CHAPTER

6

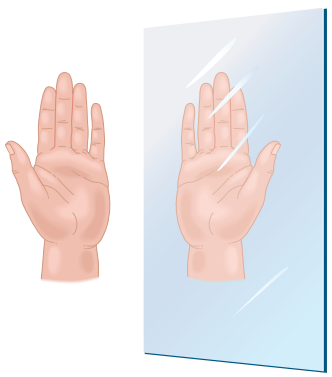
Like the mountain whose image is reflected in a lake, many organic molecules also have mirror-image counterparts.

Stereochemistry at Tetrahedral Centers

OWL

Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

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 fundamental 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 primarily arises 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, it is molecular handedness that 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 seem a bit complex at first, but the material covered in this chapter nevertheless forms the basis for much of the remainder of the book.

6.1 Enantiomers and the Tetrahedral Carbon

What causes molecular handedness? To see how molecular handedness arises, look at generalized molecules of the type CH_3X, CH_2XY, and CHXYZ shown in Figure 6.1. On the left are three molecules, and on the right are their images reflected in a mirror. The CH_3X and CH_2XY 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'll find that you can superimpose one on the other. The 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.

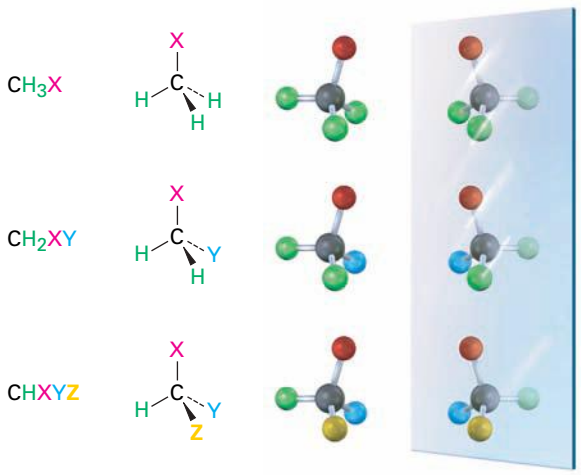


Figure 6.1 Tetrahedral carbon atoms and their mirror images. Molecules of the type CH_3X and CH_2XY are identical to their mirror images, but a molecule of the type CHXYZ is not. A CHXYZ molecule is related to its mirror image in the same way that a right hand is related to a left hand.

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 (–H, –OH, $–CH_3$, and $–CO_2H$) bonded to the central carbon atom. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.

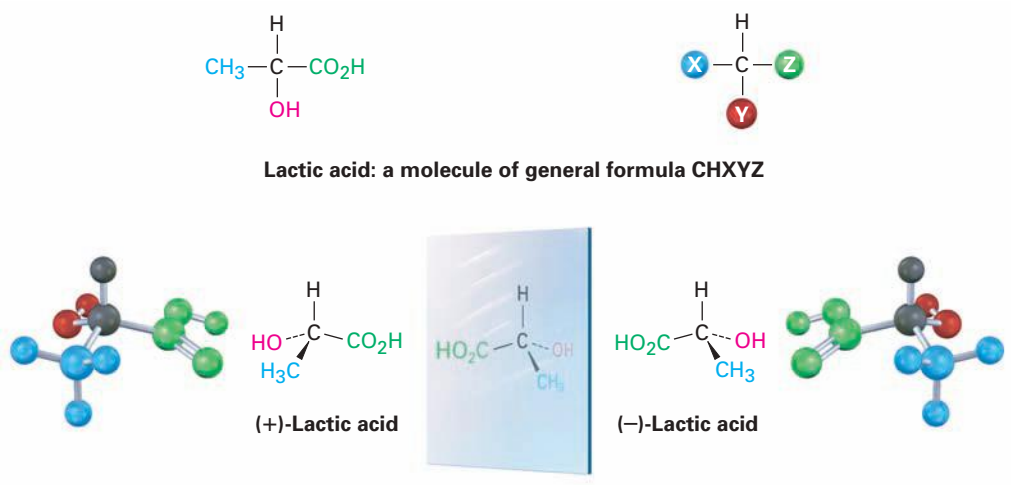


Figure 6.2 Attempts at superimposing the mirror-image forms of lactic acid: **(a)** When the –H and –OH substituents match up, the $–CO_2H$ and $–CH_3$ substituents don't. **(b)** When $–CO_2H$ and $–CH_3$ match up, –H and –OH don't. Regardless of how the molecules are oriented, they aren't identical.

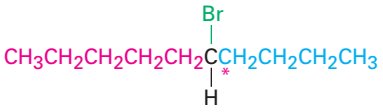
No matter how hard you try, you can't superimpose a molecule of (+)-lactic acid on a molecule of (–)-lactic acid. If any two groups match up, say –H and $–CO_2H$, the remaining two groups don't match (Figure 6.2).

6.2 The Reason for Handedness in Molecules: Chirality

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? By far the most common (although not the only) cause of chirality in an organic molecule is the presence of a carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are referred to as *stereocenters,* or **chirality centers**. Note that *chirality* is a property of the entire molecule, whereas a chirality *center* is the *cause* of chirality.

Detecting chirality centers in a complex molecule takes practice, because it's not always 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 (marked by an asterisk). A butyl substituent is very *similar* to a pentyl substituent, but it isn't identical. The difference isn't apparent until four carbons away from the chirality center, but there's still a difference.



5-Bromodecane (chiral)

Substituents on carbon 5

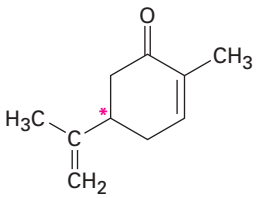
–H

–Br

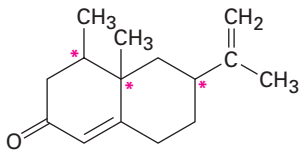
–$CH_2CH_2CH_2CH_3$ (butyl)

–$CH_2CH_2CH_2CH_2CH_3$ (pentyl)

Several other examples of chiral molecules follow. Check for yourself that the labeled atoms are indeed chirality centers. You might note that carbons in –CH_2–, –CH_3, C=O, C=C, and C≡C groups *can't* be chirality centers. (Why not?)



Carvone (spearmint oil)



Nootkatone (grapefruit oil)

Another way to identify a chiral molecule is to look for the presence of a *plane of symmetry*. A symmetry plane is one that cuts through the middle of a molecule or other 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 an exact 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 6.3).

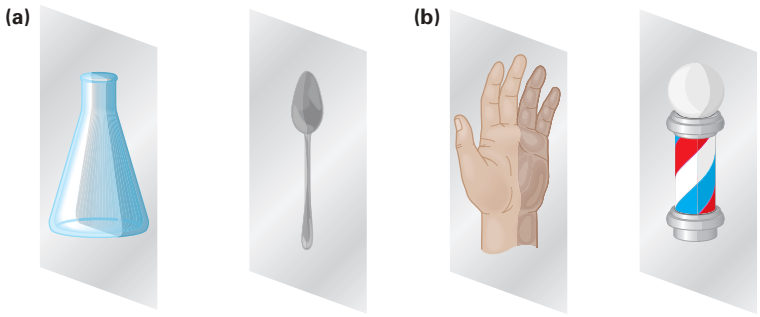


Figure 6.3 The meaning of *symmetry plane*. **(a)** Objects like a flask or spoon have planes of symmetry passing through them that make the right and left halves mirror images. **(b)** Objects like a hand or barber pole have no symmetry plane; the right "half" is not a mirror image of the left half.

A molecule that has a plane of symmetry in any of its possible conformations must be identical to its mirror image and hence must be nonchiral, or **achiral**. Thus, propanoic acid, $CH_3CH_2CO_2H$, contains a plane of symmetry when lined up as shown in Figure 6.4 and is achiral. Lactic acid, $CH_3CH(OH)CO_2H$, however, has no plane of symmetry in any conformation and is chiral.

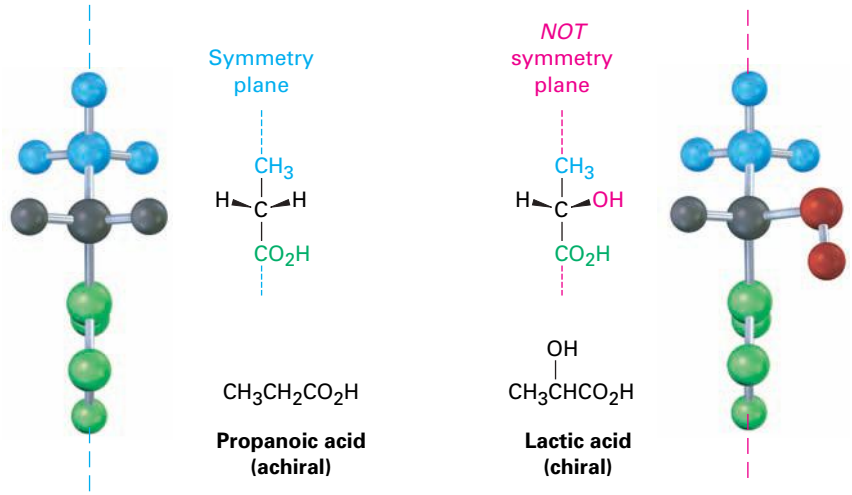


Figure 6.4 The achiral propanoic acid molecule versus the chiral lactic acid molecule. Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other side. Lactic acid has no such symmetry plane.

Worked Example 6.1

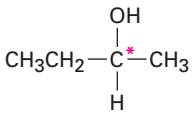
Drawing a Chiral Molecule

Draw the structure of a chiral alcohol.

Strategy

An alcohol is a compound that contains the –OH functional group. To make an alcohol chiral, we need to have four different groups bonded to a single carbon atom, say –H, –OH, $-CH_3$, and $-CH_2CH_3$.

Solution



Butan-2-ol (chiral)

Worked Example 6.2

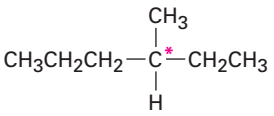
Identifying a Chiral Molecule

Is 3-methylhexane chiral?

Strategy

Draw the structure of 3-methylhexane and cross out all the CH_2 and CH_3 carbons because they can't be chirality centers. Then look closely at any carbon that remains to see if it's bonded to four different groups.

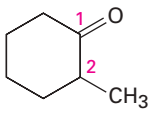
Solution Carbon 3 is bonded to –H, $–CH_3$, $–CH_2CH_3$, and $–CH_2CH_2CH_3$, so the molecule is chiral.



3-Methylhexane (chiral)

Worked Example 6.3 Identifying a Chiral Molecule

Is 2-methylcyclohexanone chiral?



2-Methylcyclohexanone

Strategy Ignore the CH_3 carbon, the four CH_2 carbons in the ring, and the C=O carbon because they can't be chirality centers. Then look carefully at C2, the only carbon that remains.

Solution Carbon 2 is bonded to four different groups: a $–CH_3$ group, an –H atom, a –C=O carbon in the ring, and a $–CH_2–$ ring carbon, so 2-methylcyclohexanone is chiral.

Problem 6.1 Which of the following objects are chiral?

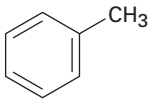
(a) Soda can **(b)** Screwdriver **(c)** Screw **(d)** Shoe

Problem 6.2 Which of the following molecules are chiral?

(a) 3-Bromopentane **(b)** 1,3-Dibromopentane
(c) 3-Methylhex-1-ene **(d)** *cis*-1,4-Dimethylcyclohexane

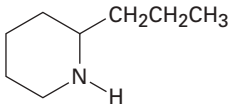
Problem 6.3 Which of the following molecules are chiral? Identify the chirality center(s) in each.

(a)



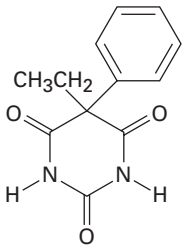
Toluene

(b)



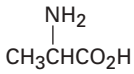
Coniine (from poison hemlock)

(c)



Phenobarbital (tranquilizer)

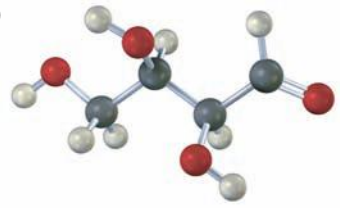
Problem 6.4 Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.



Alanine

Problem 6.5 Identify the chirality centers in the following molecules (yellow-green = Cl, pale yellow = F):

(a)



Threose
(a sugar)

(b)

Enflurane
(an anesthetic)

6.3 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 is passed 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 α. 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 6.5. 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.

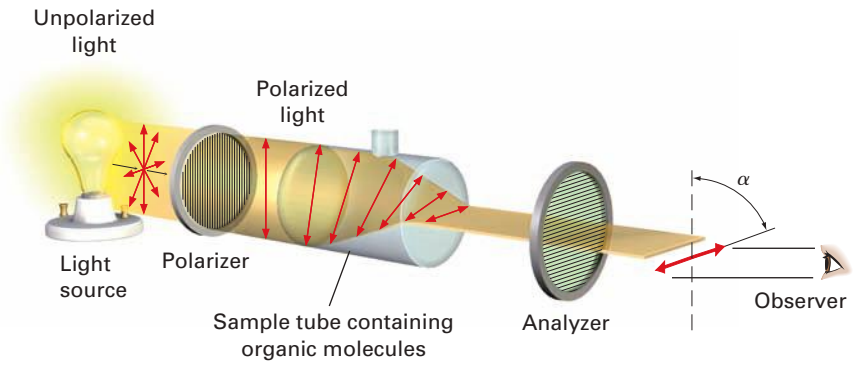


Figure 6.5 Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.

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. In addition, 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 nm = 10^{-9} m) wavelength is used with a sample pathlength l of 1 decimeter (dm; 1 dm = 10 cm) and a sample concentration c of 1 g/cm^3.

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

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 the same extent but in opposite directions. Note that the units of specific rotation are [(deg · cm^2)/g] but that values are usually expressed without the units. Some additional examples are listed in Table 6.1.

Table 6.1 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

Worked Example 6.4 Calculating an Optical Rotation

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 in degrees?

Strategy

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

Then $\alpha = l \times c \times [\alpha]_D$

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

Solution

$\alpha = -16^\circ \times 0.500 \times 0.160 = -1.3^\circ$

Problem 6.6 Is cocaine (Worked Example 6.4) dextrorotatory or levorotatory?

Problem 6.7 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°. Calculate $[\alpha]_D$ for coniine.

6.4 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 recrystallizing 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 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, as shown in Figure 6.6. Although the original sample, a 50:50 mixture of right and left, was optically inactive, *solutions of crystals from each of the sorted piles were optically active* and their specific rotations were equal in amount but opposite in sign.

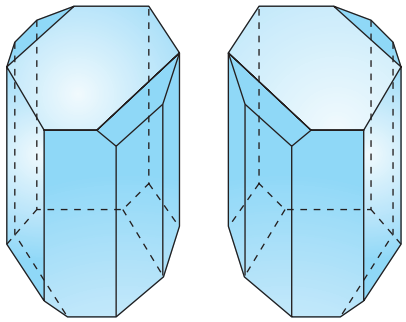
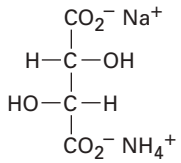


Figure 6.6 Drawings of sodium ammonium tartrate crystals taken from Pasteur's original sketches. One of the crystals is dextrorotatory in solution, and the other is levorotatory.



Sodium ammonium tartrate

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 possess precisely the inverse asymmetric arrangement." Pasteur's vision was extraordinary, for it was not until 25 years later that his theories regarding the asymmetry of chiral molecules 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 points and boiling points, but differ in the direction in which their solutions rotate plane-polarized light.

6.5 Sequence Rules for Specifying Configuration

Drawings provide visual representations of stereochemistry, but a verbal method for specifying the three-dimensional arrangement, or **configuration**, of substituents around a chirality center is also necessary. The method used employs the same sequence rules given in Section 3.4 for specifying *E* and *Z* alkene stereochemistry. Let's briefly review these sequence rules and then see how they're used to specify the configuration of a chirality center. For a more thorough review, you should reread Section 3.4.

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).

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**.

RULE 3 **Multiple-bonded atoms are equivalent to the same number of single-bonded atoms**.

Having ranked the four groups attached to a chirality center, 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 6.7). If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent (1 → 2 → 3) is clockwise, we say that the chirality center has the ***R* configuration** (Latin *rectus,* meaning "right"). If an arrow from 1 → 2 → 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 *R*ight (clockwise) turn.

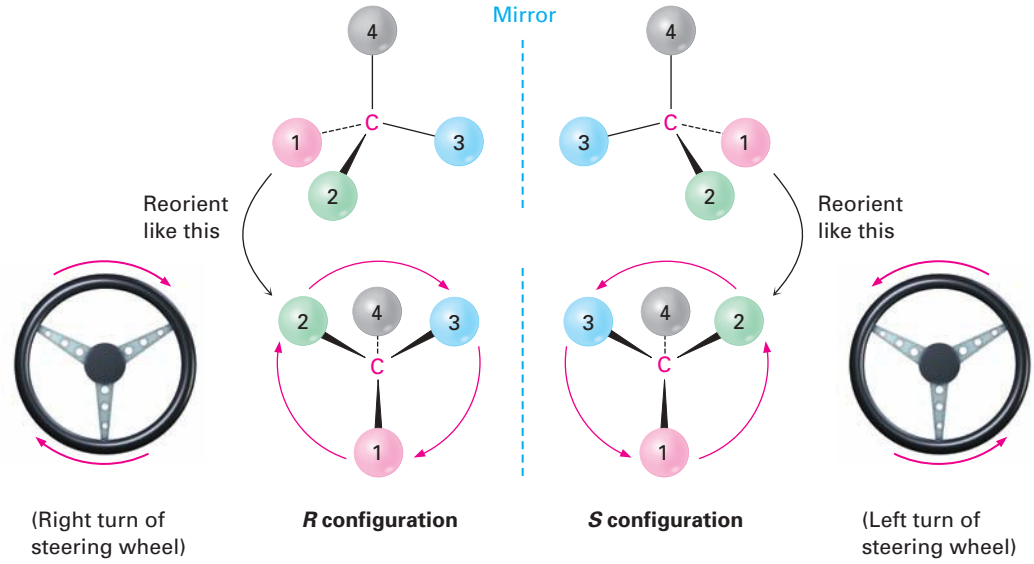


Figure 6.7 Assignment of configuration to a chirality center. When the molecule is oriented so that the lowest-ranked group (4) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel 1 → 2 → 3 is clockwise (right turn), the center has the *R* configuration. If the direction of travel 1 → 2 → 3 is counterclockwise (left turn), the center is *S*.

Look at (−)-lactic acid in Figure 6.8 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 $-CH_3$ and $-CO_2H$ because both groups have carbon as their first atom. Sequence rule 2, however, says that $-CO_2H$ ranks higher than $-CH_3$ because O (the highest second atom in $-CO_2H$) outranks H (the highest second atom in $-CH_3$). 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 ($-CO_2H$) to 3 ($-CH_3$) 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.

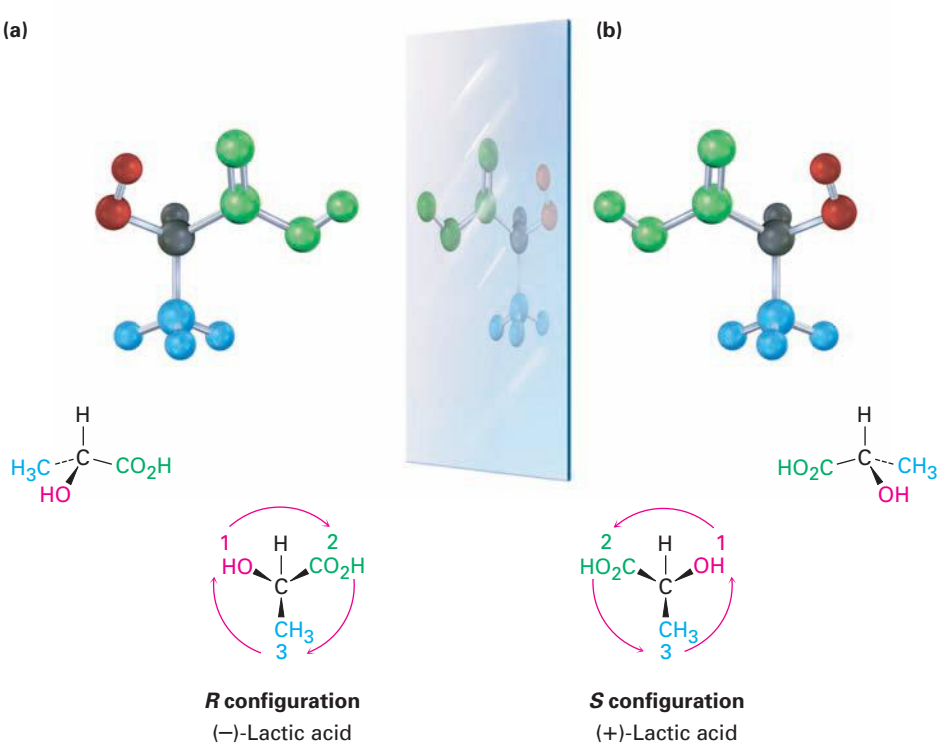


Figure 6.8 Assigning configuration to **(a)** (*R*)-(−)-lactic acid and **(b)** (*S*)-(+)-lactic acid.

Further examples are provided by naturally occurring (−)-glyceraldehyde and (+)-alanine, both of which have an *S* configuration as shown in Figure 6.9. 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 (+), but there is no simple correlation between *R*,*S* configuration and direction or magnitude of optical rotation.

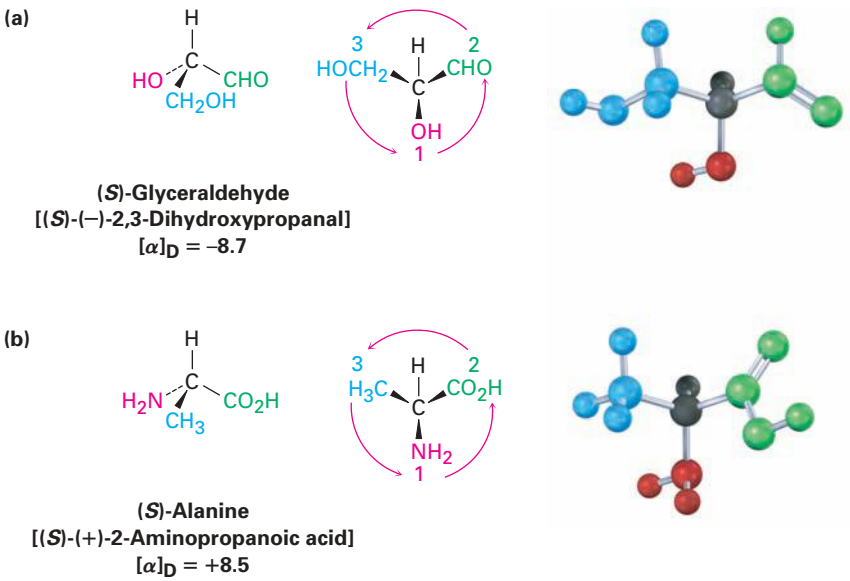
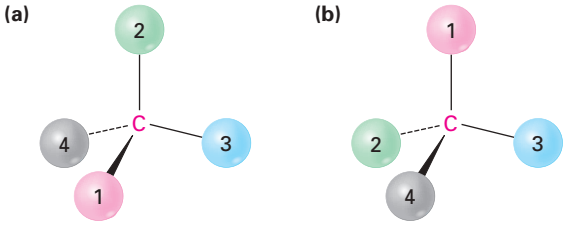


Figure 6.9 Assigning configuration to **(a)** (−)-glyceraldehyde and **(b)** (+)-alanine. Both happen to have the *S* configuration, although one is levorotatory and the other is dextrorotatory.

Worked Example 6.5

Assigning *R* and *S* 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:

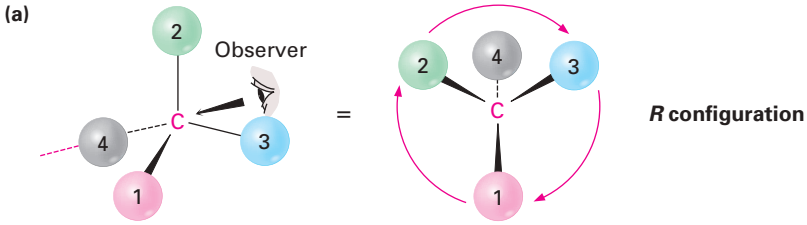


Strategy

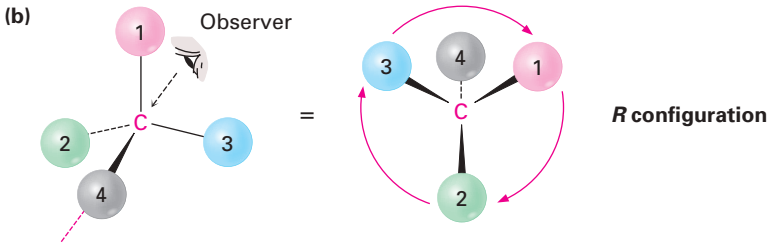
It takes practice to be able to visualize and orient a chirality center in three dimensions. You might start by indicating where the observer must be located—180° opposite the lowest-ranked group. Then imagine yourself in the position of the observer, and redraw what you would see.

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.



Worked Example 6.6

Drawing a Specific Enantiomer

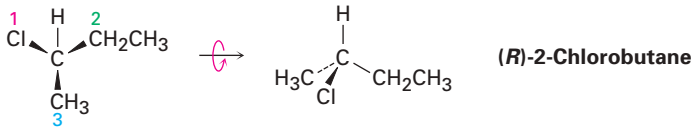
Draw a tetrahedral representation of (*R*)-2-chlorobutane.

Strategy

Begin by ranking the four substituents bonded to the chirality center: (1) –Cl, (2) $-CH_2CH_3$, (3) $-CH_3$, (4) –H. To draw a tetrahedral representation of the molecule, orient the lowest-ranked group (–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 → 2 → 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

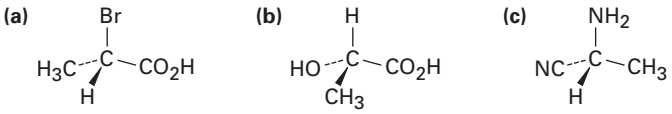


(*R*)-2-Chlorobutane

Problem 6.8 Rank the substituents in each of the following sets:

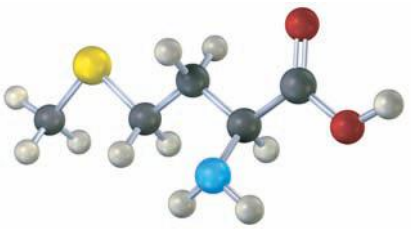
(a) –H, –OH, $-CH_2CH_3$, $-CH_2CH_2OH$
(b) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, –OH
(c) –CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-NH_2$
(d) –SH, $-CH_2SCH_3$, $-CH_3$, $-SSCH_3$

Problem 6.9 Assign *R*,*S* configurations to the following molecules:



Problem 6.10 Draw a tetrahedral representation of (*S*)-pentan-2-ol (2-hydroxypentane).

Problem 6.11 Assign *R* or *S* configuration to the chirality center in the following molecular model of the amino acid methionine (red = O, blue = N, yellow = S):



6.6 Diastereomers

Molecules like lactic acid and glyceraldehyde are relatively simple to deal with because each has only one chirality center and only two stereoisomers. The situation becomes more complex, however, for 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). Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for instance. Because threonine has two chirality centers (C2 and C3), there are $2^2 = 4$ possible

stereoisomers, as shown in Figure 6.10. Check for yourself that the *R*,*S* configurations are correct.

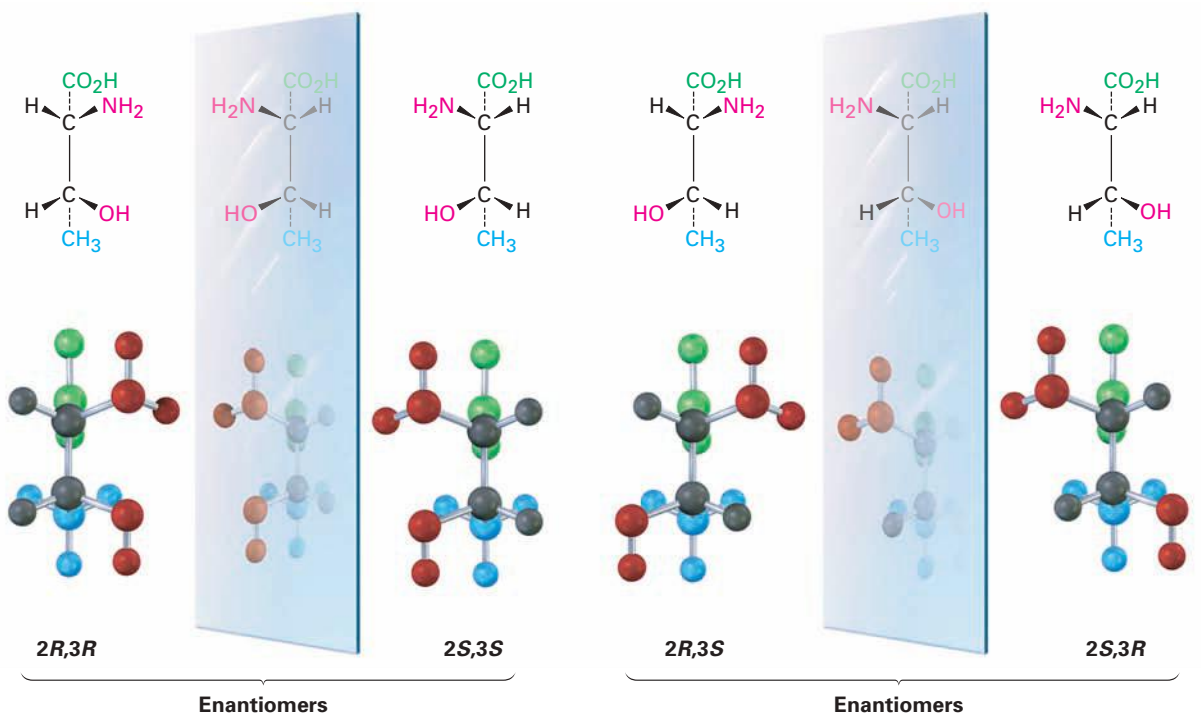


Figure 6.10 The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The 2*S*,3*S* stereoisomer is the mirror image of 2*R*,3*R*, and the 2*S*,3*R* stereoisomer is the mirror image of 2*R*,3*S*. But what is the relationship between any two molecules that are not mirror images? What, for instance, is the relationship between the 2*R*,3*R* isomer and the 2*R*,3*S* 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.

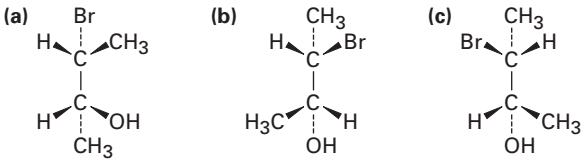
Note carefully the difference between enantiomers and diastereomers: enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. A full description of the four threonine stereoisomers is given in Table 6.2. Of the four, only the 2*S*,3*R* isomer occurs naturally in plants and animals and is an essential human

nutrient. This result is typical: most biological molecules are chiral, and often only one stereoisomer is found in nature.

Table 6.2 Relationships among the Four Stereoisomers of Threonine

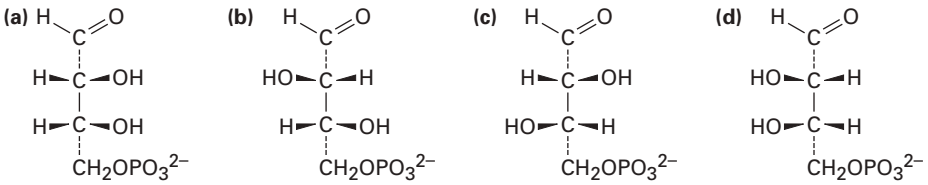
Stereoisomer	Enantiomer	Diastereomer
2*R*,3*R*	2*S*,3*S*	2*R*,3*S* and 2*S*,3*R*
2*S*,3*S*	2*R*,3*R*	2*R*,3*S* and 2*S*,3*R*
2*R*,3*S*	2*S*,3*R*	2*R*,3*R* and 2*S*,3*S*
2*S*,3*R*	2*R*,3*S*	2*R*,3*R* and 2*S*,3*S*

Problem 6.12 Assign *R* or *S* configuration to each chirality center in the following molecules:

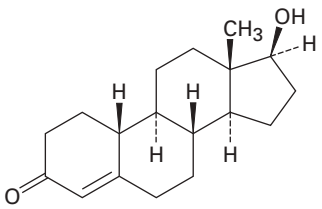


Problem 6.13 Which of the compounds in Problem 6.12 are enantiomers, and which are diastereomers?

Problem 6.14 Of the following molecules **(a)** through **(d)**, one is D-erythrose 4-phosphate, an intermediate in the Calvin photosynthetic cycle by which plants incorporate CO_2 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?

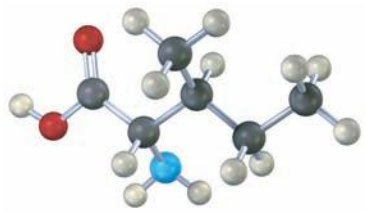


Problem 6.15 Nandrolone is an anabolic steroid used to build muscle mass. How many chirality centers does nandrolone have? How many stereoisomers of nandrolone are possible in principle?



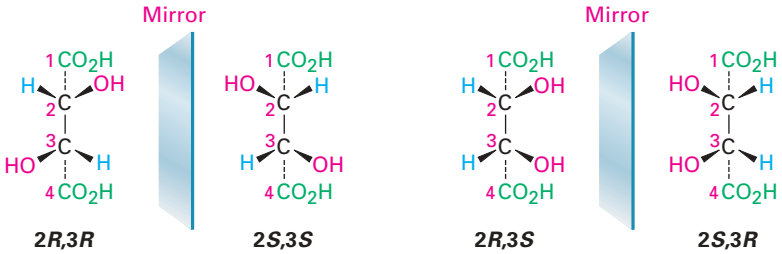
Nandrolone

Problem 6.16 Assign *R*,*S* configuration to each chirality center in the following molecular model of the amino acid isoleucine (red = O, blue = N):

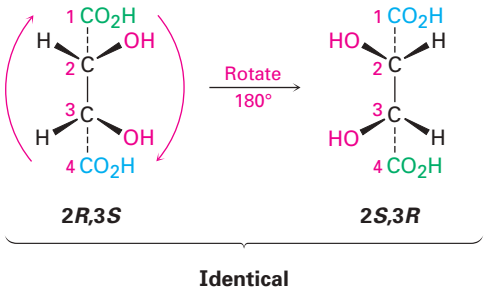


6.7 Meso Compounds

Let's look at one more example of a compound with two chirality centers: the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The mirror-image 2*R*,3*R* and 2*S*,3*S* structures are not identical and therefore represent an enantiomeric pair. A careful look, however, shows that the 2*R*,3*S* and 2*S*,3*R* structures *are* identical, as can be seen by rotating one structure 180°.



The 2*R*,3*S* and 2*S*,3*R* 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 6.11). Because of the plane of symmetry, the tartaric acid stereoisomer shown in Figure 6.11 is achiral, despite the fact that it has two chirality centers. Such compounds that are achiral, yet contain chirality centers, are

called **meso** (**me**-zo) **compounds**. Thus, tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

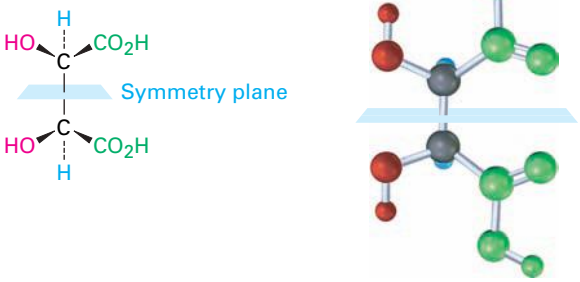


Figure 6.11 A symmetry plane cutting through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral even though it contains two chirality centers.

Some physical properties of the three stereoisomers of tartaric acid are shown in Table 6.3. The (+) and (−) enantiomers have identical melting points, solubilities, and densities but differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (−) forms. It is therefore a different compound altogether and has different physical properties.

Table 6.3 Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm³)	Solubility at 20 °C (g/100 mL H_2O)
(+)	168–170	+12	1.7598	139.0
(−)	168–170	−12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

Worked Example 6.7

Identifying Meso Compounds

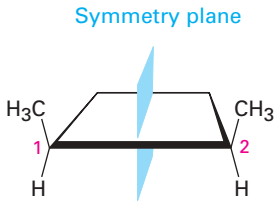
Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

Strategy

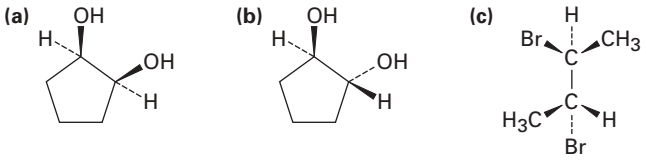
To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for a symmetry plane. Not all molecules with chirality centers are chiral; meso compounds are an exception.

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, *cis*-1,2-dimethylcyclobutane is a meso compound.



Problem 6.17 Which of the following structures represent meso compounds?



Problem 6.18 Which of the following substances have meso forms? Draw them.

(a) 2,3-Dibromobutane **(b)** 2,3-Dibromopentane

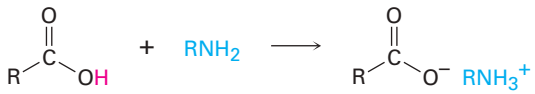
(c) 2,4-Dibromopentane

6.8 Racemic Mixtures and the Resolution of Enantiomers

To end this discussion of stereoisomerism, let's return for a final look at Pasteur's discovery of enantiomers, described in Section 6.4. Pasteur took an optically inactive tartaric acid salt and found that he could crystallize from it two optically active forms having the 2*R*,3*R* and 2*S*,3*S* 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 compound and can't interconvert with the two chiral enantiomers without breaking and re-forming 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 *racemic mixture,* or **racemate** (**ra**-suh-mate). Racemic mixtures are often denoted by the symbol (±) or by the prefix *d,l* to indicate that they contain equal amounts of dextrorotatory and levorotatory enantiomers. Such mixtures show no optical activity because the (+) rotation from one enantiomer exactly cancels the (−) rotation from the other. Through good luck, Pasteur was able to separate, or **resolve**, the racemate into its (+) and (−) enantiomers. Unfortunately, the crystallization technique he used doesn't work for most racemic mixtures, so other methods are required.

The most common method of resolution uses an acid–base reaction between a racemic mixture of chiral carboxylic acid (RCO_2H) and an amine base (RNH_2) to yield an ammonium salt.



Carboxylic acid **Amine base** **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. 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 (enantiomers). In the same way, both (+)- and (−)-lactic acid react with methylamine equally well, and the product is a racemic mixture of enantiomeric methylammonium (+)-lactate and methylammonium (−)-lactate (Figure 6.12).

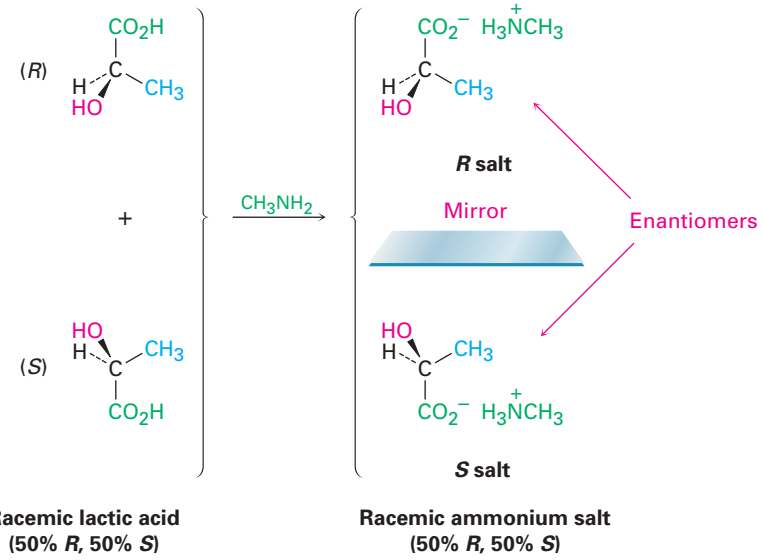


Figure 6.12 Reaction of racemic lactic acid with achiral methylamine leads to a racemic mixture of enantiomeric ammonium salts.

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, this situation is analogous to what happens when left and right hands (chiral) put on a right-handed glove (*also chiral*). The left and right hands don't put on the right-handed glove in the same way. 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 6.13). (*R*)-Lactic acid reacts with (*R*)-1-phenylethylamine to give the *R*,*R* salt, whereas (*S*)-lactic acid reacts with the same *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 HCl then allows us to isolate the two pure enantiomers of lactic acid and recover the chiral amine for further use. That is, the original racemic mixture has been resolved.

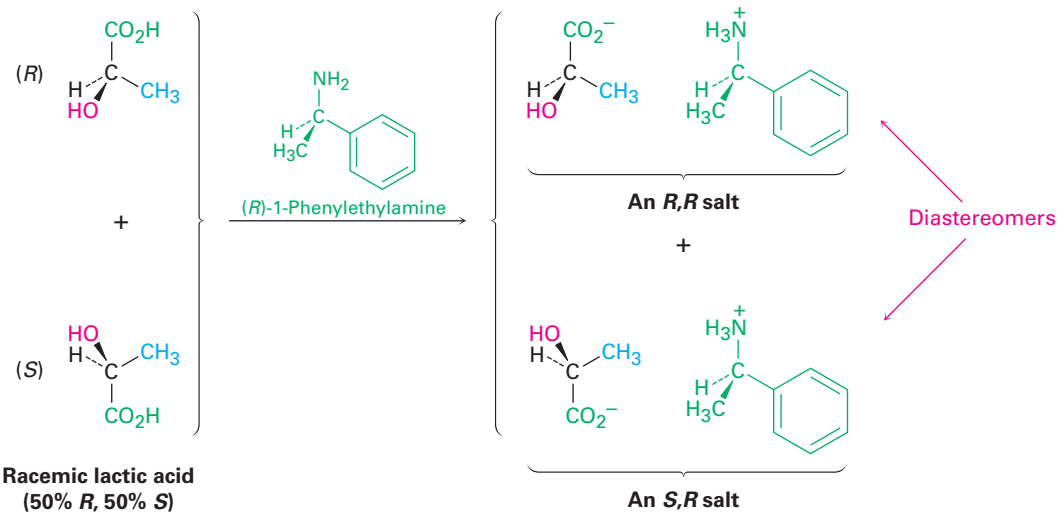
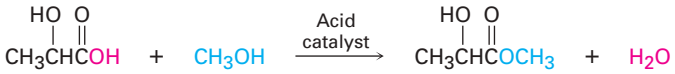


Figure 6.13 Reaction of racemic lactic acid with (*R*)-1-phenylethylamine yields a mixture of diastereomeric ammonium salts, which have different properties and can be separated.

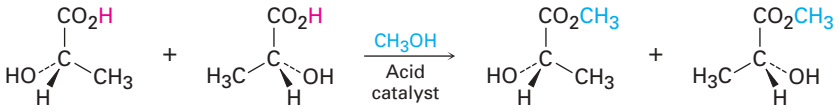
Worked Example 6.8 **Predicting Product Stereochemistry**

We'll see in Section 10.6 that carboxylic acids (RCO_2H) react with alcohols ($R'OH$) to form esters (RCO_2R'). Suppose that (±)-lactic acid reacts with CH_3OH to form the ester methyl lactate. What stereochemistry would you expect the products to have and what is their relationship?



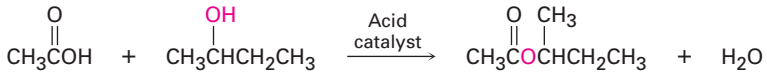
Lactic acid **Methanol** **Methyl lactate**

Solution Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products:



(*S*)-Lactic acid **(*R*)-Lactic acid** **Methyl (*S*)-lactate** **Methyl (*R*)-lactate**

Problem 6.19 Suppose that acetic acid (CH_3CO_2H) reacts with (*S*)-butan-2-ol to form an ester (see Worked Example 6.8). What stereochemistry would you expect the product(s) to have, assuming that the singly bonded oxygen atom comes from the alcohol rather than the acid?



Acetic acid **Butan-2-ol** ***sec*-Butyl acetate**

6.9 A Brief Review of Isomerism

As noted on several previous occasions, isomers are compounds that have the same chemical formula but different structures. We've seen several kinds of isomers in the past few chapters, and it might be helpful to see how they relate to one another (Figure 6.14).

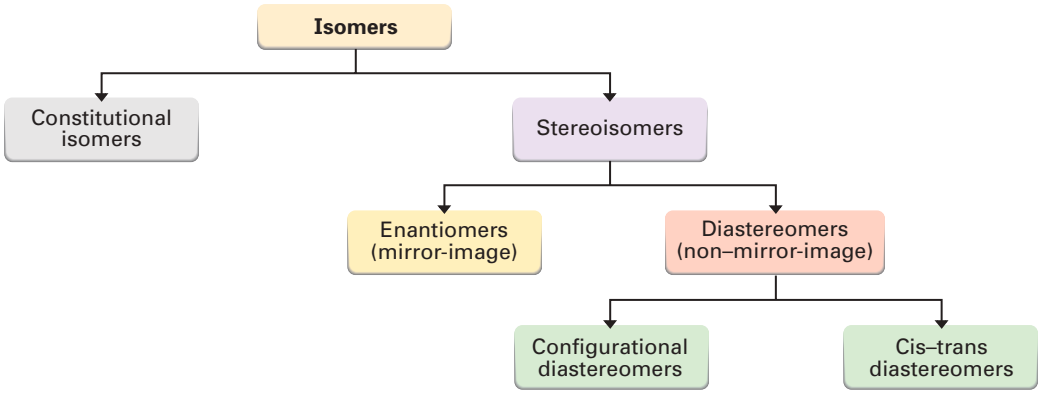
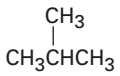


Figure 6.14 A summary of the different kinds of isomers.

There are two fundamental types of isomerism, both of which we've now encountered: constitutional isomerism and stereoisomerism.

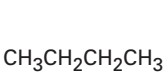
- **Constitutional isomers** (Section 2.2) are compounds whose atoms are connected differently. Among the kinds of constitutional isomers we've seen are skeletal, functional, and positional isomers.

Different carbon skeletons



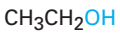
2-Methylpropane

and



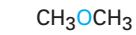
Butane

Different functional groups



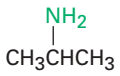
Ethyl alcohol

and



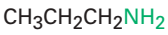
Dimethyl ether

Different position of functional groups



Isopropylamine

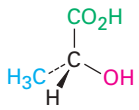
and



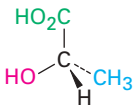
Propylamine

- **Stereoisomers** (Section 2.8) are compounds whose atoms are connected in the same way but with a different spatial arrangement. Among the kinds of stereoisomers we've seen are enantiomers, diastereomers, and cis–trans isomers (both in alkenes and in cycloalkanes). Actually, cis–trans isomers are just special kinds of diastereomers because they are non–mirror-image stereoisomers.

Enantiomers (nonsuperimposable mirror-image stereoisomers)



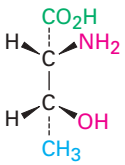
(*R*)-Lactic acid



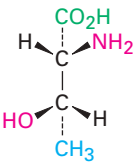
(*S*)-Lactic acid

Diastereomers (nonsuperimposable non–mirror-image stereoisomers)

Configurational diastereomers

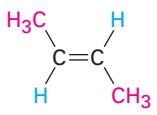


2*R*,3*R*-2-Amino-3-hydroxybutanoic acid



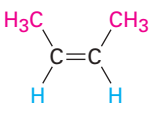
2*R*,3*S*-2-Amino-3-hydroxybutanoic acid

Cis–trans diastereomers (substituents on same side or opposite side of double bond or ring)

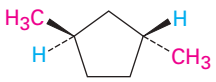


***trans*-But-2-ene**

and

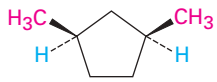


***cis*-But-2-ene**



***trans*-1,3-Dimethylcyclopentane**

and



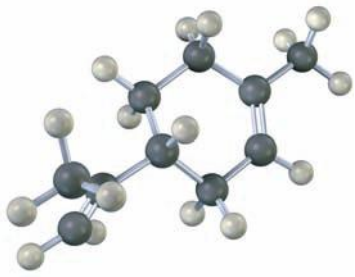
***cis*-1,3-Dimethylcyclopentane**

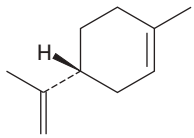
Problem 6.20 What kinds of isomers are the following pairs?

(a) (*S*)-5-Chlorohex-2-ene and chlorocyclohexane
(b) (2*R*,3*R*)-Dibromopentane and (2*S*,3*R*)-dibromopentane

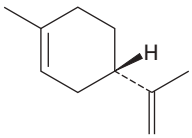
6.10 Chirality in Nature and Chiral Environments

Although the different enantiomers of a chiral molecule have the same physical properties, they almost always 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.

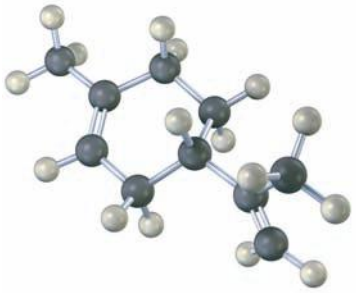




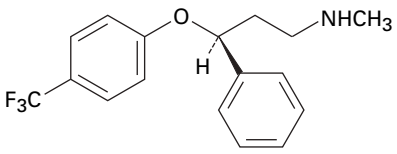
(+)-Limonene
(in citrus fruits)



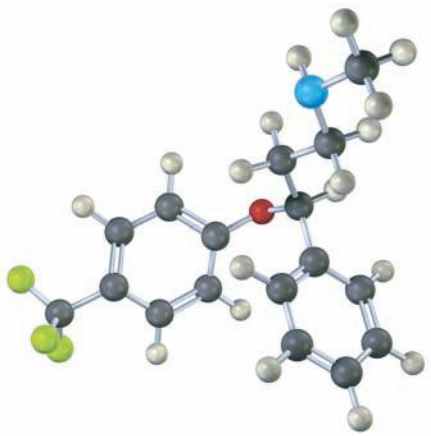
(−)-Limonene
(in pine trees)



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 it 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 the *Interlude* "Chiral Drugs" 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 in the body 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 will fit into a 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 6.15. One enantiomer fits the receptor perfectly, but the other does not.

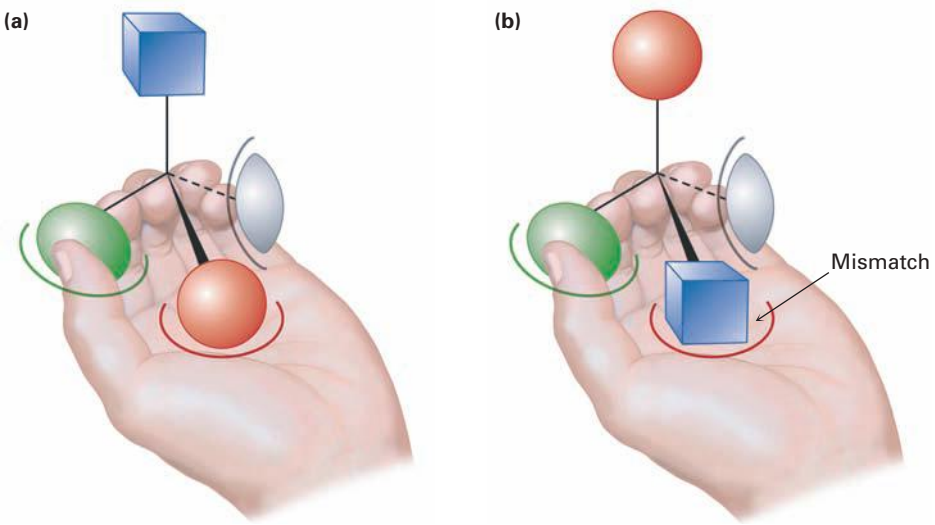


Figure 6.15 Imagine that a left hand interacts with a chiral object, much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: green thumb, red palm, and gray pinkie finger, with the blue substituent exposed. **(b)** The other enantiomer, however, 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 selective reactions can also occur on achiral molecules. Take the reaction of ethanol (CH_3CH_2OH) with the biochemical oxidizing agent NAD^+ and the enzyme yeast alcohol dehydrogenase to yield acetaldehyde (CH_3CHO). Even though ethanol is achiral, the oxidation reaction occurs with specific removal of only one of the two apparently equivalent $-CH_2-$ hydrogen atoms (Figure 6.16a).

We can understand this result by imagining that the chiral receptor on yeast alcohol dehydrogenase again has three binding sites (Figure 6.16b). When an achiral substrate interacts with the receptor, green (OH) and gray (CH_3) substituents of the substrate are held appropriately but only the blue (H_b) hydrogen substituent is also held while the red hydrogen (H_a) is specifically exposed for removal in the oxidation reaction.

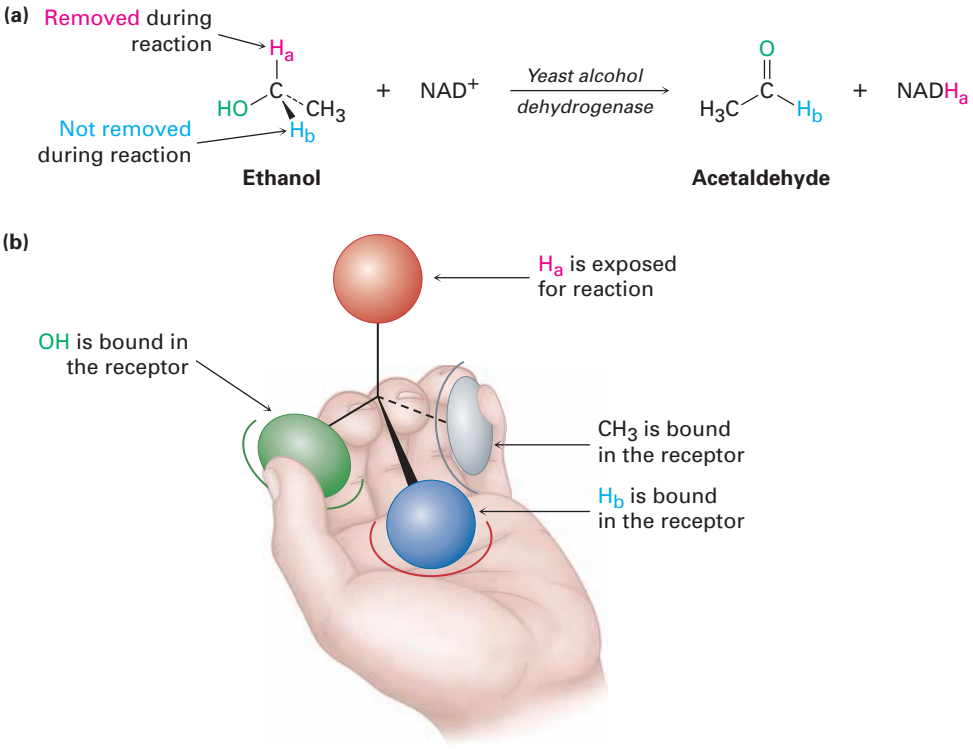


Figure 6.16 When the achiral substrate molecule ethanol is held in a chiral environment on binding to a biological receptor, the two seemingly identical hydrogens are distinguishable. Thus, only a specific hydrogen (red) is removed in an oxidation reaction.

We describe the situation by saying that the receptor provides a **chiral environment** for the substrate. In the absence of a chiral environment, the red and blue hydrogens are chemically identical, but in the presence of the chiral environment, they are chemically distinctive (Figure 6.16b) so that only one of them (red) is exposed for reaction. In effect, the chiral environment transfers its own chirality to the achiral substrate.

INTERLUDE

Chiral Drugs

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, but an estimated 33% are made entirely in the laboratory and have no relatives in nature.

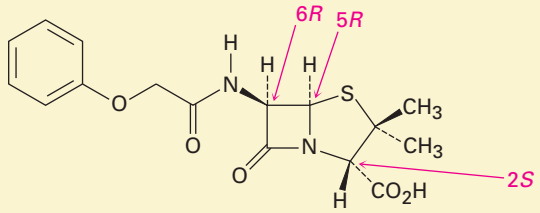
Those drugs that come from natural sources, either directly or after chemical modification, are usually chiral and are generally found only as a single enantiomer rather than as a racemate. Penicillin V, for example, an antibiotic isolated from the *Penicillium* mold, has the 2*S*,5*R*,6*R* configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.

continued

INTERLUDE

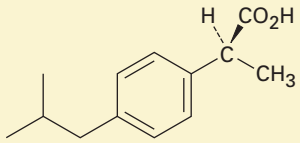
Heath Robbins/Photonica/Getty Images

The *S* enantiomer of ibuprofen soothes the aches and pains of athletic injuries. The *R* enantiomer has no effect.

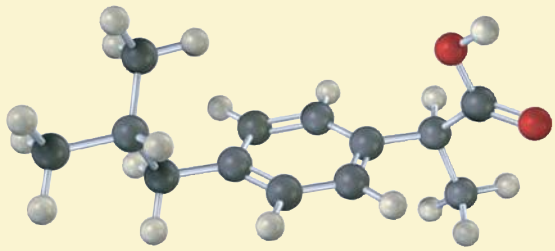


Penicillin V (2*S*,5*R*,6*R* configuration)

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 racemic mixtures. 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* enantiomers. It turns out, however, that only 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.

Summary and Key Words

achiral 193
chiral 191
chiral environment 212
chirality center 191
configuration 197
dextrorotatory 195
diastereomers 202
enantiomers 190
levorotatory 195
meso compound 205
optical activity 195
R configuration 198
racemate (racemic mixture) 206
resolution 206
S configuration 198
specific rotation, $[\alpha]_D$ 196

In this chapter, we've looked at some of the causes and consequences of molecular handedness—a topic crucial to understanding organic and biological chemistry. The subject can be a bit complex, but it is so important that it's worthwhile spending the time needed to become familiar with it.

A molecule that is not identical to its mirror image is said to be **chiral**, meaning "handed." A chiral molecule is one that does not contain a plane of symmetry. The usual cause of chirality is the presence of a tetrahedral carbon atom bonded to four different groups—a so-called **chirality center**. Chiral compounds can exist as a pair of mirror-image stereoisomers called **enantiomers**, which are related to each other as a right hand is related to a left hand. When a beam of plane-polarized light is passed through a solution of a pure enantiomer, the plane of polarization is rotated, and the compound is said to be **optically active**.

The three-dimensional **configuration** of a chirality center is specified as either ***R*** or ***S*.** Sequence rules are used to rank the four substituents on the chiral carbon, and the molecule is then oriented so that the lowest-ranked group points directly away from the viewer. If a curved arrow drawn in the direction of decreasing rank 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 configurations at all chirality centers, whereas **diastereomers** have the same configuration in at least one center but opposite configurations at the others. **Meso compounds** contain chirality centers but are achiral overall because they contain a plane of symmetry. **Racemates** are 50:50 mixtures of (+) and (−) enantiomers. Racemic mixtures and individual diastereomers differ in both their physical properties and their biological properties and can often be **resolved**.

Exercises

Visualizing Chemistry

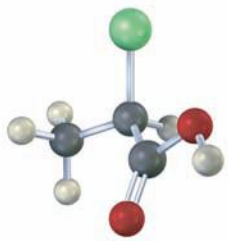
(Problems 6.1–6.20 appear within the chapter.)

OWL

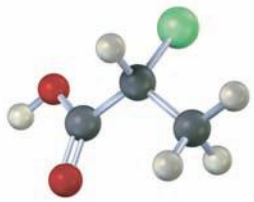
Interactive versions of these problems are assignable in OWL.

6.21 Which of the following structures are identical? (Red = O, yellow-green = Cl.)

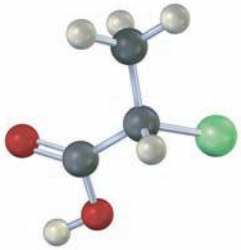
(a)



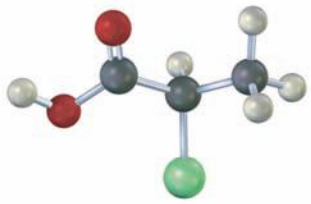
(b)



(c)

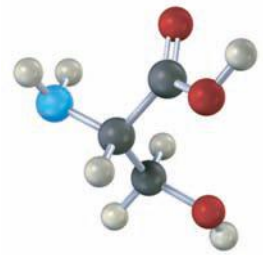


(d)



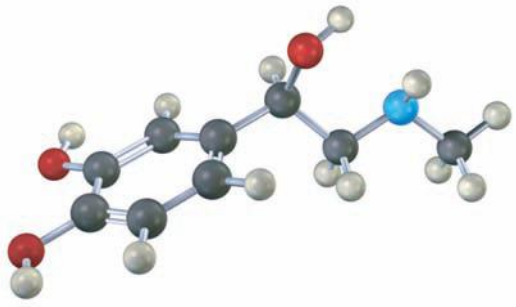
6.22 Assign *R* or *S* configuration to the chirality centers in the following molecules (red = O, blue = N):

(a)



Serine

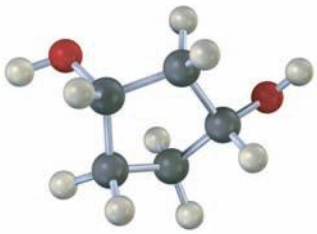
(b)



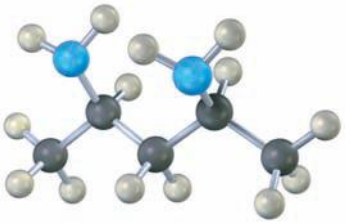
Adrenaline

6.23 Which, if any, of the following structures represent meso compounds? (Red = O, blue = N, yellow-green = Cl.)

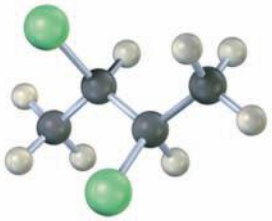
(a)



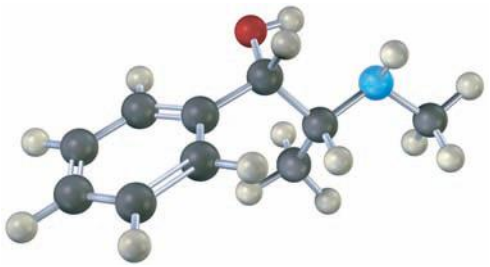
(b)



(c)

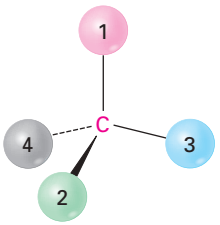


6.24 Assign *R* or *S* configuration to each chirality center in pseudoephedrine, an over-the-counter decongestant found in cold remedies (red = O, blue = N).

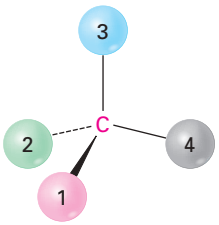


6.25 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

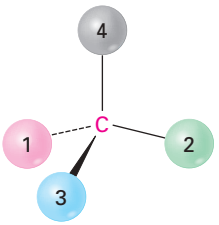
(a)



(b)



(c)



Additional Problems

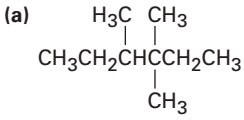
Identifying Chirality Centers

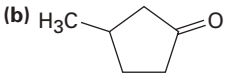
6.26 Which of the following objects are chiral?
(a) A basketball **(b)** A fork **(c)** A wine glass
(d) A golf club **(e)** A monkey wrench **(f)** A snowflake

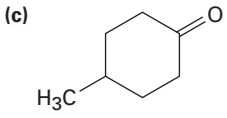
6.27 Which of the following compounds are chiral?
(a) 2,4-Dimethylheptane **(b)** 5-Ethyl-3,3-dimethylheptane
(c) *cis*-1,3-Dimethylcyclohexane **(d)** 4,5-Dimethylocta-2,6-diene

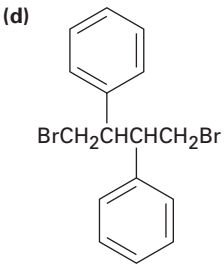
6.28 Draw chiral molecules that meet the following descriptions:
(a) A chloroalkane, $C_5H_{11}Cl$ **(b)** An alcohol, $C_6H_{14}O$
(c) An alkene, C_6H_{12} **(d)** An alkane, C_8H_{18}

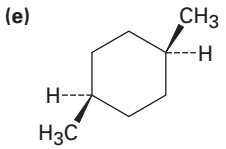
6.29 Which of the following compounds are chiral? Label all chirality centers.

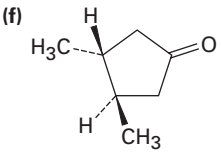








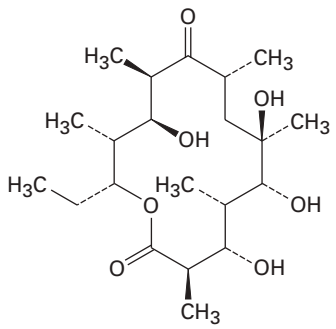




6.30 There are eight alcohols with the formula $C_5H_{12}O$. Draw them, and tell which are chiral.

6.31 Propose structures for compounds that meet the following descriptions:
(a) A chiral alcohol with four carbons
(b) A chiral carboxylic acid
(c) A compound with two chirality centers

6.32 Erythronolide B, the biological precursor of the broad-spectrum antibiotic erythromycin, has ten chirality centers. Identify them with asterisks.



Erythronolide B

Optical Activity

6.33 Cholic acid, the major steroid found in bile, was found to have a rotation of +2.22° when a 3.00 g sample was dissolved in 5.00 mL of alcohol in a sample tube with a 1.00 cm pathlength. Calculate $[\alpha]_D$ for cholic acid.

6.34 Polarimeters are so sensitive that they can measure rotations to the thousandth of a degree, an important advantage when only small amounts of a sample are available. For example, when 7.00 mg of ecdysone, an insect hormone that controls molting in the silkworm moth, was dissolved in 1.00 mL of chloroform in a cell with a 2.00 cm pathlength, an observed rotation of +0.087° was found. Calculate $[\alpha]_D$ for ecdysone.

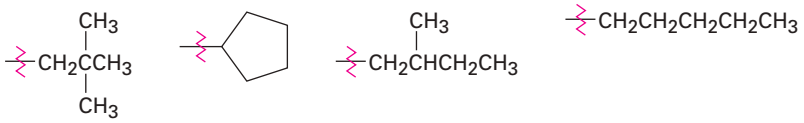
6.35 Naturally occurring (*S*)-serine has $[\alpha]_D = -6.83$. What specific rotation do you expect for (*R*)-serine?

Assigning *R,S* Configuration to Chirality Centers

6.36 Rank the substituents in each of the following sets:
(a) –H, –OH, $-OCH_3$, $-CH_3$
(b) –Br, $-CH_3$, $-CH_2Br$, –Cl
(c) $-CH{=}CH_2$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_3$
(d) $-CO_2CH_3$, $-COCH_3$, $-CH_2OCH_3$, $-OCH_3$

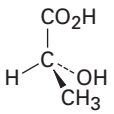
6.37 Rank the substituents in each of the following sets:

(a)

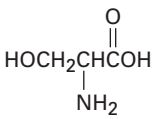


(b)

6.38 One enantiomer of lactic acid is shown below. Is it *R* or *S*? Draw its mirror image in the standard tetrahedral representation.



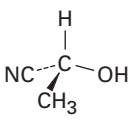
6.39 Draw tetrahedral representations of both enantiomers of the amino acid serine. Tell which of your structures is *S* and which is *R*.



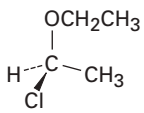
Serine

6.40 Assign *R* or *S* configuration to the chirality centers in the following molecules:

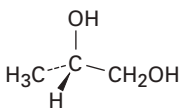
(a)



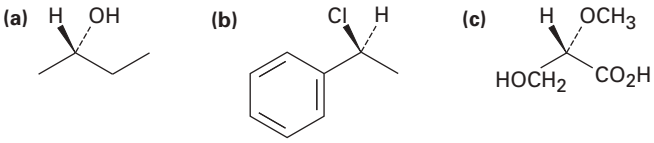
(b)



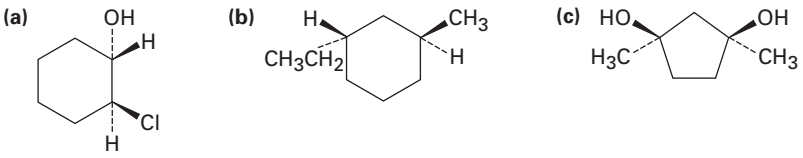
(c)



6.41 Assign *R* or *S* configuration to the chirality centers in the following molecules:



6.42 Assign *R* or *S* configuration to each chirality center in the following biological molecules:



Stereochemical Relationships

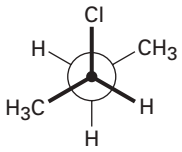
6.43 What is the relationship between the specific rotations of (2*R*,3*R*)-pentane-2,3-diol and (2*S*,3*S*)-pentane-2,3-diol? Between (2*R*,3*S*)-pentane-2,3-diol and (2*R*,3*R*)-pentane-2,3-diol?

6.44 What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-dibromooctane?

6.45 What are the stereochemical configurations of the two diastereomers of (2*S*,4*R*)-dibromooctane?

6.46 Draw examples of the following:
(a) A meso compound with the formula C_8H_{18}
(b) A compound with two chirality centers, one *R* and the other *S*

6.47 Tell whether the following Newman projection of 2-chlorobutane is *R* or *S*. (You might want to review Section 2.5.)



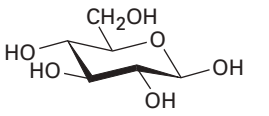
6.48 Draw a Newman projection that is enantiomeric with the one shown in Problem 6.47.

6.49 Draw a Newman projection of *meso*-tartaric acid.

6.50 Draw Newman projections of (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acid, and compare them to the projection you drew in Problem 6.49 for the meso form.

General Problems

6.51 β-Glucose has the following structure. Identify the chirality centers in β-glucose, and tell how many stereoisomers of glucose are possible.



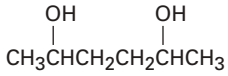
β-Glucose

6.52 Draw a tetrahedral representation of (*R*)-3-chloropent-1-ene.

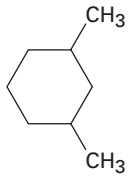
6.53 Draw the two cis–trans stereoisomers of 1,2-dimethylcyclopentane, assign *R*,*S* configurations to the chirality centers, and indicate whether the stereoisomers are chiral or meso.

6.54 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:

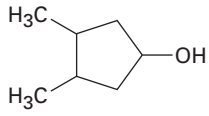
(a)



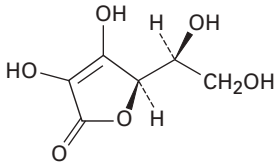
(b)



(c)

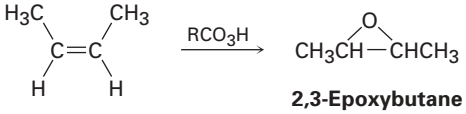


6.55 Assign *R* or *S* configuration to the chirality centers in ascorbic acid (vitamin C).



Ascorbic acid

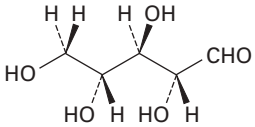
6.56 We saw in Section 4.6 that alkenes undergo reaction with peroxycarboxylic acids to give epoxides. For example, *cis*-but-2-ene gives 2,3-epoxybutane:



2,3-Epoxybutane

Assuming that both C–O bonds form from the same side of the double bond (syn stereochemistry; Section 4.5), show the stereochemistry of the product. Is the epoxide chiral? Is it optically active?

6.57 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:



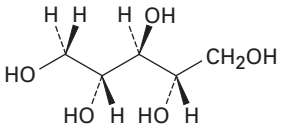
Ribose

How many chirality centers does ribose have? Identify them with asterisks. How many stereoisomers of ribose are there?

6.58 Draw the structure of the enantiomer of ribose (Problem 6.57).

6.59 Draw the structure of a diastereomer of ribose (Problem 6.57).

6.60 On catalytic hydrogenation over a platinum catalyst, ribose (Problem 6.57) is converted into ribitol. Is ribitol optically active or inactive? Explain.

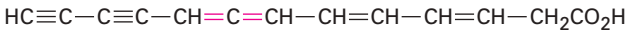


Ribitol

6.61 Draw the structure of (*R*)-2-methylcyclohexanone.

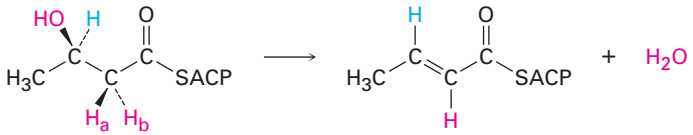
6.62 Compound **A**, C_7H_{14}, is optically active. On catalytic reduction over a palladium catalyst, 1 equivalent of H_2 is absorbed, yielding compound **B**, C_7H_{16}. On cleavage of **A** with acidic $KMnO_4$, two fragments are obtained. One fragment is acetic acid, CH_3CO_2H, and the other fragment, **C**, is an optically active carboxylic acid. Show the reactions, and propose structures for **A**, **B**, and **C**.

6.63 *Allenes* are compounds with adjacent C=C bonds. Even though they don't contain chirality centers, many allenes are chiral. For example, mycomycin, an antibiotic isolated from the bacterium *Nocardia acidophilus,* is chiral and has $[\alpha]_D = -130$. Can you explain why mycomycin is chiral? Making a molecular model should be helpful.



Mycomycin

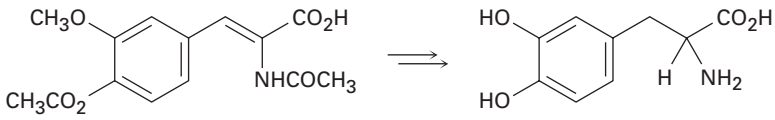
6.64 One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotonyl ACP. The reaction occurs with anti stereochemistry, meaning that the OH and H groups lost during the reaction depart from opposite sides of the molecule. Which hydrogen is lost, H_a or H_b?



(*R*)-3-Hydroxybutyryl ACP **trans-Crotonyl ACP**

IN THE MEDICINE CABINET

6.65 Compound **A** is a precursor used for synthesizing dopa, whose *S* isomer is used in treating Parkinson's disease.



A **Dopa**

(a) The first step in the synthesis is catalytic hydrogenation of the carbon–carbon double bond in **A** to yield two enantiomeric hydrogenation products. Draw them, and assign *R*,*S* configuration to each.

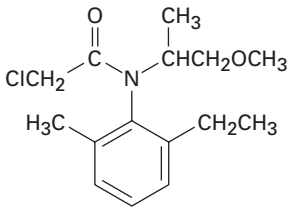
(b) Following hydrogenation, several additional transformations are carried out to yield dopa. Do you expect the enantiomers of dopa to have similar physical properties?

(c) Do you expect the enantiomers of dopa to perform equally well as drugs?

(d) The Monsanto process, commercialized in 1974, carries out the double-bond hydrogenation using a chiral catalyst that produces only a single enantiomer, which is subsequently converted into (*S*)-dopa. Show the stereochemistry of (*S*)-dopa, and explain how a chiral hydrogenation catalyst can produce a single enantiomer as product.

IN THE FIELD

6.66 Metolachlor, a herbicide previously encountered in Problems 2.74 and 5.61, kills weeds by inhibiting the enzyme fatty-acid elongase, which is needed to make a waxy coating on plant leaves. With the enzyme activity inhibited, the wax is not produced and the weed dies.



Metolachlor

(a) Only the *S* enantiomer of metolachlor inhibits fatty-acid elongase. Draw it.

(b) Why do the *R* and *S* enantiomers have different activities?