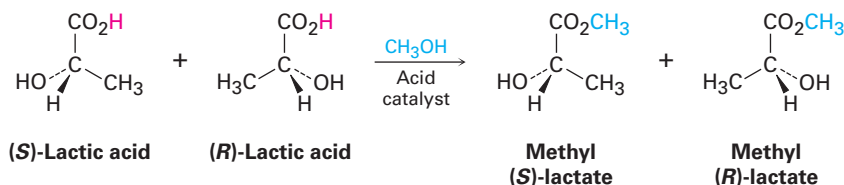
## Worked Example 5.6

We'll see in **Section 21.3** that carboxylic acids ( $\text{RCO}_2\text{H}$ ) react with alcohols ( $\text{R}'\text{OH}$ ) to form esters ( $\text{RCO}_2\text{R}'$ ). Suppose that ( $\pm$ )-lactic acid reacts with  $\text{CH}_3\text{OH}$  to form the ester, methyl lactate. What stereochemistry would you expect the product(s) to have? What is the relationship of the products?



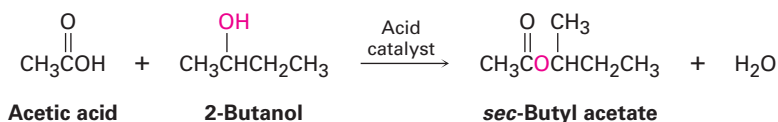
### Solution

Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products.



### Problem 5.19

Suppose that acetic acid ( $\text{CH}_3\text{CO}_2\text{H}$ ) reacts with (*S*)-2-butanol to form an ester (see Worked Example 5.6). What stereochemistry would you expect the product(s) to have? What is the relationship of the products?

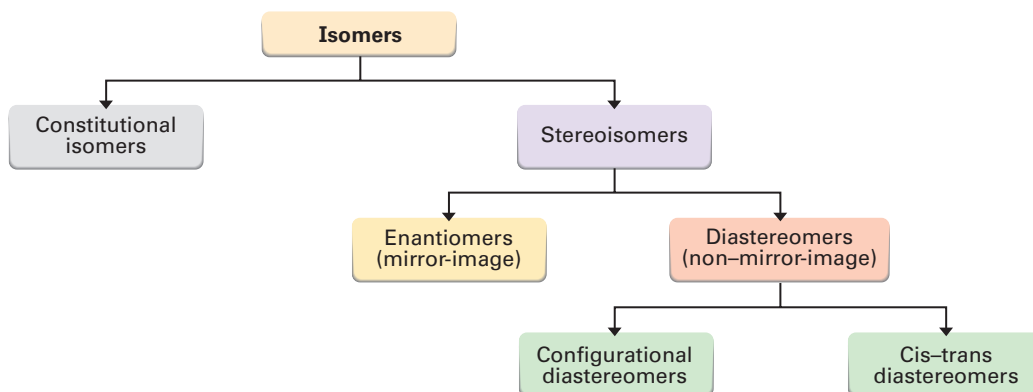


**Problem 5.20**

What stereoisomers would result from reaction of ( $\pm$ )-lactic acid with (*S*)-1-phenylethylamine, and what is the relationship between them?

## 5.9 A Review of Isomerism

As noted on several previous occasions, isomers are compounds with the same chemical formula but different structures. We've seen several kinds of isomers in the past few chapters, and it's a good idea at this point to see how they relate to one another (**Figure 5.14**).

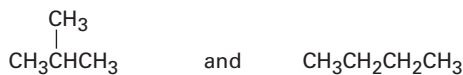


**Figure 5.14** A summary of the different kinds of isomers.

There are two fundamental types of isomers, both of which we've now encountered: constitutional isomers and stereoisomers.

**Constitutional isomers** (**Section 3.2**) are compounds whose atoms are connected differently. Among the kinds of constitutional isomers we've seen are skeletal, functional, and positional isomers.

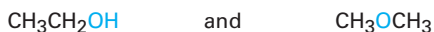
**Different carbon skeletons**



**2-Methylpropane**

**Butane**

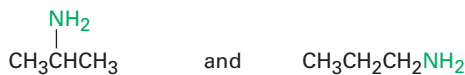
**Different functional groups**



**Ethyl alcohol**

**Dimethyl ether**

**Different position of functional groups**

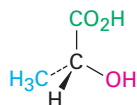


**Isopropylamine**

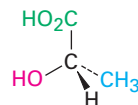
**Propylamine**

**Stereoisomers (Section 4.2)** are compounds whose atoms are connected in the same order but with a different spatial arrangement. Among the kinds of stereoisomers we've seen are enantiomers, diastereomers, and cis–trans isomers of cycloalkanes. Actually, cis–trans isomers are just a subclass of diastereomers because they are non–mirror-image stereoisomers:

**Enantiomers**  
(nonsuperimposable mirror-image stereoisomers)

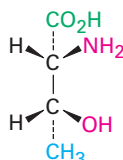


**(R)-Lactic acid**

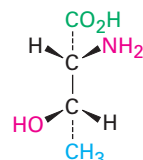


**(S)-Lactic acid**

**Diastereomers**  
(nonsuperimposable non–mirror-image stereoisomers)



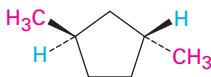
**2R,3R-2-Amino-3-hydroxybutanoic acid**



**2R,3S-2-Amino-3-hydroxybutanoic acid**

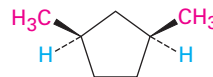
**Configurational diastereomers**

**Cis–trans diastereomers**  
(substituents on same side or opposite side of double bond or ring)



**trans-1,3-Dimethylcyclopentane**

and



**cis-1,3-Dimethylcyclopentane**

### Problem 5.21

What kinds of isomers are the following pairs?

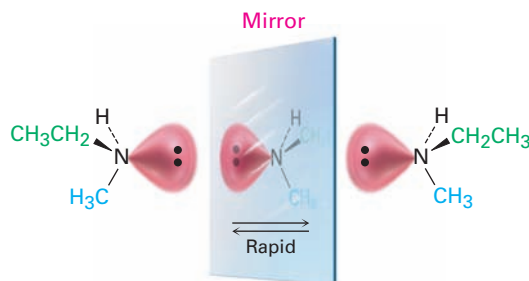
- (a) (S)-5-Chloro-2-hexene and chlorocyclohexane  
(b) (2R,3R)-Dibromopentane and (2S,3R)-dibromopentane

## 5.10 Chirality at Nitrogen, Phosphorus, and Sulfur

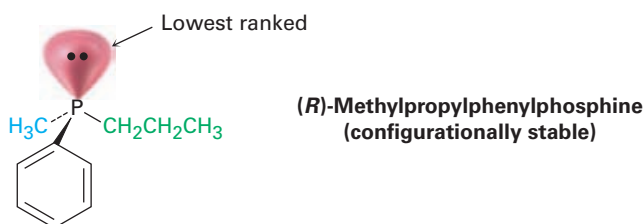
Although the most common cause of chirality is the presence of four different substituents bonded to a tetrahedral atom, that atom doesn't necessarily have to be carbon. Nitrogen, phosphorus, and sulfur are all commonly encountered in organic molecules, and all can be chirality centers. We know, for instance, that trivalent nitrogen is tetrahedral, with its lone pair of electrons acting as the fourth "substituent" (Section 1.10). Is trivalent nitrogen chiral? Does a compound such as ethylmethylamine exist as a pair of enantiomers?

The answer is both yes and no. Yes in principle, but no in practice. Most trivalent nitrogen compounds undergo a rapid umbrella-like inversion that

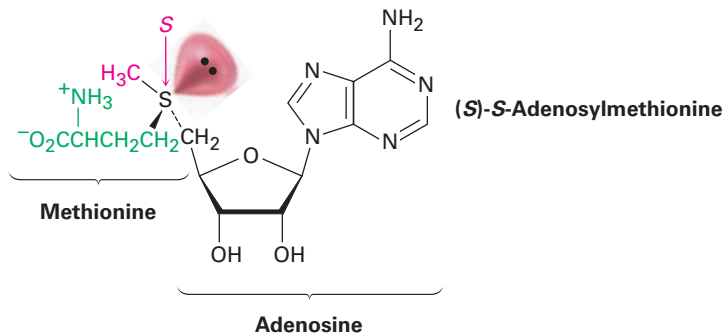
interconverts enantiomers, so we can't isolate individual enantiomers except in special cases.



A similar situation occurs in trivalent phosphorus compounds, or *phosphines*. It turns out, though, that inversion at phosphorus is substantially slower than inversion at nitrogen, so stable chiral phosphines *can* be isolated. (*R*)- and (*S*)-methylpropylphenylphosphine, for example, are configurationally stable for several hours at 100 °C. We'll see the importance of phosphine chirality in **Section 26.7** in connection with the synthesis of chiral amino acids.

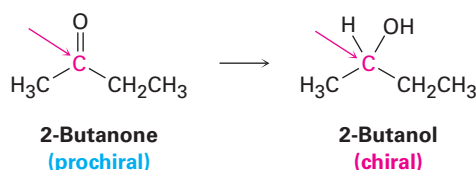


Divalent sulfur compounds are achiral, but trivalent sulfur compounds called *sulfonium salts* ( $R_3S^+$ ) can be chiral. Like phosphines, sulfonium salts undergo relatively slow inversion, so chiral sulfonium salts are configurationally stable and can be isolated. Perhaps the best known example is the coenzyme *S*-adenosylmethionine, the so-called biological methyl donor, which is involved in many metabolic pathways as a source of  $CH_3$  groups. (The "*S*" in the name *S*-adenosylmethionine stands for *sulfur* and means that the adenosyl group is attached to the sulfur atom of the amino acid methionine.) The molecule has *S* stereochemistry at sulfur and is configurationally stable for several days at room temperature. Its *R* enantiomer is also known but is not biologically active.

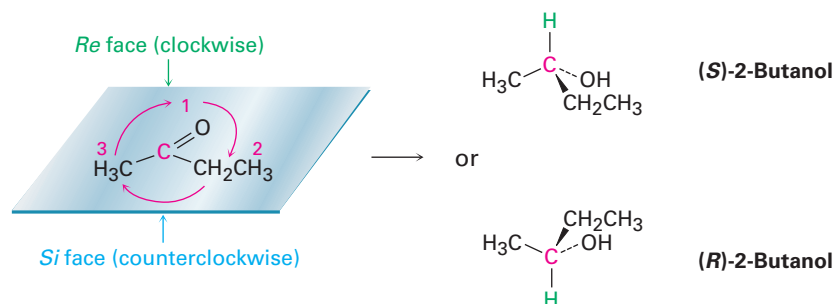


## 5.11 Prochirality

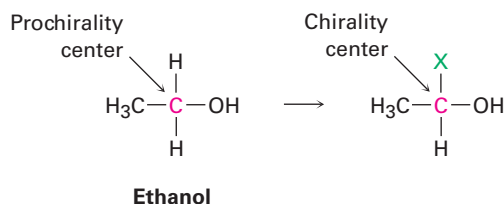
Closely related to the concept of chirality, and particularly important in biological chemistry, is the notion of *prochirality*. A molecule is said to be **prochiral** if it can be converted from achiral to chiral in a single chemical step. For instance, an unsymmetrical ketone like 2-butanone is prochiral because it can be converted to the chiral alcohol 2-butanol by addition of hydrogen, as we'll see in **Section 17.4**.



Which enantiomer of 2-butanol is produced depends on which face of the planar carbonyl group undergoes reaction. To distinguish between the possibilities, we use the stereochemical descriptors *Re* and *Si*. Rank the three groups attached to the trigonal, *sp*<sup>2</sup>-hybridized carbon, and imagine curved arrows from the highest to second-highest to third-highest ranked substituents. The face on which the arrows curve clockwise is designated *Re* (similar to *R*), and the face on which the arrows curve counterclockwise is designated *Si* (similar to *S*). In this particular example, addition of hydrogen from the *Re* faces gives (*S*)-butan-2-ol, and addition from the *Si* face gives (*R*)-butan-2-ol.

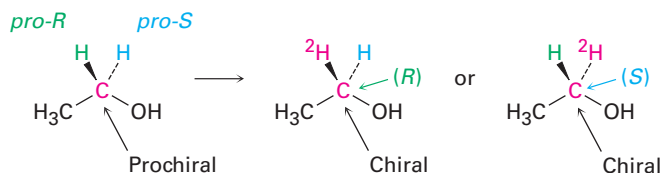


In addition to compounds with planar, *sp*<sup>2</sup>-hybridized atoms, compounds with tetrahedral, *sp*<sup>3</sup>-hybridized atoms can also be prochiral. An *sp*<sup>3</sup>-hybridized atom is said to be a **prochirality center** if, by changing one of its attached groups, it becomes a chirality center. The –CH<sub>2</sub>OH carbon atom of ethanol, for instance, is a prochirality center because changing one of its attached –H atoms converts it into a chirality center.

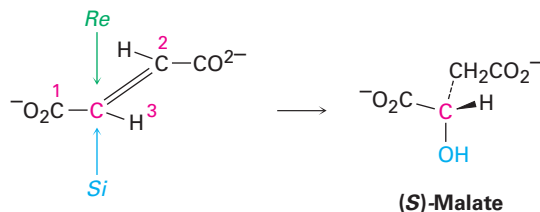




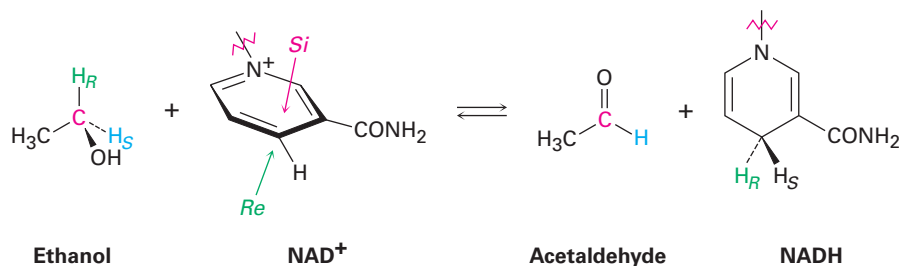
To distinguish between the two identical atoms (or groups of atoms) on a prochirality center, we imagine a change that will raise the ranking of one atom over the other without affecting its rank with respect to other attached groups. On the  $-\text{CH}_2\text{OH}$  carbon of ethanol, for instance, we might imagine replacing one of the  $^1\text{H}$  atoms (protium) by  $^2\text{H}$  (deuterium). The newly introduced  $^2\text{H}$  atom ranks higher than the remaining  $^1\text{H}$  atom, but it remains lower than other groups attached to the carbon. Of the two identical atoms in the original compound, that atom whose replacement leads to an *R* chirality center is said to be *pro-R* and that atom whose replacement leads to an *S* chirality center is said to be *pro-S*.



A large number of biological reactions involve prochiral compounds. One of the steps in the citric acid cycle by which food is metabolized, for instance, is the addition of  $\text{H}_2\text{O}$  to fumarate to give malate. Addition of  $-\text{OH}$  occurs on the *Si* face of a fumarate carbon and gives (*S*)-malate as product.

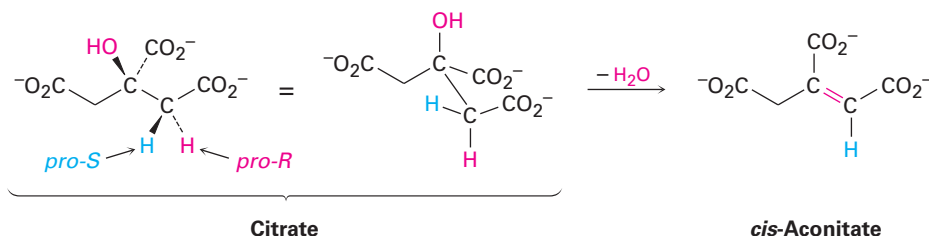


As another example, studies with deuterium-labeled substrates have shown that the reaction of ethanol with the coenzyme nicotinamide adenine dinucleotide ( $\text{NAD}^+$ ) catalyzed by yeast alcohol dehydrogenase occurs with exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of  $\text{NAD}^+$ .



Determining the stereochemistry of reactions at prochirality centers is a powerful method for studying detailed mechanisms in biochemical reactions.

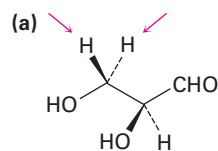
As just one example, the conversion of citrate to (*cis*)-aconitate in the citric acid cycle has been shown to occur with loss of a *pro-R* hydrogen, implying that the OH and H groups leave from opposite sides of the molecule.



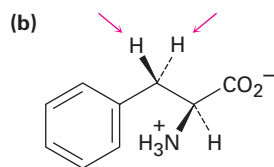
Note that when drawing compounds like threonine, cholesterol, and coprostanol, which have more than one chiral center, the wedges and dashes in a structure are used only to imply *relative* stereochemistry within the molecule rather than absolute stereochemistry, unless stated otherwise.

### Problem 5.22

Identify the indicated hydrogens in the following molecules as *pro-R* or *pro-S*:



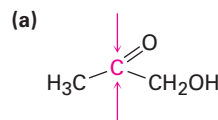
(S)-Glyceraldehyde



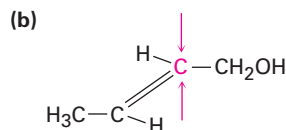
Phenylalanine

### Problem 5.23

Identify the indicated faces of carbon atoms in the following molecules as *Re* or *Si*:



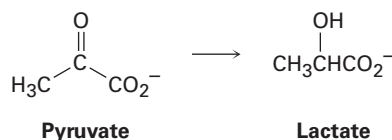
Hydroxyacetone



Crotyl alcohol

### Problem 5.24

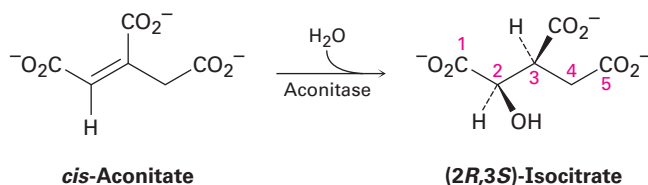
The lactic acid that builds up in tired muscles is formed from pyruvate. If the reaction occurs with addition of hydrogen to the *Re* face of pyruvate, what is the stereochemistry of the product?



### Problem 5.25

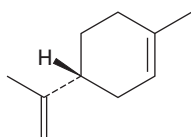
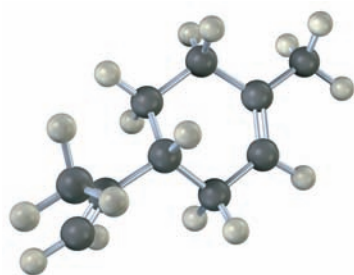
The aconitase-catalyzed addition of water to *cis*-aconitate in the citric acid cycle occurs with the following stereochemistry. Does the addition of the OH group occur on the *Re* or

the *Si* face of the substrate? What about the addition of the H? Do the H and OH groups add from the same side of the double bond or from opposite sides?

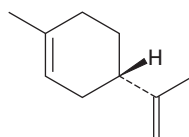


## 5.12 Chirality in Nature and Chiral Environments

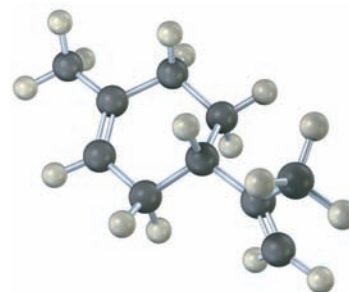
Although the different enantiomers of a chiral molecule have the same physical properties, they usually have different biological properties. For example, the (+) enantiomer of limonene has the odor of oranges and lemons, but the (–) enantiomer has the odor of pine trees.



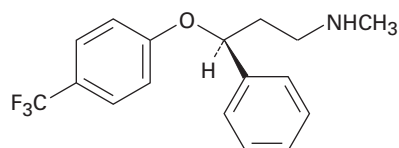
**(+)-Limonene**  
(in citrus fruits)



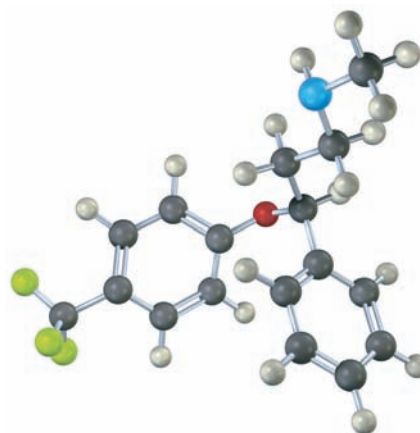
**(–)-Limonene**  
(in pine trees)



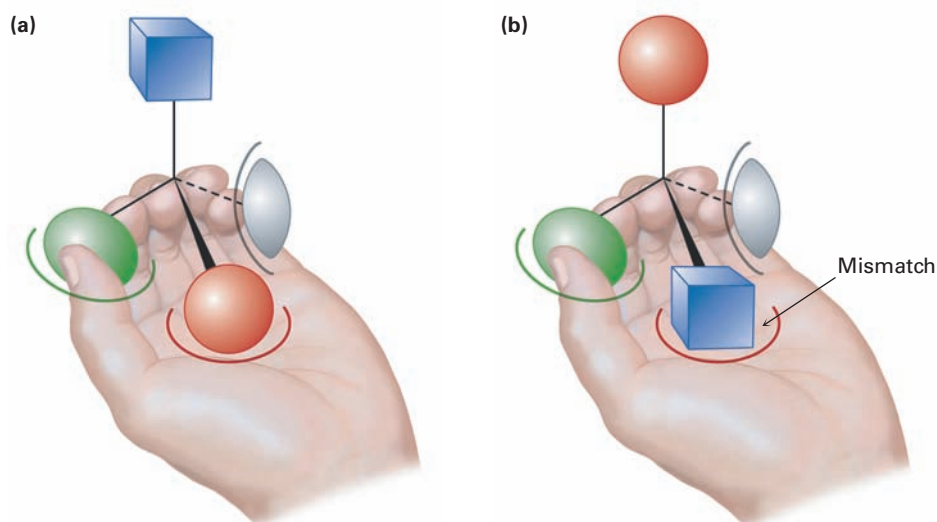
More dramatic examples of how a change in chirality can affect the biological properties of a molecule are found in many drugs, such as fluoxetine, a heavily prescribed medication sold under the trade name Prozac. Racemic fluoxetine is an extraordinarily effective antidepressant but has no activity against migraine. The pure *S* enantiomer, however, works remarkably well in preventing migraine. Other examples of how chirality affects biological properties are given in *A Deeper Look* at the end of this chapter.



**(*S*)-Fluoxetine**  
(prevents migraine)



Why do different enantiomers have different biological properties? To have a biological effect, a substance typically must fit into an appropriate receptor that has an exactly complementary shape. But because biological receptors are chiral, only one enantiomer of a chiral substrate can fit in, just as only a right hand can fit into right-handed glove. The mirror-image enantiomer will be a misfit, like a left hand in a right-handed glove. A representation of the interaction between a chiral molecule and a chiral biological receptor is shown in **Figure 5.15**: one enantiomer fits the receptor perfectly, but the other does not.



**Figure 5.15** Imagine that a left hand interacts with a chiral object, much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: **green thumb**, **red palm**, and gray pinkie finger, with the **blue substituent exposed**. **(b)** The other enantiomer, however, can't fit into the hand. When the green thumb and gray pinkie finger interact appropriately, the palm holds a blue substituent rather than a red one, with the **red substituent exposed**.

The hand-in-glove fit of a chiral substrate into a chiral receptor is relatively straightforward, but it's less obvious how a prochiral substrate can undergo a selective reaction. Take the reaction of ethanol with  $\text{NAD}^+$  catalyzed by yeast alcohol dehydrogenase. As we saw at the end of **Section 5.11**, the reaction occurs with exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of the  $\text{NAD}^+$  carbon.

We can understand this result by imagining that the chiral enzyme receptor again has three binding sites, as was previously the case in Figure 5.15. When green and gray substituents of a prochiral substrate are held appropriately, however, only one of the two red substituents—say, the *pro-S* one—is also held while the other, *pro-R*, substituent is exposed for reaction.

We describe the situation by saying that the receptor provides a **chiral environment** for the substrate. In the absence of a chiral environment, the two red substituents are chemically identical, but in the presence of the chiral environment, they are chemically distinctive (**Figure 5.16a**). The situation is similar to what happens when you pick up a coffee mug. By itself, the mug has a plane of symmetry and is achiral. When you pick up the mug, however, your hand provides a chiral environment so that one side becomes much more accessible and easier to drink from than the other (**Figure 5.16b**).

**Figure 5.16 (a)** When a prochiral molecule is held in a chiral environment, the **two seemingly identical substituents** are distinguishable.

**(b)** Similarly, when an achiral coffee mug is held in the chiral environment of your hand, it's much easier to drink from one side than the other because the two sides of the mug are now distinguishable.

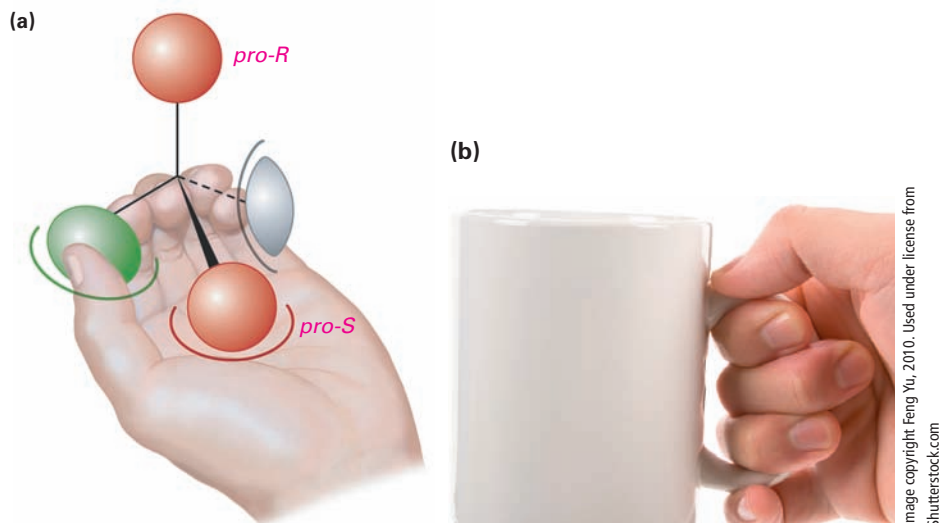


Image copyright Feng Yu, 2010. Used under license from Shutterstock.com



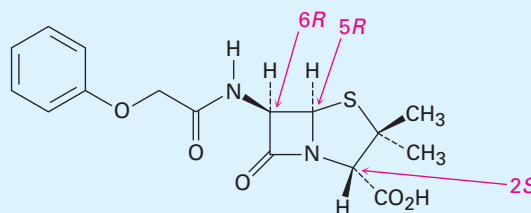
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The *S* enantiomer of ibuprofen soothes the aches and pains of athletic injuries much more effectively than the *R* enantiomer.

## Chiral Drugs | A DEEPER LOOK

The hundreds of different pharmaceutical agents approved for use by the U.S. Food and Drug Administration come from many sources. Many drugs are isolated directly from plants or bacteria, and others are made by chemical modification of naturally occurring compounds. An estimated 33%, however, are made entirely in the laboratory and have no relatives in nature.

Those drugs that come from natural sources, either directly or after chemical modification, are usually chiral and are generally found only as a single enantiomer rather than as a racemate. Penicillin V, for example, an antibiotic isolated from the *Penicillium* mold, has the *2S,5R,6R* configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.

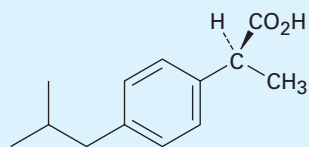


Penicillin V (*2S,5R,6R* configuration)

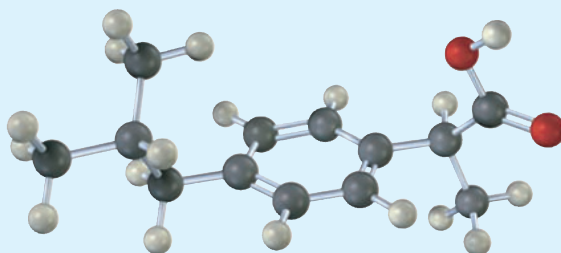
In contrast to drugs from natural sources, those drugs that are made entirely in the laboratory either are achiral or, if chiral, are often produced and sold as racemates. Ibuprofen, for example, has one chirality center and is sold commercially under such trade names as Advil, Nuprin, and Motrin as a 50 : 50 mixture of *R* and *S*. It turns out, however, that only

(continued)

the *S* enantiomer is active as an analgesic and anti-inflammatory agent. The *R* enantiomer of ibuprofen is inactive, although it is slowly converted in the body to the active *S* form.



**(*S*)-Ibuprofen**  
(an active analgesic agent)



Not only is it chemically wasteful to synthesize and administer an enantiomer that does not serve the intended purpose, many instances are now known where the presence of the “wrong” enantiomer in a racemic mixture either affects the body’s ability to utilize the “right” enantiomer or has unintended pharmacological effects of its own. The presence of (*R*)-ibuprofen in the racemic mixture, for instance, slows the rate at which the *S* enantiomer takes effect in the body, from 12 minutes to 38 minutes.

To get around this problem, pharmaceutical companies attempt to devise methods of *enantioselective synthesis*, which allow them to prepare only a single enantiomer rather than a racemic mixture. Viable methods have been developed for the preparation of (*S*)-ibuprofen, which is now being marketed in Europe. We’ll look further into enantioselective synthesis in the Chapter 19 *A Deeper Look*.

## Summary

In this chapter, we’ve looked at some of the causes and consequences of molecular handedness—a topic of particular importance in understanding biological chemistry. The subject can be a bit complex but is so important that it’s worthwhile spending the time needed to become familiar with it.

An object or molecule that is not superimposable on its mirror image is said to be **chiral**, meaning “handed.” A chiral molecule is one that does not have a plane of symmetry cutting through it so that one half is a mirror image of the other half. The most common cause of chirality in organic molecules is the presence of a tetrahedral,  $sp^3$ -hybridized carbon atom bonded to four different groups—a so-called **chirality center**. Chiral compounds can exist as a pair of nonsuperimposable mirror-image stereoisomers called **enantiomers**. Enantiomers are identical in all physical properties except for their **optical activity**, or direction in which they rotate plane-polarized light.

The stereochemical **configuration** of a chirality center can be specified as either ***R*** (*rectus*) or ***S*** (*sinister*) by using the **Cahn–Ingold–Prelog rules**. First

## Key words

**absolute configuration**, 154  
**achiral**, 144  
**Cahn–Ingold–Prelog rules**, 151  
**chiral**, 144  
**chiral environment**, 171  
**chirality center**, 145  
**configuration**, 150  
**dextrorotatory**, 148  
**diastereomers**, 157  
**enantiomers**, 143  
**epimers**, 157  
**levorotatory**, 148

**Key words—cont'd**

meso compound, 159  
 optically active, 148  
*pro-R* configuration, 168  
*pro-S* configuration, 168  
 prochiral, 167  
 prochirality center, 167  
*R* configuration, 152  
 racemate, 161  
*Re* face, 167  
 resolution, 161  
*S* configuration, 152  
*Si* face, 167  
 specific rotation,  $[\alpha]_D$ , 148


rank the four substituents on the chiral carbon atom, and then orient the molecule so that the lowest-ranked group points directly back. If a curved arrow drawn in the direction of decreasing rank ( $1 \rightarrow 2 \rightarrow 3$ ) for the remaining three groups is clockwise, the chirality center has the *R* configuration. If the direction is counterclockwise, the chirality center has the *S* configuration.

Some molecules have more than one chirality center. Enantiomers have opposite configuration at all chirality centers, whereas **diastereomers** have the same configuration in at least one center but opposite configurations at the others. **Epimers** are diastereomers that differ in configuration at only one chirality center. A compound with  $n$  chirality centers can have a maximum of  $2n$  stereoisomers.

**Meso compounds** contain chirality centers but are achiral overall because they have a plane of symmetry. Racemic mixtures, or **racemates**, are 50:50 mixtures of (+) and (–) enantiomers. Racemates and individual diastereomers differ in their physical properties, such as solubility, melting point, and boiling point.

A molecule is **prochiral** if it can be converted from achiral to chiral in a single chemical step. A prochiral  $sp^2$ -hybridized atom has two faces, described as either *Re* or *Si*. An  $sp^3$ -hybridized atom is a **prochirality center** if, by changing one of its attached atoms, a chirality center results. The atom whose replacement leads to an *R* chirality center is ***pro-R***, and the atom whose replacement leads to an *S* chirality center is ***pro-S***.

**Exercises**

 Interactive versions of these problems are assignable in OWL for Organic Chemistry.

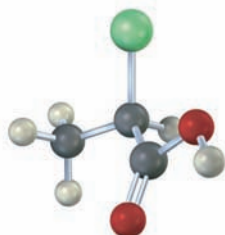
▲ denotes problems linked to the Key Ideas in this chapter.

**Visualizing Chemistry**

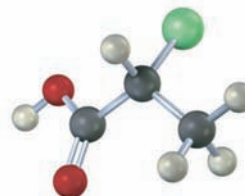
(Problems 5.1–5.25 appear within the chapter.)

5.26 Which of the following structures are identical? (Green = Cl.)

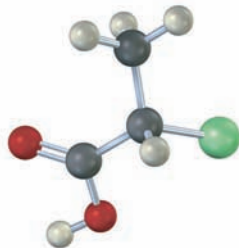
(a)



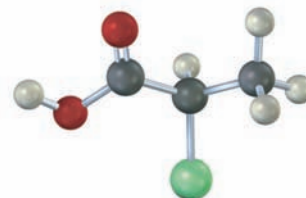
(b)



(c)



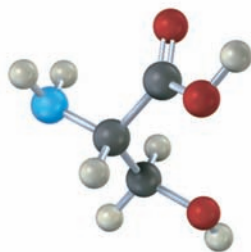
(d)



▲ Problems linked to Key Ideas in this chapter

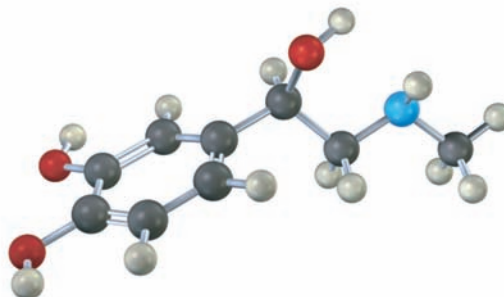
5.27 ▲ Assign *R* or *S* configuration to the chirality centers in the following molecules (blue = N):

(a)



Serine

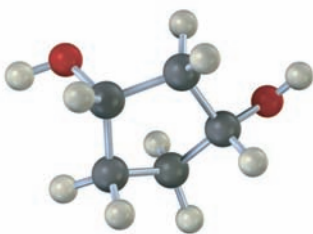
(b)



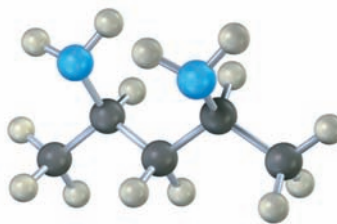
Adrenaline

5.28 Which, if any, of the following structures represent meso compounds? (Blue = N, green = Cl.)

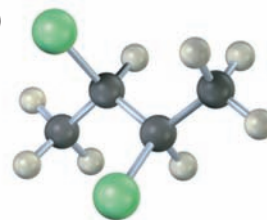
(a)



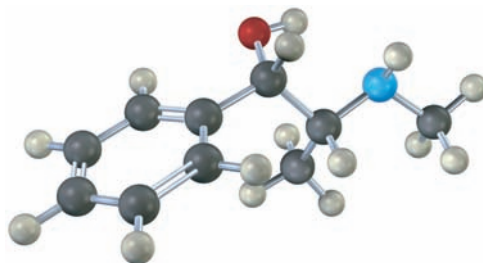
(b)



(c)

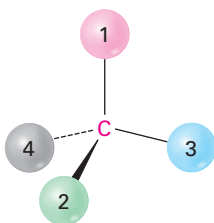


5.29 ▲ Assign *R* or *S* configuration to each chirality center in pseudoephedrine, an over-the-counter decongestant found in cold remedies (blue = N).

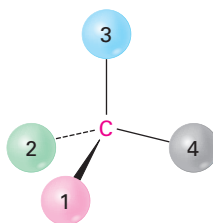


5.30 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

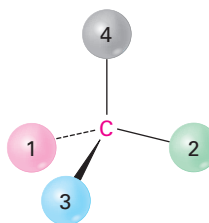
(a)



(b)



(c)



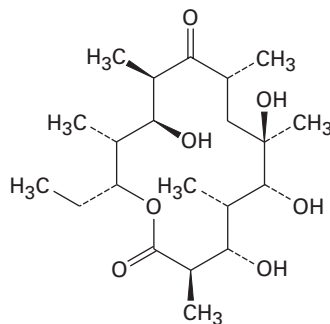
▲ Problems linked to Key Ideas in this chapter



## Additional Problems

## Chirality and Optical Activity

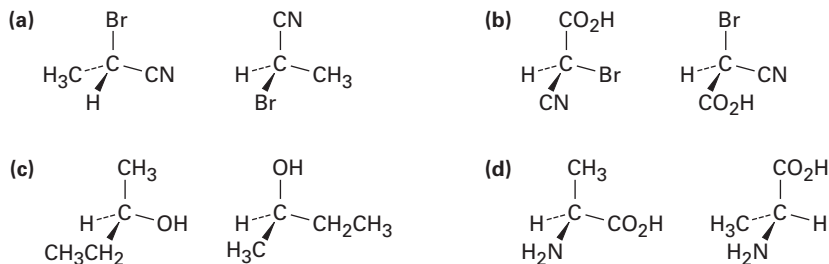
- 5.31 Which of the following objects are chiral?  
 (a) A basketball (b) A fork (c) A wine glass  
 (d) A golf club (e) A spiral staircase (f) A snowflake
- 5.32 ▲ Which of the following compounds are chiral? Draw them, and label the chirality centers.  
 (a) 2,4-Dimethylheptane (b) 5-Ethyl-3,3-dimethylheptane  
 (c) *cis*-1,4-Dichlorocyclohexane
- 5.33 ▲ Draw chiral molecules that meet the following descriptions:  
 (a) A chloroalkane,  $C_5H_{11}Cl$  (b) An alcohol,  $C_6H_{14}O$   
 (c) An alkene,  $C_6H_{12}$  (d) An alkane,  $C_8H_{18}$
- 5.34 ▲ Eight alcohols have the formula  $C_5H_{12}O$ . Draw them. Which are chiral?
- 5.35 Draw compounds that fit the following descriptions:  
 (a) A chiral alcohol with four carbons  
 (b) A chiral carboxylic acid with the formula  $C_5H_{10}O_2$   
 (c) A compound with two chirality centers  
 (d) A chiral aldehyde with the formula  $C_3H_5BrO$
- 5.36 Erythronolide B is the biological precursor of erythromycin, a broad-spectrum antibiotic. How many chirality centers does erythronolide B have? Identify them.



Erythronolide B

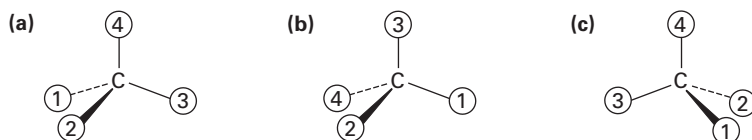
## Assigning Configuration to Chirality Centers

- 5.37 Which of the following pairs of structures represent the same enantiomer, and which represent different enantiomers?

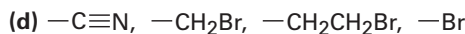
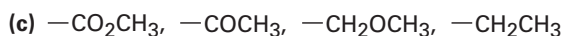
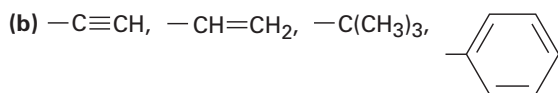
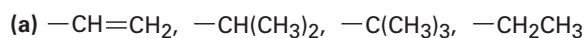


▲ Problems linked to Key Ideas in this chapter

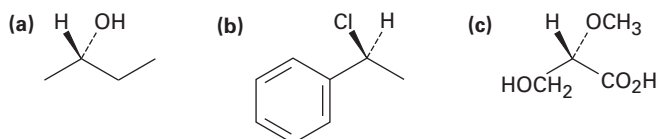
- 5.38** What is the relationship between the specific rotations of (2*R*,3*R*)-dichloropentane and (2*S*,3*S*)-dichloropentane? Between (2*R*,3*S*)-dichloropentane and (2*R*,3*R*)-dichloropentane?
- 5.39** What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-2,4-octanediol? (A diol is a compound with two –OH groups.)
- 5.40** What are the stereochemical configurations of the two diastereomers of (2*S*,4*R*)-2,4-octanediol? (A diol is a compound with two –OH groups.)
- 5.41** Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



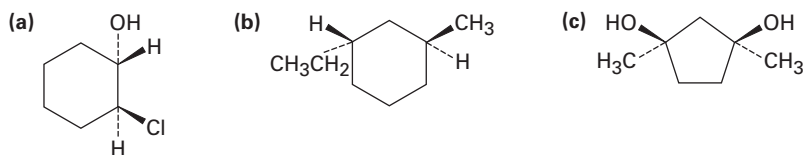
- 5.42** Assign Cahn–Ingold–Prelog rankings to the following sets of substituents:



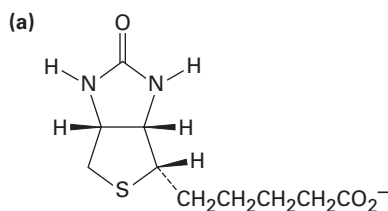
- 5.43** Assign *R* or *S* configurations to the chirality centers in the following molecules:



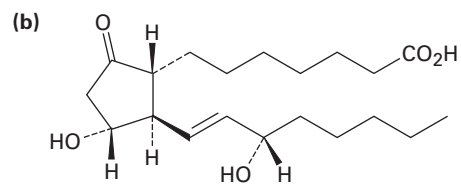
- 5.44** Assign *R* or *S* configuration to each chirality center in the following molecules:



5.45 Assign *R* or *S* configuration to each chirality center in the following biological molecules:



Biotin

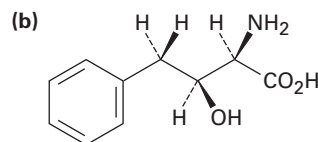
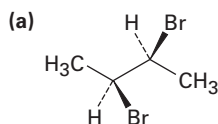
Prostaglandin E<sub>1</sub>

5.46 Draw tetrahedral representations of the following molecules:

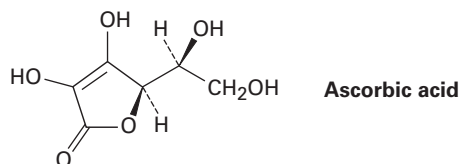
(a) (*S*)-2-Chlorobutane

(b) (*R*)-3-Chloro-1-pentene [H<sub>2</sub>C=CHCH(Cl)CH<sub>2</sub>CH<sub>3</sub>]

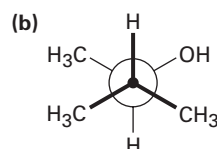
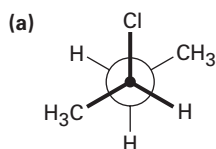
5.47 Assign *R* or *S* configuration to each chirality center in the following molecules:



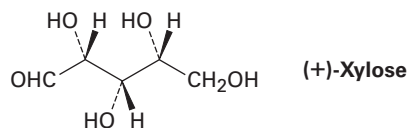
5.48 Assign *R* or *S* configurations to the chirality centers in ascorbic acid (vitamin C).



5.49 Assign *R* or *S* stereochemistry to the chirality centers in the following Newman projections:



5.50 Xylose is a common sugar found in many types of wood, including maple and cherry. Because it is much less prone to cause tooth decay than sucrose, xylose has been used in candy and chewing gum. Assign *R* or *S* configurations to the chirality centers in xylose.



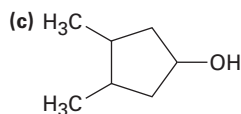
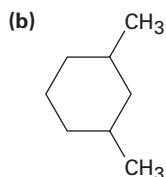
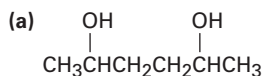
▲ Problems linked to Key Ideas in this chapter

## Meso Compounds

5.51 Draw examples of the following:

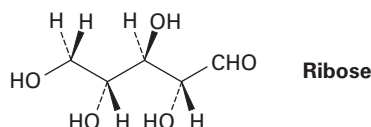
- A meso compound with the formula  $C_8H_{18}$
- A meso compound with the formula  $C_9H_{20}$
- A compound with two chirality centers, one *R* and the other *S*

5.52 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:



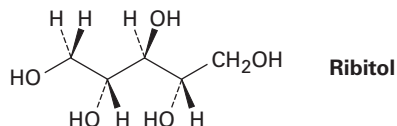
5.53 Draw the structure of a meso compound that has five carbons and three chirality centers.

5.54 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:



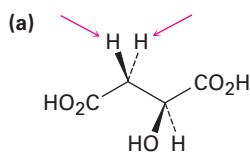
- How many chirality centers does ribose have? Identify them.
- How many stereoisomers of ribose are there?
- Draw the structure of the enantiomer of ribose.
- Draw the structure of a diastereomer of ribose.

5.55 On reaction with hydrogen gas with a platinum catalyst, ribose (Problem 5.54) is converted into ribitol. Is ribitol optically active or inactive? Explain.

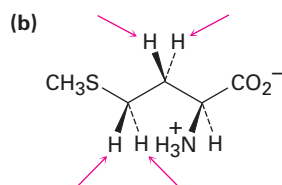


## Prochirality

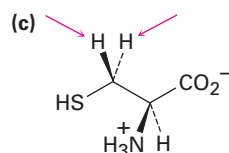
5.56 Identify the indicated hydrogens in the following molecules as *pro-R* or *pro-S*:



**Malic acid**



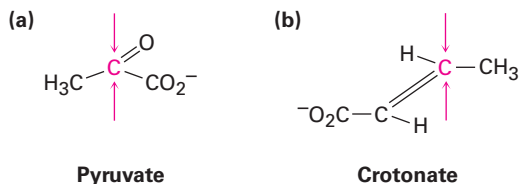
**Methionine**



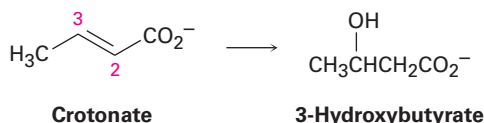
**Cysteine**

▲ Problems linked to Key Ideas in this chapter

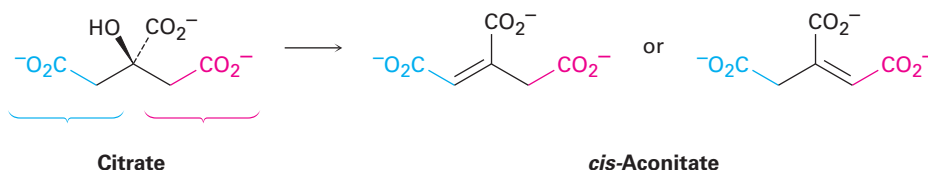
5.57 Identify the indicated faces in the following molecules as *Re* or *Si*:



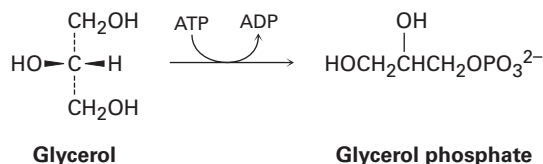
5.58 One of the steps in fat metabolism is the hydration of crotonate to yield 3-hydroxybutyrate. The reaction occurs by addition of  $\text{OH}^-$  to the *Si* face at C3, followed by protonation at C2, also from the *Si* face. Draw the product of the reaction, showing the stereochemistry of each step.



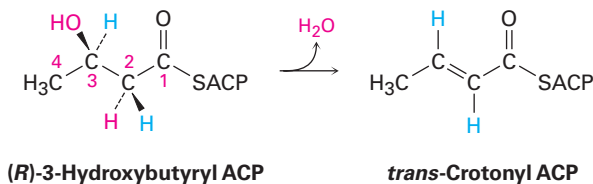
5.59 The dehydration of citrate to yield *cis*-aconitate, a step in the citric acid cycle, involves the *pro-R* "arm" of citrate rather than the *pro-S* arm. Which of the following two products is formed?



5.60 The first step in the metabolism of glycerol, formed by digestion of fats, is phosphorylation of the *pro-R*  $\text{CH}_2\text{OH}$  group by reaction with adenosine triphosphate (ATP) to give the corresponding glycerol phosphate plus adenosine diphosphate (ADP). Show the stereochemistry of the product.



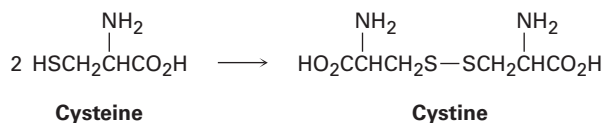
5.61 One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotonyl ACP. Does the reaction remove the *pro-R* or the *pro-S* hydrogen from C2?



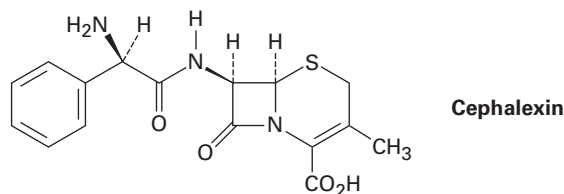
▲ Problems linked to Key Ideas in this chapter

### General Problems

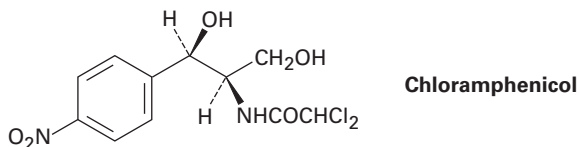
- 5.62** Draw all possible stereoisomers of 1,2-cyclobutanedicarboxylic acid, and indicate the interrelationships. Which, if any, are optically active? Do the same for 1,3-cyclobutanedicarboxylic acid.
- 5.63** Draw tetrahedral representations of the two enantiomers of the amino acid cysteine,  $\text{HSCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ , and identify each as *R* or *S*.
- 5.64** The naturally occurring form of the amino acid cysteine (Problem 5.63) has the *S* configuration at its chirality center. On treatment with a mild oxidizing agent, two cysteines join to give cystine, a disulfide. Assuming that the chirality center is not affected by the reaction, is cystine optically active? Explain.



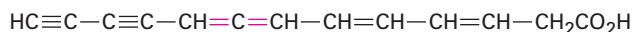
- 5.65** Draw tetrahedral representations of the following molecules:
- (a) The *2S,3R* enantiomer of 2,3-dibromopentane
- (b) The meso form of 3,5-heptanediol
- 5.66** Assign *R,S* configurations to the chiral centers in cephalixin, trade-named Keflex, the most widely prescribed antibiotic in the United States.



- 5.67** Chloramphenicol, a powerful antibiotic isolated in 1949 from the *Streptomyces venezuelae* bacterium, is active against a broad spectrum of bacterial infections and is particularly valuable against typhoid fever. Assign *R,S* configurations to the chirality centers in chloramphenicol.



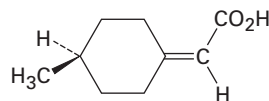
- 5.68** *Allenes* are compounds with adjacent carbon-carbon double bonds. Many allenes are chiral, even though they don't contain chirality centers. Mycomycin, for example, a naturally occurring antibiotic isolated from the bacterium *Nocardia acidophilus*, is chiral and has  $[\alpha]_D = -130$ . Explain why mycomycin is chiral.



**Mycomycin**

▲ Problems linked to Key Ideas in this chapter

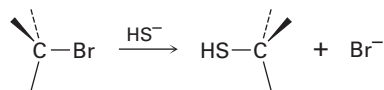
- 5.69** Long before chiral allenes were known (Problem 5.68), the resolution of 4-methylcyclohexylideneacetic acid into two enantiomers had been carried out. Why is it chiral? What geometric similarity does it have to allenes?



**4-Methylcyclohexylideneacetic acid**

- 5.70** (*S*)-1-Chloro-2-methylbutane undergoes light-induced reaction with  $\text{Cl}_2$  to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane.
- Write the reaction, showing the correct stereochemistry of the reactant.
  - One of the two products is optically active, but the other is optically inactive. Which is which?
- 5.71** How many stereoisomers of 2,4-dibromo-3-chloropentane are there? Draw them, and indicate which are optically active.
- 5.72** Draw both *cis*- and *trans*-1,4-dimethylcyclohexane in their more stable chair conformations.
- How many stereoisomers are there of *cis*-1,4-dimethylcyclohexane, and how many of *trans*-1,4-dimethylcyclohexane?
  - Are any of the structures chiral?
  - What are the stereochemical relationships among the various stereoisomers of 1,4-dimethylcyclohexane?
- 5.73** Draw both *cis*- and *trans*-1,3-dimethylcyclohexane in their more stable chair conformations.
- How many stereoisomers are there of *cis*-1,3-dimethylcyclohexane, and how many of *trans*-1,3-dimethylcyclohexane?
  - Are any of the structures chiral?
  - What are the stereochemical relationships among the various stereoisomers of 1,3-dimethylcyclohexane?
- 5.74** *cis*-1,2-Dimethylcyclohexane is optically inactive even though it has two chirality centers. Explain.

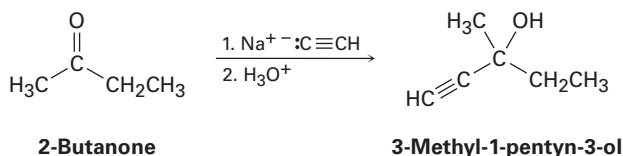
- 5.75 We'll see in Chapter 11 that alkyl halides react with hydrosulfide ion ( $\text{HS}^-$ ) to give a product whose stereochemistry is *inverted* from that of the reactant.



**An alkyl  
bromide**

Draw the reaction of (*S*)-2-bromobutane with  $\text{HS}^-$  ion to yield 2-butanethiol,  $\text{CH}_3\text{CH}_2\text{CH}(\text{SH})\text{CH}_3$ . Is the stereochemistry of the product *R* or *S*?

- 5.76 Ketones react with sodium acetylide (the sodium salt of acetylene,  $\text{Na}^+ \text{:C}\equiv\text{CH}$ ) to give alcohols. For example, the reaction of sodium acetylide with 2-butanone yields 3-methyl-1-pentyn-3-ol:

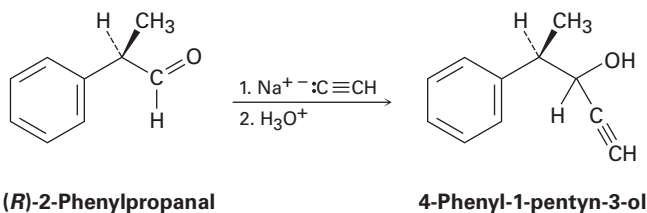


**2-Butanone**

**3-Methyl-1-pentyn-3-ol**

- (a) Is the product chiral?  
 (b) Assuming that the reaction takes place with equal likelihood from both *Re* and *Si* faces of the carbonyl group, is the product optically active? Explain.

- 5.77 Imagine that a reaction similar to that in Problem 5.76 is carried out between sodium acetylide and (*R*)-2-phenylpropanal to yield 4-phenyl-1-pentyn-3-ol:



**(*R*)-2-Phenylpropanal**

**4-Phenyl-1-pentyn-3-ol**

- (a) Is the product chiral?  
 (b) Draw both major and minor reaction products, assuming that the reaction takes place preferentially from the *Re* face of the carbonyl group. Is the product mixture optically active? Explain.