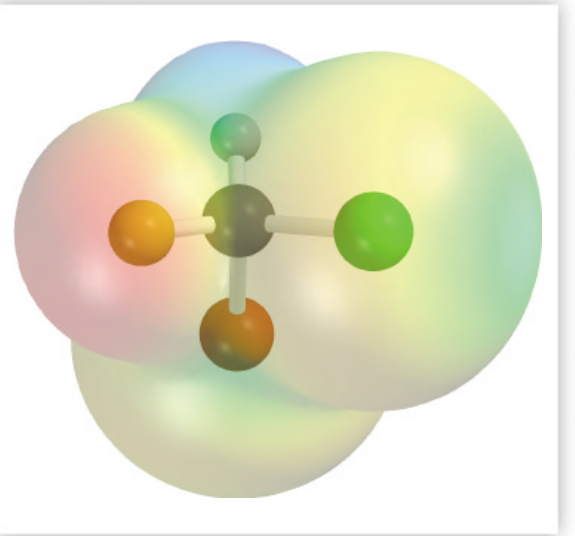


CHAPTER 7

STEREOCHEMISTRY

The Greek word *stereos* means "solid," and *stereochemistry* refers to chemistry in three dimensions. The foundations of organic stereochemistry were laid by Jacobus van't Hoff* and Joseph Achille Le Bel in 1874. Independently of each other, van't Hoff and Le Bel proposed that the four bonds to carbon were directed toward the corners of a tetrahedron. One consequence of a tetrahedral arrangement of bonds to carbon is that two compounds may be different because the arrangement of their atoms in space is different. Isomers that have the same constitution but differ in the spatial arrangement of their atoms are called **stereoisomers.** We have already had considerable experience with certain types of stereoisomers—those involving cis and trans substitution patterns in alkenes and in cycloalkanes.

Our major objectives in this chapter are to develop a feeling for molecules as three-dimensional objects and to become familiar with stereochemical principles, terms, and notation. A full understanding of organic and biological chemistry requires an awareness of the spatial requirements for interactions between molecules; this chapter provides the basis for that understanding.

7.1 MOLECULAR CHIRALITY: ENANTIOMERS

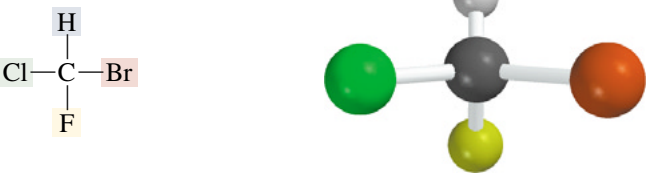
Everything has a mirror image, but not all things are superposable on their mirror images. Mirror-image superposability characterizes many objects we use every day. Cups and saucers, forks and spoons, chairs and beds are all identical with their mirror images. Many other objects though—and this is the more interesting case—are not. Your left hand and your right hand, for example, are mirror images of each other but can't be made to coincide point for point, palm to palm, knuckle to knuckle, in three dimensions. In 1894, William

*Van't Hoff was the recipient of the first Nobel Prize in chemistry in 1901 for his work in chemical dynamics and osmotic pressure—two topics far removed from stereochemistry.

Thomson (Lord Kelvin) coined a word for this property. He defined an object as **chiral** if it is not superposable on its mirror image. Applying Thomson's term to chemistry, we say that a *molecule is chiral if its two mirror-image forms are not superposable in three dimensions.* The work "chiral" is derived from the Greek word *cheir,* meaning "hand," and it is entirely appropriate to speak of the "handedness" of molecules. The opposite of chiral is **achiral.** A molecule that *is* superposable on its mirror image is achiral.

In organic chemistry, chirality most often occurs in molecules that contain a carbon that is attached to four different groups. An example is bromochlorofluoromethane (BrClFCH).

Bromochlorofluoromethane is a known compound, and samples selectively enriched in each enantiomer have been described in the chemical literature. In 1989 two chemists at Polytechnic University (Brooklyn, New York) described a method for the preparation of BrClFCH that is predominantly one enantiomer.



Bromochlorofluoromethane

As shown in Figure 7.1, the two mirror images of bromochlorofluoromethane cannot be superposed on each other. *Since the two mirror images of bromochlorofluoromethane are not superposable, BrClFCH is chiral.*

The two mirror images of bromochlorofluoromethane have the same constitution. That is, the atoms are connected in the same order. But they differ in the arrangement of their atoms in space; they are **stereoisomers.** Stereoisomers that are related as an object and its nonsuperposable mirror image are classified as **enantiomers.** The word "enantiomer" describes a particular relationship between two objects. One cannot look at a single molecule in isolation and ask if it is an enantiomer any more than one can look at an individual human being and ask, "Is that person a cousin?" Furthermore, just as an object has one, and only one, mirror image, a chiral molecule can have one, and only one, enantiomer.

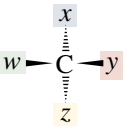
Notice in Figure 7.1*c,* where the two enantiomers of bromochlorofluoromethane are similarly oriented, that the difference between them corresponds to an interchange of the positions of bromine and chlorine. It will generally be true for species of the type C*(w, x, y, z),* where *w, x, y,* and *z* are different atoms or groups, that an exchange of two of them converts a structure to its enantiomer, but an exchange of three returns the original structure, albeit in a different orientation.

Consider next a molecule such as chlorodifluoromethane (ClF_2CH), in which two of the atoms attached to carbon are the same. Figure 7.2 on page 262 shows two molecular models of ClF_2CH drawn so as to be mirror images. As is evident from these drawings, it is a simple matter to merge the two models so that all the atoms match. *Since mirror-image representations of chlorodifluoromethane are superposable on each other, ClF_2CH is achiral.*

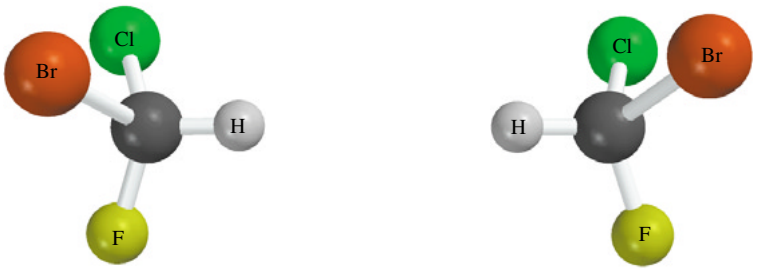
The surest test for chirality is a careful examination of mirror-image forms for superposability. Working with models provides the best practice in dealing with molecules as three-dimensional objects and is strongly recommended.

7.2 THE STEREOGENIC CENTER

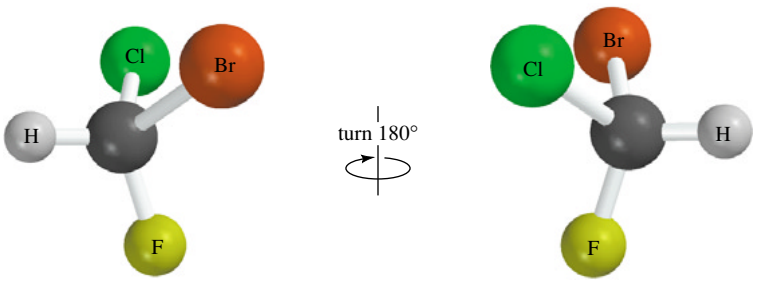
As we've just seen, molecules of the general type



(*a*) Structures A and B are mirror-image representations of bromochlorofluoromethane (BrClFCH).



(*b*) To test for superposability, reorient B by turning it 180°.



(*c*) Compare A and B. The two do not match. A and B cannot be superposed on each other. Bromochlorofluoromethane is therefore a chiral molecule. The two mirror-image forms are enantiomers of each other.

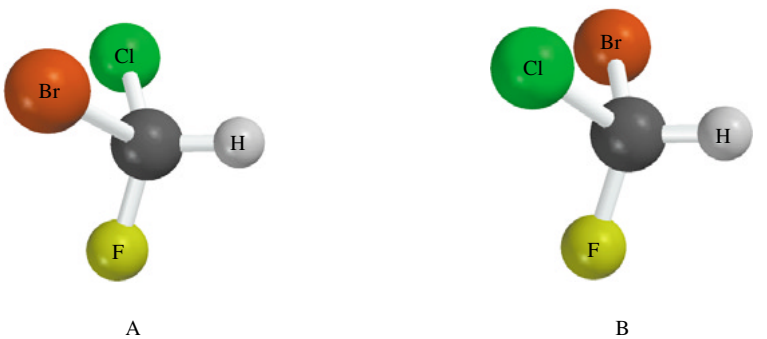


FIGURE 7.1 A molecule with four different groups attached to a single carbon is chiral. Its two mirror-image forms are not superposable.

are chiral when *w, x, y,* and *z* are different substituents. A tetrahedral carbon atom that bears four different substituents is variously referred to as a *chiral center,* a *chiral carbon atom,* an *asymmetric center,* or an *asymmetric carbon atom.* A more modern term is **stereogenic center,** and that is the term that we'll use. (*Stereocenter* is synonymous with *stereogenic center.*)

An article in the December 1987 issue of the *Journal of Chemical Education* gives a thorough discussion of molecular chirality and some of its past and present terminology.

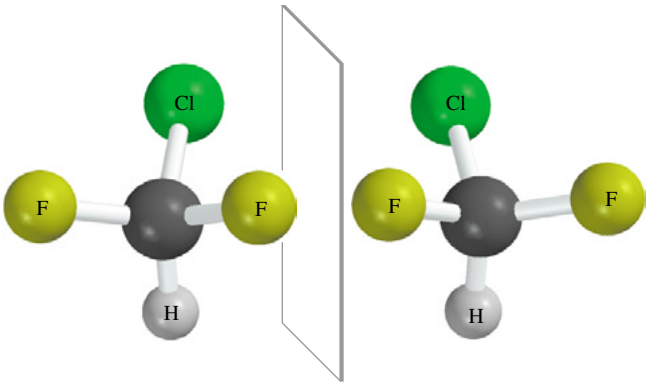
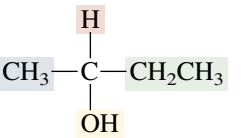
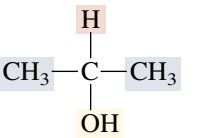


FIGURE 7.2 Mirror-image forms of chlorodifluoromethane are superposable on each other. Chlorodifluoromethane is achiral.

Noting the presence of one (but not more than one) stereogenic center in a molecule is a simple, rapid way to determine that it is chiral. For example, C-2 is a stereogenic center in 2-butanol; it bears a hydrogen atom and methyl, ethyl, and hydroxyl groups as its four different substituents. By way of contrast, none of the carbon atoms bear four different groups in the achiral alcohol 2-propanol.



2-Butanol
Chiral; four different substituents at C-2

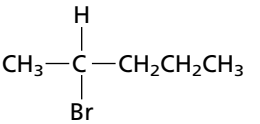


2-Propanol
Achiral; two of the substituents at C-2 are the same

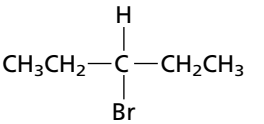
PROBLEM 7.1 Examine the following for stereogenic centers:

(a) 2-Bromopentane
(b) 3-Bromopentane
(c) 1-Bromo-2-methylbutane
(d) 2-Bromo-2-methylbutane

SAMPLE SOLUTION A stereogenic carbon has four different substituents. (a) In 2-bromopentane, C-2 satisfies this requirement. (b) None of the carbons in 3-bromopentane have four different substituents, and so none of its atoms are stereogenic centers.

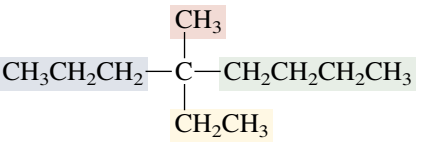


2-Bromopentane

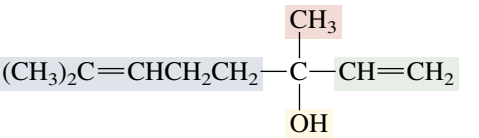


3-Bromopentane

Molecules with stereogenic centers are very common, both as naturally occurring substances and as the products of chemical synthesis. (Carbons that are part of a double bond or a triple bond can't be stereogenic centers.)

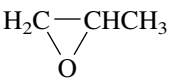


4-Ethyl-4-methyloctane
(a chiral alkane)

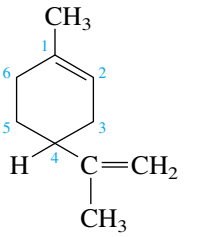


Linalool
(a pleasant-smelling oil obtained from orange flowers)

A carbon atom in a ring can be a stereogenic center if it bears two different substituents and the path traced around the ring from that carbon in one direction is different from that traced in the other. The carbon atom that bears the methyl group in 1,2-epoxypropane, for example, is a stereogenic center. The sequence of groups is O—CH_2 as one proceeds clockwise around the ring from that atom, but is CH_2—O in the anticlockwise direction. Similarly, C-4 is a stereogenic center in limonene.



1-2-Epoxypropane
(product of epoxidation of propene)



Limonene
(a constituent of lemon oil)

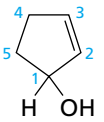
Examine the molecular models of the two enantiomers of 1,2-epoxypropane on *Learning By Modeling* and test them for superposability.

PROBLEM 7.2 Identify the stereogenic centers, if any, in

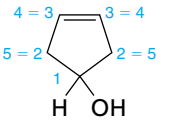
(a) 2-Cyclopenten-1-ol and 3-cyclopenten-1-ol

(b) 1,1,2-Trimethylcyclobutane and 1,1,3-Trimethylcyclobutane

SAMPLE SOLUTION (a) The hydroxyl-bearing carbon in 2-cyclopenten-1-ol is a stereogenic center. There is no stereogenic center in 3-cyclopenten-1-ol, since the sequence of atoms 1 → 2 → 3 → 4 → 5 is equivalent regardless of whether one proceeds clockwise or anticlockwise.

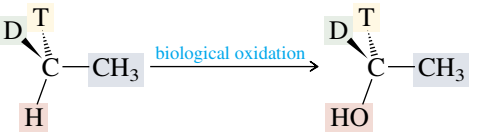


2-Cyclopenten-1-ol



3-Cyclopenten-1-ol
(does not have a stereogenic carbon)

Even isotopes qualify as different substituents at a stereogenic center. The stereochemistry of biological oxidation of a derivative of ethane that is chiral because of deuterium (D = ^{2}H) and tritium (T = ^{3}H) atoms at carbon, has been studied and shown to proceed as follows:



The stereochemical relationship between the reactant and the product, revealed by the isotopic labeling, shows that oxygen becomes bonded to carbon on the same side from which H is lost.

One final, very important point about stereogenic centers. *Everything we have said in this section concerns molecules that have one and only one stereogenic center; molecules with more than one stereogenic center may or may not be chiral.* Molecules that have more than one stereogenic center will be discussed in Sections 7.10 through 7.13.

7.3 SYMMETRY IN ACHIRAL STRUCTURES

Certain structural features can sometimes help us determine by inspection whether a molecule is chiral or achiral. For example, a molecule that has a *plane of symmetry* or a *center of symmetry* is superposable on its mirror image and is achiral.

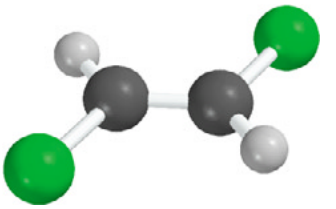
A **plane of symmetry** bisects a molecule so that one half of the molecule is the mirror image of the other half. The achiral molecule chlorodifluoromethane, for example, has the plane of symmetry shown in Figure 7.3.

A point in a molecule is a **center of symmetry** if any line drawn from it to some element of the structure will, when extended an equal distance in the opposite direction, encounter an identical element. The cyclobutane derivative in Figure 7.4 lacks a plane of symmetry, yet is achiral because it possesses a center of symmetry.

PROBLEM 7.3 Locate any planes of symmetry or centers of symmetry in each of the following compounds. Which of the compounds are chiral? Which are achiral?

(a) (*E*)-1,2-Dichloroethene
(b) (*Z*)-1,2,Dichloroethene
(c) *cis*-1,2-Dichlorocyclopropane
(d) *trans*-1,2-Dichlorocyclopropane

SAMPLE SOLUTION (a) (*E*)-1,2-Dichloroethene is planar. The molecular plane is a plane of symmetry.



Furthermore, (*E*)-1,2-dichloroethene has a center of symmetry located at the midpoint of the carbon–carbon double bond. It is achiral.

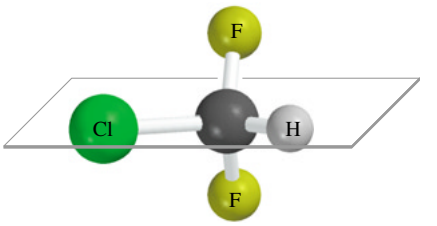


FIGURE 7.3 A plane of symmetry defined by the atoms H—C—Cl divides chlorodifluoromethane into two mirror-image halves.

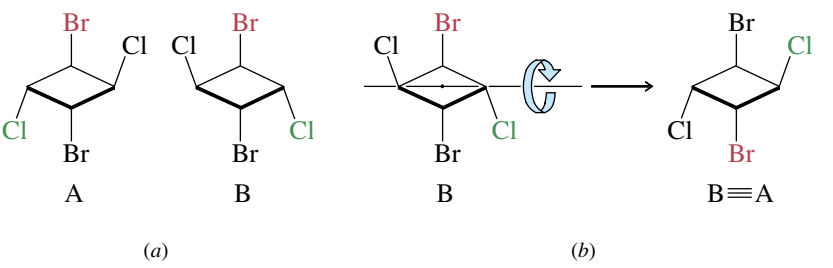


FIGURE 7.4 (*a*) Structural formulas A and B are drawn as mirror images. (*b*) The two mirror images are superposable by rotating form B 180° about an axis passing through the center of the molecule. The center of the molecule is a center of symmetry.

Any molecule with a plane of symmetry or a center of symmetry is achiral, but their absence is not sufficient for a molecule to be chiral. A molecule lacking a center of symmetry or a plane of symmetry is *likely* to be chiral, but the superposability test should be applied to be certain.

7.4 PROPERTIES OF CHIRAL MOLECULES: OPTICAL ACTIVITY

The phenomenon of optical activity was discovered by the French physicist Jean-Baptiste Biot in 1815.

The experimental facts that led van't Hoff and Le Bel to propose that molecules having the same constitution could differ in the arrangement of their atoms in space concerned the physical property of **optical activity.** Optical activity is the ability of a chiral substance to rotate the plane of **plane-polarized light** and is measured using an instrument called a **polarimeter.** (Figure 7.5).

The light used to measure optical activity has two properties: it consists of a single wavelength and it is plane-polarized. The wavelength used most often is 589 nm (called the *D line*), which corresponds to the yellow light produced by a sodium lamp. Except for giving off light of a single wavelength, a sodium lamp is like any other lamp in that its light is unpolarized, meaning that the plane of its electric field vector can have any orientation along the line of travel. A beam of unpolarized light is transformed to plane-polarized light by passing it through a polarizing filter, which removes all the waves except those that have their electric field vector in the same plane. This plane-polarized light now passes through the sample tube containing the substance to be examined, either in the liquid phase or as a solution in a suitable solvent (usually water, ethanol, or chloroform). The sample is "optically active" if it rotates the plane of polarized light. The direction and magnitude of rotation are measured using a second polarizing filter (the "analyzer") and cited as α, the observed rotation.

To be optically active, the sample must contain a chiral substance and one enantiomer must be present in excess of the other. A substance that does not rotate the plane of polarized light is said to be optically inactive. *All achiral substances are optically inactive.*

What causes optical rotation? The plane of polarization of a light wave undergoes a minute rotation when it encounters a chiral molecule. Enantiomeric forms of a chiral molecule cause a rotation of the plane of polarization in exactly equal amounts but in

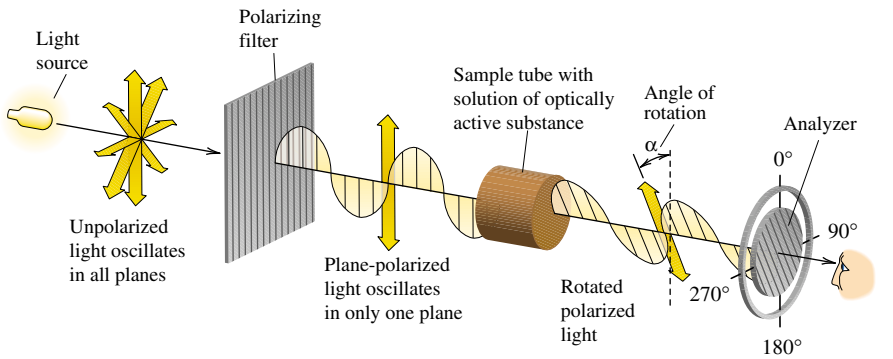


FIGURE 7.5 The sodium lamp emits light moving in all planes. When the light passes through the first polarizing filter, only one plane emerges. The plane-polarized beam enters the sample compartment, which contains a solution enriched in one of the enantiomers of a chiral substance. The plane rotates as it passes through the solution. A second polarizing filter (called the analyzer) is attached to a movable ring calibrated in degrees that is used to measure the angle of rotation α.
(Adapted from M. Silberberg, Chemistry, *2d edition, McGraw-Hill Higher Education, New York, 1992, p. 616.)*

opposite directions. A solution containing equal quantities of enantiomers therefore exhibits no net rotation because all the tiny increments of clockwise rotation produced by molecules of one "handedness" are canceled by an equal number of increments of anticlockwise rotation produced by molecules of the opposite handedness.

Mixtures containing equal quantities of enantiomers are called **racemic mixtures.** Racemic mixtures are optically inactive. Conversely, when one enantiomer is present in excess, a net rotation of the plane of polarization is observed. At the limit, where all the molecules are of the same handedness, we say the substance is **optically pure.** Optical purity, or *percent enantiomeric excess,* is defined as:

$$\begin{aligned}\text{Optical purity} &= \text{percent enantiomeric excess}\\ &= \text{percent of one enantiomer} - \text{percent of other enantiomer}\end{aligned}$$

Thus, a material that is 50% optically pure contains 75% of one enantiomer and 25% of the other.

Rotation of the plane of polarized light in the clockwise sense is taken as positive (+), and rotation in the anticlockwise sense is taken as a negative (−) rotation. The classical terms for positive and negative rotations are *dextrorotatory* and *levorotatory,* from the Latin prefixes *dextro-* ("to the right") and *levo-* ("to the left"), respectively. At one time, the symbols *d* and *l* were used to distinguish between enantiomeric forms of a substance. Thus the dextrorotatory enantiomer of 2-butanol was called *d*-2-butanol, and the levorotatory form *l*-2-butanol; a racemic mixture of the two was referred to as *dl*-2-butanol. Current custom favors using algebraic signs instead, as in (+)-2-butanol, (−)-2-butanol, and (±)-2-butanol, respectively.

The observed rotation α of an optically pure substance depends on how many molecules the light beam encounters. A filled polarimeter tube twice the length of another produces twice the observed rotation, as does a solution twice as concentrated. To account for the effects of path length and concentration, chemists have defined the term **specific rotation,** given the symbol $[\alpha]$. Specific rotation is calculated from the observed rotation according to the expression

$$[\alpha] = \frac{100\alpha}{cl}$$

where c is the concentration of the sample in grams per 100 mL of solution, and l is the length of the polarimeter tube in decimeters. (One decimeter is 10 cm.)

If concentration is expressed as grams per milliliter of solution instead of grams per 100 mL, an equivalent expression is

$$[\alpha] = \frac{\alpha}{cl}$$

Specific rotation is a physical property of a substance, just as melting point, boiling point, density, and solubility are. For example, the lactic acid obtained from milk is exclusively a single enantiomer. We cite its specific rotation in the form $[\alpha]_D^{25} = +3.8°$. The temperature in degrees Celsius and the wavelength of light at which the measurement was made are indicated as superscripts and subscripts, respectively.

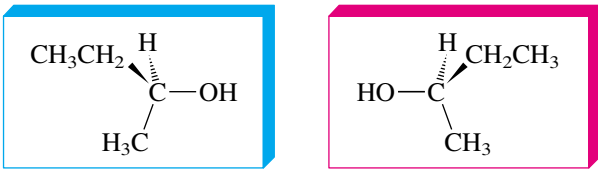
PROBLEM 7.4 Cholesterol, when isolated from natural sources, is obtained as a single enantiomer. The observed rotation α of a 0.3-g sample of cholesterol in 15 mL of chloroform solution contained in a 10-cm polarimeter tube is −0.78°. Calculate the specific rotation of cholesterol.

PROBLEM 7.5 A sample of synthetic cholesterol was prepared consisting entirely of the enantiomer of natural cholesterol. A mixture of natural and synthetic cholesterol has a specific rotation $[\alpha]_D^{20}$ of −13°. What fraction of the mixture is natural cholesterol?

It is convenient to distinguish between enantiomers by prefixing the sign of rotation to the name of the substance. For example, we refer to one of the enantiomers of 2-butanol as (+)-2-butanol and the other as (−)-2-butanol. Optically pure (+)-2-butanol has a specific rotation $[\alpha]_D^{27}$ of +13.5°; optically pure (−)-2-butanol has an exactly opposite specific rotation $[\alpha]_D^{27}$ of −13.5°.

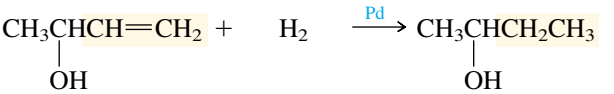
7.5 ABSOLUTE AND RELATIVE CONFIGURATION

The spatial arrangement of substituents at a stereogenic center is its **absolute configuration.** Neither the sign nor the magnitude of rotation by itself can tell us the absolute configuration of a substance. Thus, one of the following structures is (+)-2-butanol and the other is (−)-2-butanol, but without additional information we can't tell which is which.



In several places throughout the chapter we will use red and blue frames to call attention to structures that are enantiomeric.

Although no absolute configuration was known for any substance before 1951, organic chemists had experimentally determined the configurations of thousands of compounds relative to one another (their **relative configurations**) through chemical interconversion. To illustrate, consider (+)-3-buten-2-ol. Hydrogenation of this compound yields (+)-2-butanol.

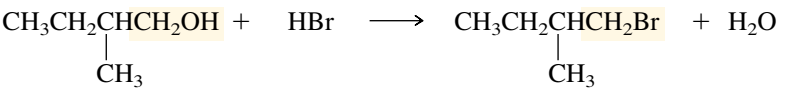


3-Buten-2-ol $[\alpha]_D^{27}$ +33.2° | Hydrogen | 2-Butanol $[\alpha]_D^{27}$ +13.5°

Make a molecular model of one of the enantiomers of 3-buten-2-ol and the 2-butanol formed from it.

Since hydrogenation of the double bond does not involve any of the bonds to the stereogenic center, the spatial arrangement of substituents in (+)-3-buten-2-ol must be the same as that of the substituents in (+)-2-butanol. The fact that these two compounds have the same sign of rotation when they have the same relative configuration is established by the hydrogenation experiment; it could not have been predicted in advance of the experiment.

Sometimes compounds that have the same relative configuration have optical rotations of opposite sign. For example, treatment of (−)-2-methyl-1-butanol with hydrogen bromide converts it to (+)-1-bromo-2-methylbutane.

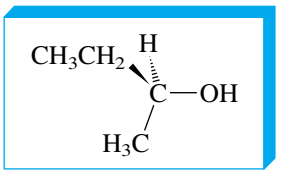


2-Methyl-1-butanol $[\alpha]_D^{25}$ −5.8° | Hydrogen bromide | 1-Bromo-2-methylbutane $[\alpha]_D^{25}$ +4.0° | Water

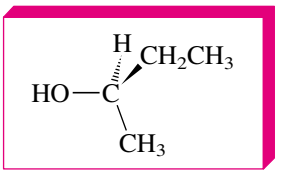
Make a molecular model of one of the enantiomers of 2-methyl-1-1-butanol and the 1-bromo-2-methylbutane formed from it.

This reaction does not involve any of the bonds to the stereogenic center, and so both the starting alcohol (−) and the product bromide (+) have the same relative configuration.

An elaborate network connecting signs of rotation and relative configurations was developed that included the most important compounds of organic and biological chemistry. When, in 1951, the absolute configuration of a salt of (+)-tartaric acid was determined, the absolute configurations of all the compounds whose configurations had been related to (+)-tartaric acid stood revealed as well. Thus, returning to the pair of 2-butanol enantiomers that introduced this section, their absolute configurations are now known to be as shown.

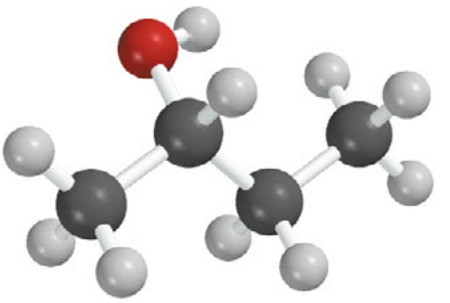


(+)-2-Butanol



(−)-2-Butanol

PROBLEM 7.6 Does the molecular model shown represent (+)-2-butanol or (−)-2-butanol?



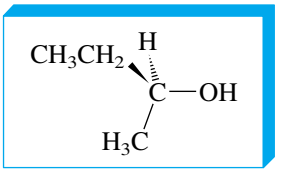
7.6 THE CAHN–INGOLD–PRELOG *R–S* NOTATIONAL SYSTEM

Just as it makes sense to have a nomenclature system by which we can specify the constitution of a molecule in words rather than pictures, so too is it helpful to have one that lets us describe stereochemistry. We have already had some experience with this idea when we distinguished between *E* and *Z* stereoisomers of alkenes.

In the *E–Z* system, substituents are ranked by atomic number according to a set of rules devised by R. S. Cahn, Sir Christopher Ingold, and Vladimir Prelog (Section 5.4). Actually, Cahn, Ingold, and Prelog first developed their ranking system to deal with the problem of the absolute configuration at a stereogenic center, and this is the system's major application. Table 7.1 shows how the Cahn–Ingold–Prelog system, called the **sequence rules,** is used to specify the absolute configuration at the stereogenic center in (+)-2-butanol.

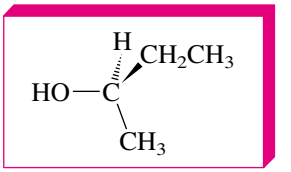
The January 1994 issue of the *Journal of Chemical Education* contains an article that describes how to use your hands to assign *R* and *S* configurations.

As outlined in Table 7.1, (+)-2-butanol has the *S* configuration. Its mirror image is (−)-2-butanol, which has the *R* configuration.



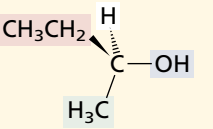
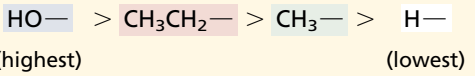
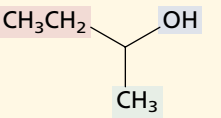
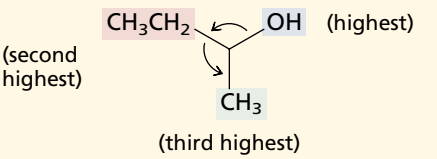
(*S*)-2-Butanol

and



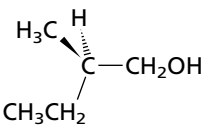
(*R*)-2-Butanol

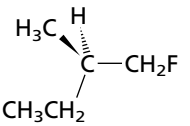
TABLE 7.1 Absolute Configuration According to the Cahn–Ingold–Prelog Notational System

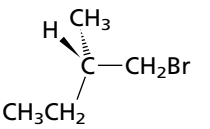
Step number	Example
	Given that the absolute configuration of (+)-2-butanol is  (+)-2-Butanol
1. Identify the substituents at the stereogenic center, and rank them in order of decreasing precedence according to the system described in Section 5.4. Precedence is determined by atomic number, working outward from the point of attachment at the stereogenic center.	In order of decreasing precedence, the four substituents attached to the stereogenic center of 2-butanol are  (highest) (lowest)
2. Orient the molecule so that the lowest ranked substituent points away from you.	As represented in the wedge-and-dash drawing at the top of this table, the molecule is already appropriately oriented. Hydrogen is the lowest ranked substituent attached to the stereogenic center and points away from us.
3. Draw the three highest ranked substituents as they appear to you when the molecule is oriented so that the lowest ranked group points away from you.	
4. If the order of decreasing precedence of the three highest ranked substituents appears in a clockwise sense, the absolute configuration is *R* (Latin *rectus,* "right," "correct"). If the order of decreasing precedence is anticlockwise, the absolute configuration is *S* (Latin *sinister,* "left").	The order of decreasing precedence is *anticlockwise.* The configuration at the stereogenic center is *S.*  (second highest) (highest) (third highest)

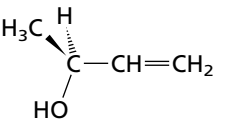
Often, the *R* or *S* configuration and the sign of rotation are incorporated into the name of the compound, as in (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol.

PROBLEM 7.7 Assign absolute configurations as *R* or *S* to each of the following compounds:

(a)  (+)-2-Methyl-1-butanol

(b)  (+)-1-Fluoro-2-methylbutane

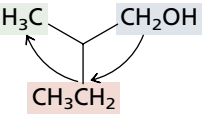
(c)  (+)-1-Bromo-2-methylbutane

(d)  (+)-3-Buten-2-ol

SAMPLE SOLUTION (a) The highest ranking substituent at the stereogenic center of 2-methyl-1-butanol is CH_2OH; the lowest is H. Of the remaining two, ethyl outranks methyl.

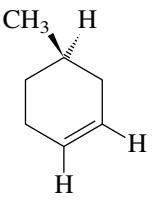
Order of precedence: $CH_2OH > CH_3CH_2 > CH_3 > H$

The lowest ranking substituent (hydrogen) points away from us in the drawing. The three highest ranking groups trace a clockwise path from $CH_2OH \rightarrow CH_3CH_2 \rightarrow CH_3$.



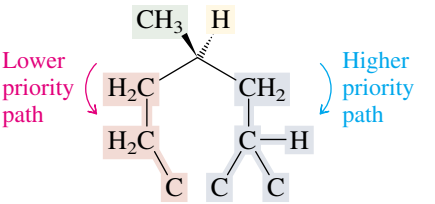
This compound therefore has the *R* configuration. It is (*R*)-(+)-2-methyl-1-butanol.

Compounds in which a stereogenic center is part of a ring are handled in an analogous fashion. To determine, for example, whether the configuration of (+)-4-methylcyclohexene is *R* or *S*, treat the right- and left-hand paths around the ring as if they were independent substituents.



(+)-4-Methylcyclohexene

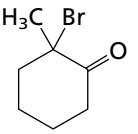
is treated as



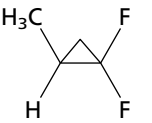
With the lowest ranked substituent (hydrogen) directed away from us, we see that the order of decreasing sequence rule precedence is *clockwise*. The absolute configuration is *R*.

PROBLEM 7.8 Draw three-dimensional representations or make molecular models of

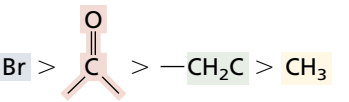
(a) The *R* enantiomer of



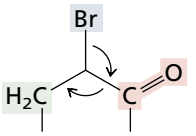
(b) The *S* enantiomer of



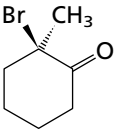
SAMPLE SOLUTION (a) The stereogenic center is the one that bears the bromine. In order of decreasing precedence, the substituents attached to the stereogenic center are



When the lowest ranked substituent (the methyl group) is away from us, the order of decreasing precedence of the remaining groups must appear in a clockwise sense in the *R* enantiomer.



which leads to the structure



(*R*)-2-Bromo-2-methylcyclohexanone

Since its introduction in 1956, the Cahn–Ingold–Prelog system has become the standard method of stereochemical notation.

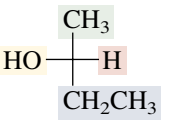
7.7 FISCHER PROJECTIONS

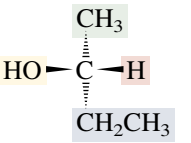
Stereochemistry deals with the three-dimensional arrangement of a molecule's atoms, and we have attempted to show stereochemistry with wedge-and-dash drawings and computer-generated models. It is possible, however, to convey stereochemical information in an abbreviated form using a method devised by the German chemist Emil Fischer.

Fischer was the foremost organic chemist of the late nineteenth century. He won the 1902 Nobel Prize in chemistry for his pioneering work in carbohydrate and protein chemistry.

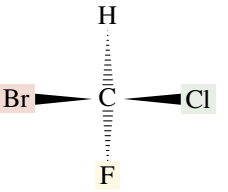
Let's return to bromochlorofluoromethane as a simple example of a chiral molecule. The two enantiomers of BrClFCH are shown as ball-and-stick models, as wedge-and-dash drawings, and as **Fischer projections** in Figure 7.6. Fischer projections are always generated the same way: the molecule is oriented so that the vertical bonds at the stereogenic center are directed away from you and the horizontal bonds point toward you. A projection of the bonds onto the page is a cross. The stereogenic carbon lies at the center of the cross but is not explicitly shown.

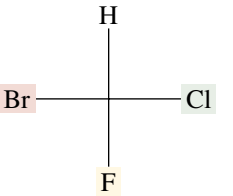
It is customary to orient the molecule so that the carbon chain is vertical with the lowest numbered carbon at the top as shown for the Fischer projection of (*R*)-2-butanol.

The Fischer projection 

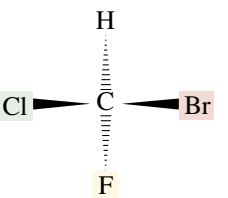
corresponds to 

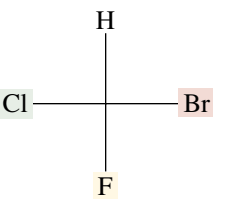
(*R*)-2-Butanol





(*R*)-Bromochlorofluoromethane





(*S*)-Bromochlorofluoromethane

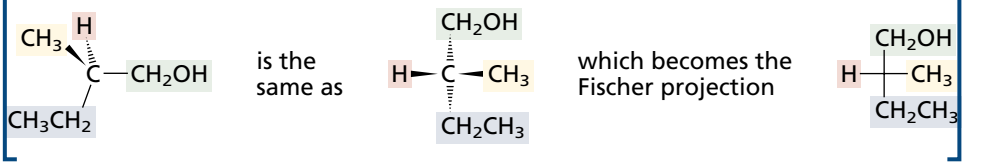
FIGURE 7.6 Ball-and-stick models *(left)*, wedge-and-dash drawings *(center)*, and Fischer projections *(right)* of the *R* and *S* enantiomers of bromochlorofluoromethane.

When specifying a configuration as *R* or *S*, the safest procedure is to convert a Fischer projection to a three-dimensional representation, remembering that the horizontal bonds always point toward you.

Edward Siloac, an undergraduate organic chemistry student at the University of Virginia, published a paper in the June 1999 issue of the *Journal of Chemical Education* (pp. 798–799) that described how to use your hands to translate Fischer projections to *R* and *S* configurations.

PROBLEM 7.9 Write Fischer projections for each of the compounds of Problem 7.7.

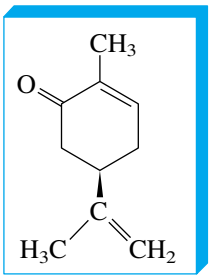
SAMPLE SOLUTION (a) The structure of (*R*)-(+)-2-methyl-1-butanol is shown in the structure that follows at the left. View the structural formula from a position chosen so that the $HOCH_2—C—CH_2CH_3$ segment is aligned vertically, with the vertical bonds pointing away from you. Replace the wedge-and-dash bonds by lines to give the Fischer projection shown at the right.



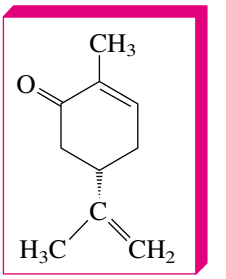
7.8 PHYSICAL PROPERTIES OF ENANTIOMERS

The usual physical properties such as density, melting point, and boiling point are identical within experimental error for both enantiomers of a chiral compound.

Enantiomers can have striking differences, however, in properties that depend on the arrangement of atoms in space. Take, for example, the enantiomeric forms of carvone. (*R*)-(−)-Carvone is the principal component of spearmint oil. Its enantiomer, (*S*)-(+)-carvone, is the principal component of caraway seed oil. The two enantiomers do not smell the same; each has its own characteristic odor.



(*R*)-(−)-Carvone
(from spearmint oil)



(*S*)-(+)-Carvone
(from caraway seed oil)

The difference in odor between (*R*)- and (*S*)-carvone results from their different behavior toward receptor sites in the nose. It is believed that volatile molecules occupy only those odor receptors that have the proper shape to accommodate them. Because the receptor sites are themselves chiral, one enantiomer may fit one kind of receptor while the other enantiomer fits a different kind. An analogy that can be drawn is to hands and gloves. Your left hand and your right hand are enantiomers. You can place your left hand into a left glove but not into a right one. The receptor (the glove) can accommodate one enantiomer of a chiral object (your hand) but not the other.

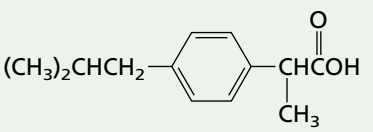
An article entitled "When Drug Molecules Look in the Mirror" in the June 1996 issue of the *Journal of Chemical Education* (pp. 481–484) describes numerous examples of common drugs in which the two enantiomers have different biological properties.

The term "chiral recognition" refers to the process whereby some chiral receptor or reagent interacts selectively with one of the enantiomers of a chiral molecule. Very high levels of chiral recognition are common in biological processes. (−)-Nicotine, for example, is much more toxic than (+)-nicotine, and (+)-adrenaline is more active in the

CHIRAL DRUGS

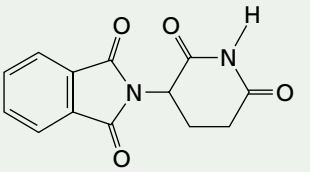
A recent estimate places the number of prescription and over-the-counter drugs marketed throughout the world at about 2000. Approximately one-third of these are either naturally occurring substances themselves or are prepared by chemical modification of natural products. Most of the drugs derived from natural sources are chiral and are almost always obtained as a single enantiomer rather than as a racemic mixture. Not so with the over 500 chiral substances represented among the more than 1300 drugs that are the products of synthetic organic chemistry. Until recently, such substances were, with few exceptions, prepared, sold, and administered as racemic mixtures even though the desired therapeutic activity resided in only one of the enantiomers. Spurred by a number of factors ranging from safety and efficacy to synthetic methodology and economics, this practice is undergoing rapid change as more and more chiral synthetic drugs become available in enantiomerically pure form.

Because of the high degree of chiral recognition inherent in most biological processes (Section 7.8), it is unlikely that both enantiomers of a chiral drug will exhibit the same level, or even the same kind, of effect. At one extreme, one enantiomer has the desired effect, and the other exhibits no biological activity at all. In this case, which is relatively rare, the racemic form is simply a drug that is 50% pure and contains 50% "inert ingredients." Real cases are more complicated. For example, it is the *S* enantiomer that is responsible for the pain-relieving properties of ibuprofen, normally sold as a racemic mixture. The 50% of racemic ibuprofen that is the *R* enantiomer is not completely wasted, however, because enzyme-catalyzed reactions in our body convert much of it to active (*S*)-ibuprofen.



Ibuprofen

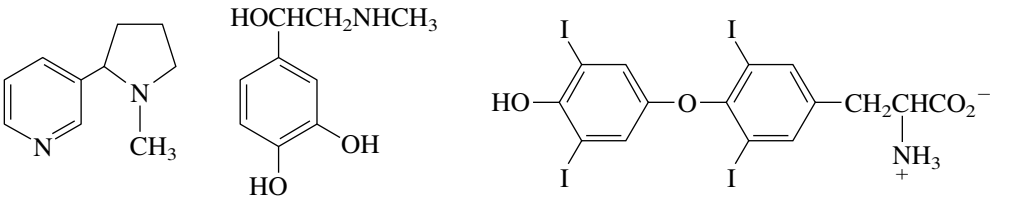
A much more serious drawback to using chiral drugs as racemic mixtures is illustrated by thalidomide, briefly employed as a sedative and antinausea drug in Europe and Great Britain during the period 1959–1962. The desired properties are those of (*R*)-thalidomide. (*S*)-Thalidomide, however, has a very different spectrum of biological activity and was shown to be responsible for over 2000 cases of serious birth defects in children born to women who took it while pregnant.



Thalidomide

Basic research directed toward understanding the factors that control the stereochemistry of chemical reactions has led to new synthetic methods that make it practical to prepare chiral molecules in enantiomerically pure form. Recognizing this, most major pharmaceutical companies are examining their existing drugs to see which ones are the best candidates for synthesis as single enantiomers and, when preparing a new drug, design its synthesis so as to provide only the desired enantiomer. In 1992, the United States Food and Drug Administration (FDA) issued guidelines that encouraged such an approach, but left open the door for approval of new drugs as racemic mixtures when special circumstances warrant. One incentive to developing enantiomerically pure versions of existing drugs is that the novel production methods they require may make them eligible for patent protection separate from that of the original drugs. Thus the temporary monopoly position that patent law views as essential to fostering innovation can be extended by transforming a successful chiral, but racemic, drug into an enantiomerically pure version.

constriction of blood vessels than (−)-adrenaline. (−)-Thyroxine is an amino acid of the thyroid gland, which speeds up metabolism and causes nervousness and loss of weight. Its enantiomer, (+)-thyroxine, exhibits none of these effects but is sometimes given to heart patients to lower their cholesterol levels.

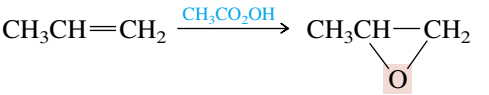


Nicotine Adrenaline Thyroxine

(Can you find the stereogenic center in each of these?)

7.9 REACTIONS THAT CREATE A STEREOGENIC CENTER

Many of the reactions we've already encountered can yield a chiral product from an achiral starting material. Epoxidation of propene, for example, creates a stereogenic center by addition of oxygen to the double bond.



Propene (achiral) 1,2-Epoxypropane (chiral)

In this, as in other reactions in which achiral reactants yield chiral products, the product is formed as a *racemic mixture* and is *optically inactive*. Remember, for a substance to be optically active, not only must it be chiral but one enantiomer must be present in excess of the other.

Figure 7.7 shows why equal amounts of (*R*)- and (*S*)-1,2-epoxypropane are formed in this reaction. The peroxy acid is just as likely to transfer oxygen to one face of the double bond as the other, the rates of formation of the *R* and *S* enantiomers of the product are the same and a racemic mixture of the two results.

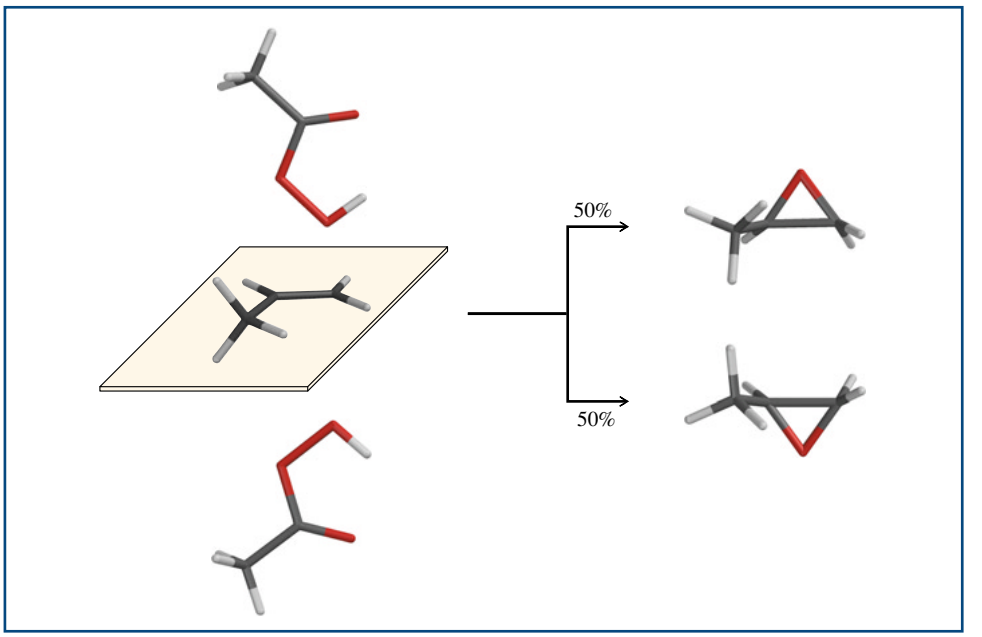


FIGURE 7.7 Epoxidation of propene produces equal amounts of (*R*)- and (*S*)-1,2-epoxypropane.

It is often helpful, especially in a multistep reaction, to focus on the step that creates the stereogenic center. In the ionic addition of hydrogen bromide to 2-butene, for example, the stereogenic center is generated when bromide ion attacks *sec*-butyl cation.

$$CH_3CH{=}CHCH_3 \xrightarrow{HBr} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 \quad \text{via} \quad CH_3\overset{+}{C}HCH_2CH_3$$

(*E*)- or (*Z*)-2-butene (achiral) — 2-Bromobutane (chiral) — *sec*-Butyl cation (achiral)

As seen in Figure 7.8, the bonds to the positively charged carbon are coplanar and define a plane of symmetry in the carbocation, which is achiral. The rates at which bromide ion attacks the carbocation at its two mirror-image faces are equal, and the product, 2-bromobutane, although chiral, is optically inactive because it is formed as a racemic mixture.

It is a general principle that *optically active products cannot be formed when optically inactive substrates react with optically inactive reagents.* This principle holds irrespective of whether the addition is syn or anti, concerted or stepwise. No matter how many steps are involved in a reaction, if the reactants are achiral, formation of one enantiomer is just as likely as the other, and a racemic mixture results.

When a reactant is chiral but optically inactive because it is *racemic,* any products derived from its reactions with optically inactive reagents will be *optically inactive.* For example, 2-butanol is chiral and may be converted with hydrogen bromide to 2-bromobutane, which is also chiral. If racemic 2-butanol is used, each enantiomer will react at the same rate with the achiral reagent. Whatever happens to (*R*)-(−)-2-butanol is mirrored in a corresponding reaction of (*S*)-(+)-2-butanol, and a racemic, optically inactive product results.

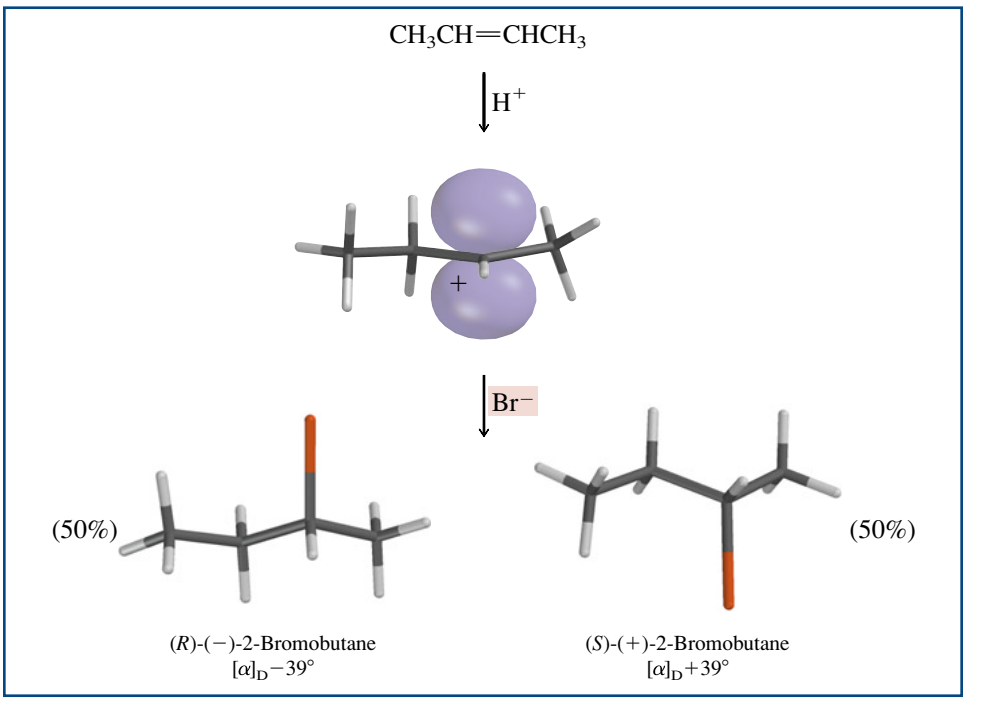
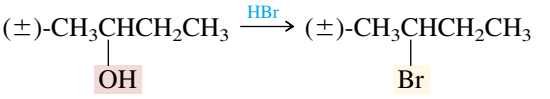
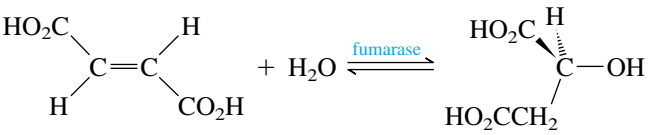


FIGURE 7.8 Electrophilic addition of hydrogen bromide to (*E*) and (*Z*)-2-butene proceeds by way of an achiral carbocation, which leads to equal quantities of (*R*)- and (*S*)-2-bromobutane.



2-Butanol (chiral but racemic) 2-Bromobutane (chiral but racemic)

Optically inactive starting materials can give optically active products if they are treated with an optically active reagent or if the reaction is catalyzed by an optically active substance. The best examples are found in biochemical processes. Most biochemical reactions are catalyzed by enzymes. Enzymes are chiral and enantiomerically homogeneous; they provide an asymmetric environment in which chemical reaction can take place. Ordinarily, enzyme-catalyzed reactions occur with such a high level of stereoselectivity that one enantiomer of a substance is formed exclusively even when the substrate is achiral. The enzyme *fumarase,* for example, catalyzes the hydration of fumaric acid to malic acid in apples and other fruits. Only the *S* enantiomer of malic acid is formed in this reaction.



Fumaric acid (*S*)-(−)-Malic acid

The reaction is reversible, and its stereochemical requirements are so pronounced that neither the cis isomer of fumaric acid (maleic acid) nor the *R* enantiomer of malic acid can serve as a substrate for the fumarase-catalyzed hydration–dehydration equilibrium.

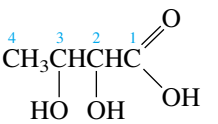
PROBLEM 7.10 Biological reduction of pyruvic acid, catalyzed by the enzyme lactate dehydrogenase, gives (+)-lactic acid, represented by the Fischer projection shown. What is the configuration of (+)-lactic acid according to the Cahn–Ingold–Prelog *R*–*S* notational system? Making a molecular model of the Fischer projection will help.

Pyruvic acid (+)-Lactic acid

We'll continue with the three-dimensional details of chemical reactions later in this chapter. First though, we need to develop some additional stereochemical principles concerning structures with more than one stereogenic center.

7.10 CHIRAL MOLECULES WITH TWO STEREOGENIC CENTERS

When a molecule contains two stereogenic centers, as does 2,3-dihydroxybutanoic acid, how many stereoisomers are possible?



2,3-Dihydroxybutanoic acid

We can use straightforward reasoning to come up with the answer. The absolute configuration at C-2 may be *R* or *S*. Likewise, C-3 may have either the *R* or the *S* configuration. The four possible combinations of these two stereogenic centers are

(2*R*,3*R*)	(stereoisomer I)	(2*S*,3*S*)	(stereoisomer II)
(2*R*,3*S*)	(stereoisomer III)	(2*S*,3*R*)	(stereoisomer IV)

Figure 7.9 presents structural formulas for these four stereoisomers. Stereoisomers I and II are enantiomers of each other; the enantiomer of (*R*,*R*) is (*S*,*S*). Likewise stereoisomers III and IV are enantiomers of each other, the enantiomer of (*R*,*S*) being (*S*,*R*).

Stereoisomer I is not a mirror image of III or IV, so is not an enantiomer of either one. Stereoisomers that are not related as an object and its mirror image are called **diastereomers;** *diastereomers are stereoisomers that are not enantiomers.* Thus, stereoisomer I is a diastereomer of III and a diastereomer of IV. Similarly, II is a diastereomer of III and IV.

To convert a molecule with two stereogenic centers to its enantiomer, the configuration at both centers must be changed. Reversing the configuration at only one stereogenic center converts it to a diastereomeric structure.

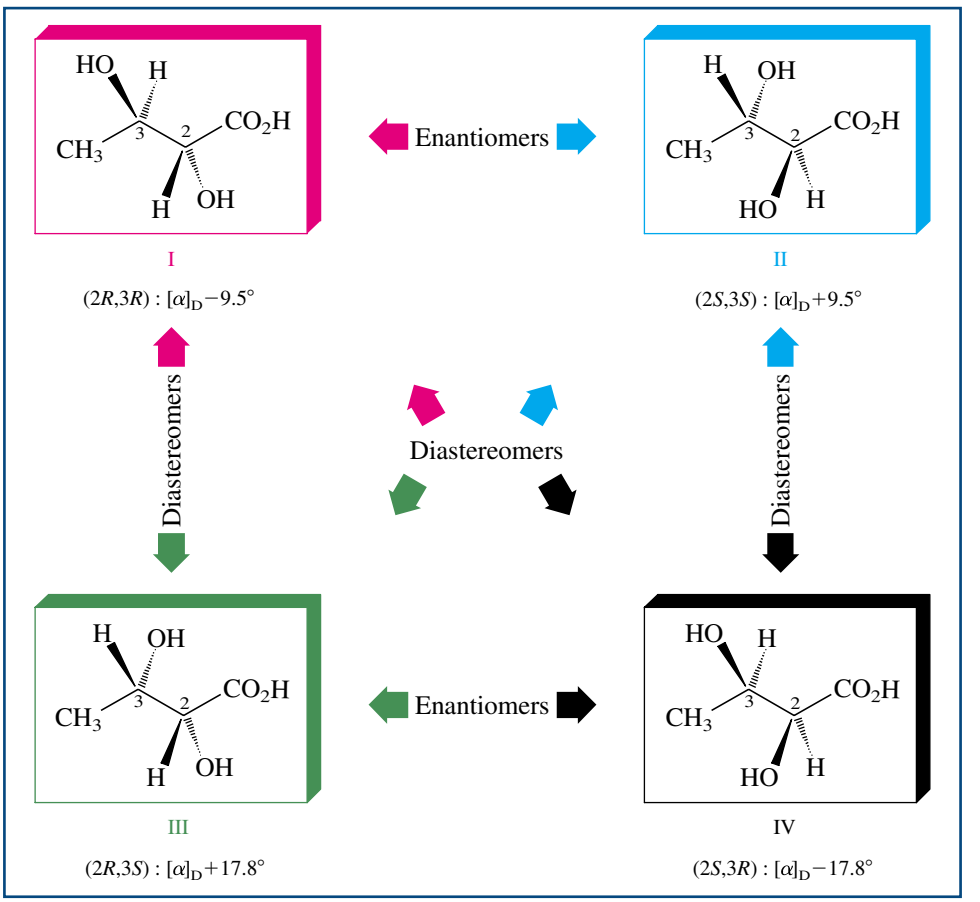


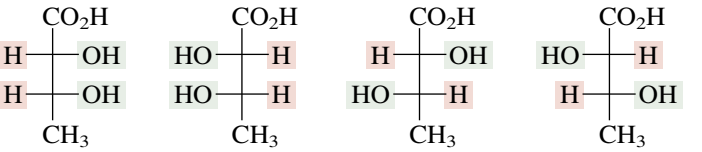
FIGURE 7.9 Stereoisomeric 2,3-dihydroxybutanoic acids. Stereoisomers I and II are enantiomers. Stereoisomers III and IV are enantiomers. All other relationships are diastereomeric (see text).

Enantiomers must have equal and opposite specific rotations. Diastereomeric substances can have different rotations, with respect to both sign and magnitude. Thus, as Figure 7.9 shows, the (2*R*,3*R*) and (2*S*,3*S*) enantiomers (I and II) have specific rotations that are equal in magnitude but opposite in sign. The (2*R*,3*S*) and (2*S*,3*R*) enantiomers (III and IV) likewise have specific rotations that are equal to each other but opposite in sign. The magnitudes of rotation of I and II are different, however, from those of their diastereomers III and IV.

In writing Fischer projections of molecules with two stereogenic centers, the molecule is arranged in an *eclipsed* conformation for projection onto the page, as shown in Figure 7.10. Again, horizontal lines in the projection represent bonds coming toward you; vertical bonds point away.

Organic chemists use an informal nomenclature system based on Fischer projections to distinguish between diastereomers. When the carbon chain is vertical and like substituents are on the same side of the Fischer projection, the molecule is described as the **erythro** diastereomer. When like substituents are on opposite sides of the Fischer projection, the molecule is described as the **threo** diastereomer. Thus, as seen in the Fischer projections of the stereoisomeric 2,3-dihydroxybutanoic acids, compounds I and II are erythro stereoisomers and III and IV are threo.

Erythro and threo describe the *relative configuration* (Section 7.5) of two stereogenic centers within a single molecule.



Because diastereomers are not mirror images of each other, they can have quite different physical and chemical properties. For example, the (2*R*,3*R*) stereoisomer of 3-amino-2-butanol is a liquid, but the (2*R*,3*S*) diastereomer is a crystalline solid.

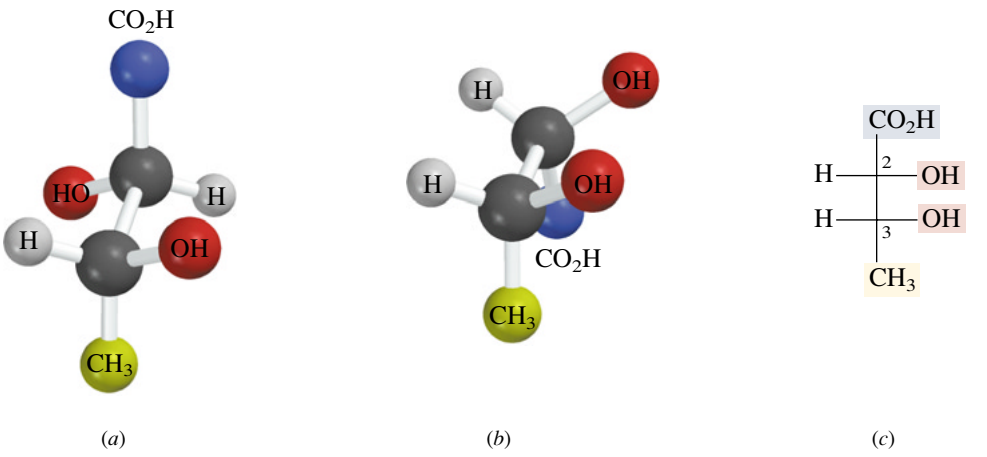
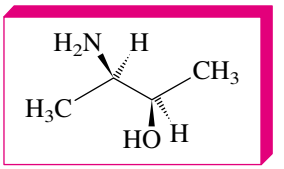
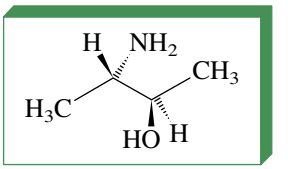


FIGURE 7.10 Representations of (2*R*,3*R*)-dihydroxybutanoic acid. (*a*) The staggered conformation is the most stable but is not properly arranged to show stereochemistry according to the Fischer projection method. (*b*) Rotation about the C-2—C-3 bond gives the eclipsed conformation, and projection of the eclipsed conformation onto the page gives (*c*) a correct Fischer projection.



(2*R*,3*R*)-3-Amino-2-butanol
(liquid)



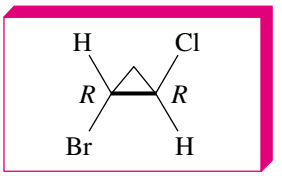
(2*R*,3*S*)-3-Amino-2-butanol
(solid, mp 49°C)

A molecule framed in green is a diastereomer of one framed in red or blue.

PROBLEM 7.11 Draw Fischer projections or make molecular models of the four stereoisomeric 3-amino-2-butanols, and label each erythro or threo as appropriate.

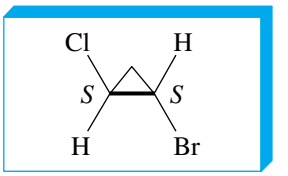
PROBLEM 7.12 One other stereoisomer of 3-amino-2-butanol is a crystalline solid. Which one?

The situation is the same when the two stereogenic centers are present in a ring. There are four stereoisomeric 1-bromo-2-chlorocyclopropanes: a pair of enantiomers in which the halogens are trans and a pair in which they are cis. The cis compounds are diastereomers of the trans.



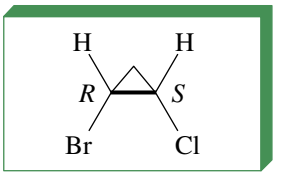
(1*R*,2*R*)-1-Bromo-2-chlorocyclopropane

Enantiomers



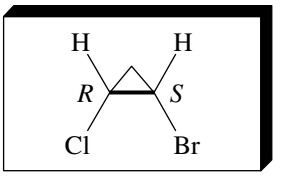
(1*S*,2*S*)-1-Bromo-2-chlorocyclopropane

A molecule framed in black is an enantiomer of a green-framed one. Both are diastereomers of their red or blue-framed stereoisomers.



(1*R*,2*S*)-1-Bromo-2-chlorocyclopropane

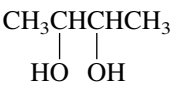
Enantiomers



(1*S*,2*R*)-1-Bromo-2-chlorocyclopropane

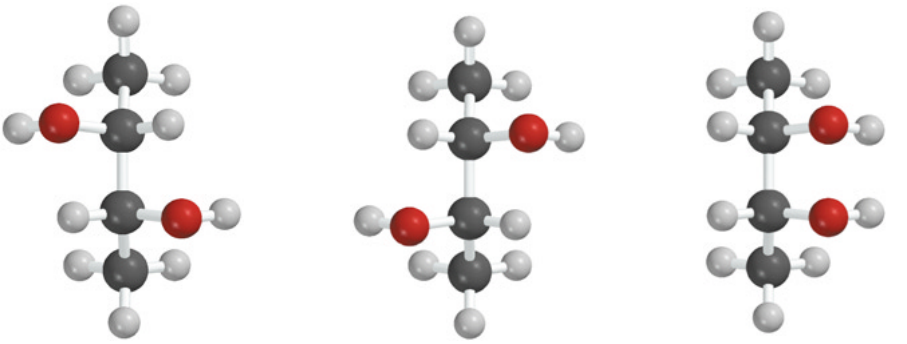
7.11 ACHIRAL MOLECULES WITH TWO STEREOGENIC CENTERS

Now think about a molecule, such as 2,3-butanediol, which has two stereogenic centers that are equivalently substituted.



2,3-Butanediol

Only *three,* not four, stereoisomeric 2,3-butanediols are possible. These three are shown in Figure 7.11. The (2*R*,3*R*) and (2*S*,3*S*) forms are enantiomers of each other and have equal and opposite optical rotations. A third combination of stereogenic centers, (2*R*,3*S*), however, gives an *achiral* structure that is superposable on its (2*S*,3*R*) mirror image. Because it is achiral, this third stereoisomer is *optically inactive.* We call achiral molecules that have stereogenic centers **meso forms.** The meso form in Figure 7.11 is known as *meso*-2,3-butanediol.



(2*R*,3*R*)-2,3-Butanediol (2*S*,3*S*)-2,3-Butanediol *meso*-2,3-Butanediol

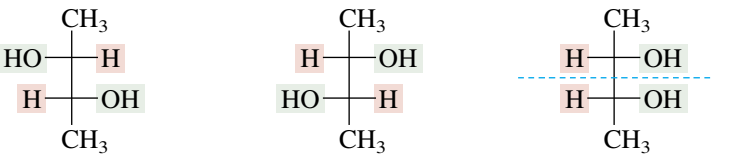
(*a*) (*b*) (*c*)

FIGURE 7.11 Stereoisomeric 2,3-butanediols shown in their eclipsed conformations for convenience. Stereoisomers (*a*) and (*b*) are enantiomers of each other. Structure (*c*) is a diastereomer of (*a*) and (*b*), and is achiral. It is called *meso*-2,3-butanediol.

One way to demonstrate that *meso*-2,3-butanediol is achiral is to recognize that its eclipsed conformation has a plane of symmetry that passes through and is perpendicular to the C-2—C-3 bond, as illustrated in Figure 7.12*a*. The anti conformation is achiral as well. As Figure 7.12*b* shows, this conformation is characterized by a center of symmetry at the midpoint of the C-2—C-3 bond.

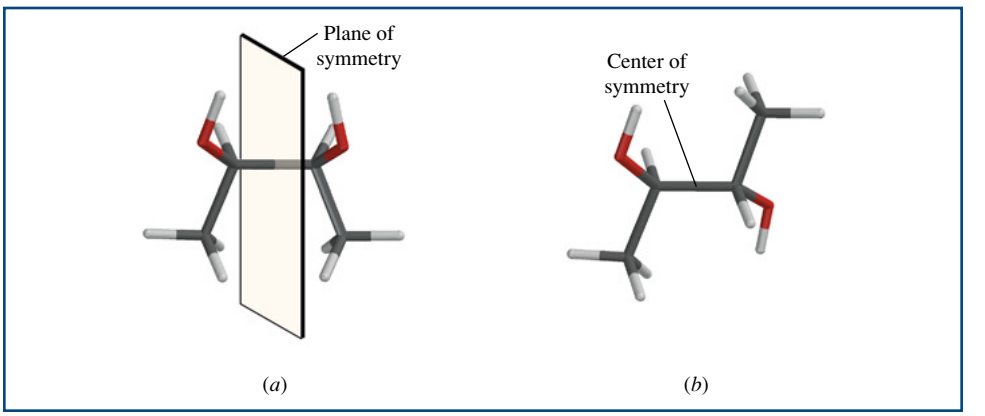
Fischer projection formulas can help us identify meso forms. Of the three stereoisomeric 2,3-butanediols, notice that only in the meso stereoisomer does a dashed line through the center of the Fischer projection divide the molecule into two mirror-image halves.

In the same way that a Fischer formula is a projection of the eclipsed conformation onto the page, the line drawn through its center is a projection of the plane of symmetry which is present in the eclipsed conformation of *meso*-2,3-butanediol.



(2*R*,3*R*)-2,3-Butanediol (2*S*,3*S*)-2,3-Butanediol *meso*-2,3-Butanediol

When using Fischer projections for this purpose, however, be sure to remember what three-dimensional objects they stand for. One should not, for example, test for superposition of the two chiral stereoisomers by a procedure that involves moving any part of a Fischer projection out of the plane of the paper in any step.



(*a*) (*b*)

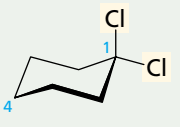
FIGURE 7.12 (*a*) The eclipsed conformation of *meso*-2,3-butanediol has a plane of symmetry. (*b*) The anti conformation of *meso*-2,3-butanediol has a center of symmetry.

CHIRALITY OF DISUBSTITUTED CYCLOHEXANES

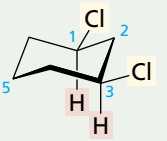
Disubstituted cyclohexanes present us with a challenging exercise in stereochemistry. Consider the seven possible dichlorocyclohexanes: 1,1-; *cis*- and *trans*-1,2-; *cis*- and *trans*-1,3-; and *cis*- and *trans*-1,4-. Which are chiral? Which are achiral?

Four isomers—the ones that are achiral because they have a plane of symmetry—are relatively easy to identify:

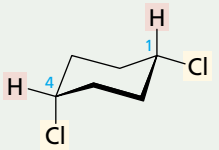
ACHIRAL DICHLOROCYCLOHEXANES



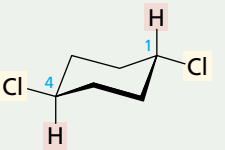
1,1
(plane of symmetry through C-1 and C-4)



cis-1,3
(plane of symmetry through C-2 and C-5)



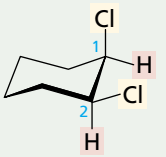
cis-1,4
(plane of symmetry through C-1 and C-4)



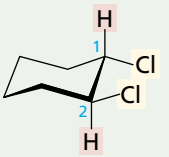
trans-1,4
(plane of symmetry through C-1 and C-4)

The remaining three isomers are chiral:

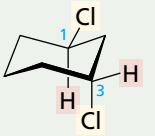
CHIRAL DICHLOROCYCLOHEXANES



cis-1,2

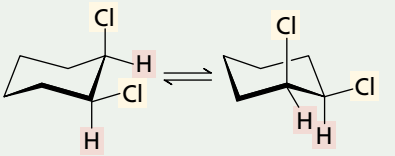


trans-1,2



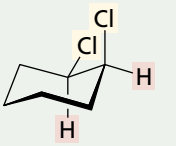
trans-1,3

Among all the isomers, *cis*-1,2-dichlorocyclohexane is unique in that the ring-flipping process typical of cyclohexane derivatives (Section 3.8) converts it to its enantiomer.



A A′

which is equivalent to



A′

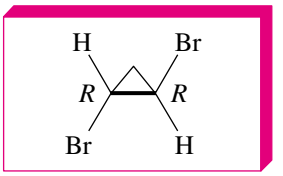
Structures A and A′ are nonsuperposable mirror images of each other. Thus although *cis*-1,2-dichlorocyclohexane is chiral, it is optically inactive when chair–chair interconversion occurs. Such interconversion is rapid at room temperature and converts optically active A to a racemic mixture of A and A′. Since A and A′ are enantiomers interconvertible by a conformational change, they are sometimes referred to as **conformational enantiomers.**

The same kind of spontaneous racemization occurs for any *cis*-1,2 disubstituted cyclohexane in which both substituents are the same. Since such compounds are chiral, it is incorrect to speak of them as meso compounds, which are achiral by definition. Rapid chair–chair interconversion, however, converts them to a 1:1 mixture of enantiomers, and this mixture is optically inactive.

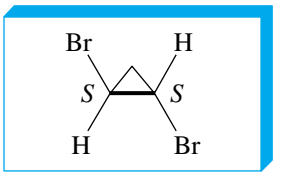
PROBLEM 7.13 A meso stereoisomer is possible for one of the following compounds. Which one?

2,3-Dibromopentane; 2,4-dibromopentane; 3-bromo-2-pentanol; 4-bromo-2-pentanol

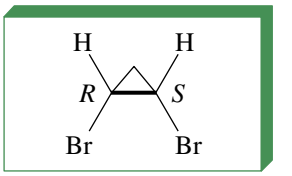
Turning to cyclic compounds, we see that there are three, not four, stereoisomeric 1,2-dibromocyclopropanes. Of these, two are enantiomeric *trans*-1,2-dibromocyclopropanes. The cis diastereomer is a meso form; it has a plane of symmetry.



(1*R*,2*R*)-1,2-Dibromocyclopropane



(1*S*,2*S*)-Dibromocyclopropane



meso-1,2-Dibromocyclopropane

PROBLEM 7.14 One of the stereoisomers of 1,3-dimethylcyclohexane is a meso form. Which one?

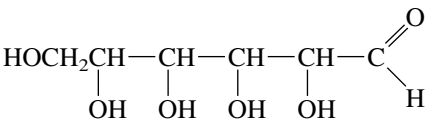
7.12 MOLECULES WITH MULTIPLE STEREOGENIC CENTERS

Many naturally occurring compounds contain several stereogenic centers. By an analysis similar to that described for the case of two stereogenic centers, it can be shown that the maximum number of stereoisomers for a particular constitution is 2^n, where n is equal to the number of stereogenic centers.

PROBLEM 7.15 Using *R* and *S* descriptors, write all the possible combinations for a molecule with three stereogenic centers.

When two or more of a molecule's stereogenic centers are equivalently substituted, meso forms are possible, and the number of stereoisomers is then less than 2^n. Thus, 2^n represents the *maximum* number of stereoisomers for a molecule containing n stereogenic centers.

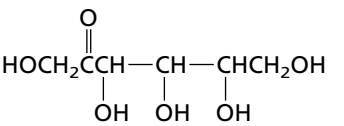
The best examples of substances with multiple stereogenic centers are the *carbohydrates* (Chapter 25). One class of carbohydrates, called *hexoses,* has the constitution



A hexose

Since there are four stereogenic centers and no possibility of meso forms, there are 2^4, or 16, stereoisomeric hexoses. All 16 are known, having been isolated either as natural products or as the products of chemical synthesis.

PROBLEM 7.16 A second category of six-carbon carbohydrates, called *2-hexuloses,* has the constitution shown. How many stereoisomeric 2-hexuloses are possible?



A 2-hexulose

Steroids are another class of natural products with multiple stereogenic centers. One such compound is *cholic acid,* which can be obtained from bile. Its structural formula is given in Figure 7.13. Cholic acid has 11 stereogenic centers, and so there are a total (including cholic acid) of 2^{11}, or 2048, stereoisomers that have this constitution. Of

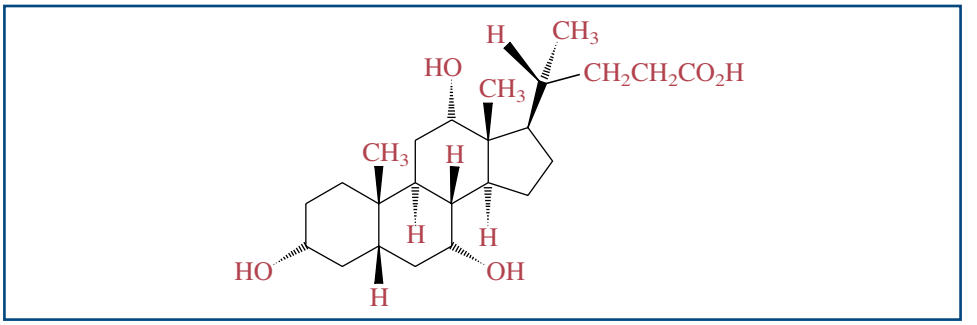
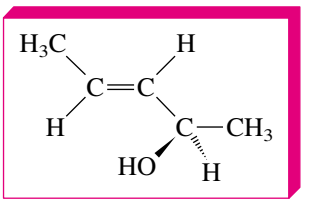


FIGURE 7.13 The structure of cholic acid. Its 11 stereogenic centers are those carbons at which stereochemistry is indicated in the diagram.

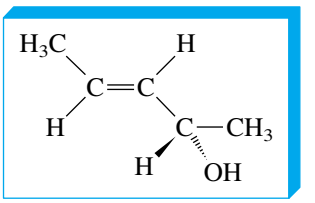
these 2048 stereoisomers, how many are diastereomers of cholic acid? Remember! Diastereomers are stereoisomers that are not enantiomers, and any object can have only one mirror image. Therefore, of the 2048 stereoisomers, one is cholic acid, one is its enantiomer, and the other 2046 are diastereomers of cholic acid. Only a small fraction of these compounds are known, and (+)-cholic acid is the only one ever isolated from natural sources.

Eleven stereogenic centers may seem like a lot, but it is nowhere close to a world record. It is a modest number when compared with the more than 100 stereogenic centers typical for most small proteins and the thousands of stereogenic centers that are present in nucleic acids.

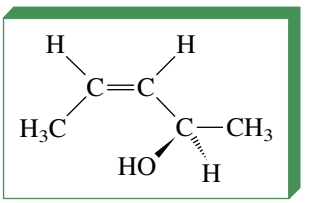
A molecule that contains both stereogenic centers and double bonds has additional opportunities for stereoisomerism. For example, the configuration of the stereogenic center in 3-penten-2-ol may be either *R* or *S,* and the double bond may be either *E* or *Z.* There are therefore four stereoisomers of 3-penten-2-ol even though it has only one stereogenic center.



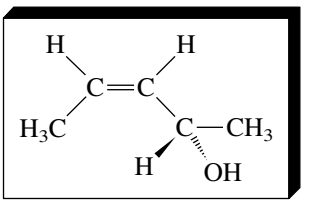
(2*R*,3*E*)-3-Penten-2-ol



(2*S*,3*E*)-3-Penten-2-ol



(2*R*,3*Z*)-3-Penten-2-ol



(2*S*,3*Z*)-3-Penten-2-ol

The relationship of the (2*R*,3*E*) stereoisomer to the others is that it is the enantiomer of (2*S*,3*E*)-3-penten-2-ol and is a diastereomer of the (2*R*,3*Z*) and (2*S*,3*Z*) isomers.

7.13 REACTIONS THAT PRODUCE DIASTEREOMERS

Once we grasp the idea of stereoisomerism in molecules with two or more stereogenic centers, we can explore further details of addition reactions of alkenes.

When bromine adds to (*Z*)- or (*E*)-2-butene, the product 2,3-dibromobutane contains two equivalently substituted stereogenic centers:

$$CH_3CH{=}CHCH_3 \xrightarrow{Br_2} CH_3\underset{Br}{C}H\underset{Br}{C}HCH_3$$

(*Z*)- or (*E*)-2-butene 2,3-Dibromobutane

Three stereoisomers are possible: a pair of enantiomers and a meso form.

Two factors combine to determine which stereoisomers are actually formed in the reaction.

1. The (*E*)- or (*Z*)-configuration of the starting alkene
2. The anti stereochemistry of addition

Figures 7.14 and 7.15 depict the stereochemical relationships associated with anti addition of bromine to (*E*)- and (*Z*)-2-butene, respectively. The trans alkene (*E*)-2-butene yields only *meso*-2,3-dibromobutane, but the cis alkene (*Z*)-2-butene gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-dibromobutane.

Bromine addition to alkenes is an example of a **stereospecific reaction.** A stereospecific reaction is one in which stereoisomeric starting materials yield products that are stereoisomers of each other. In this case the starting materials, in separate reactions, are the *E* and *Z* stereoisomers of 2-butene. The chiral dibromides from (*Z*)-2-butene are stereoisomers (diastereomers) of the meso dibromide formed from (*E*)-2-butene.

Notice further that, consistent with the principle developed in Section 7.9, optically inactive starting materials (achiral alkenes and bromine) yield optically inactive products (a racemic mixture or a meso structure) in these reactions.

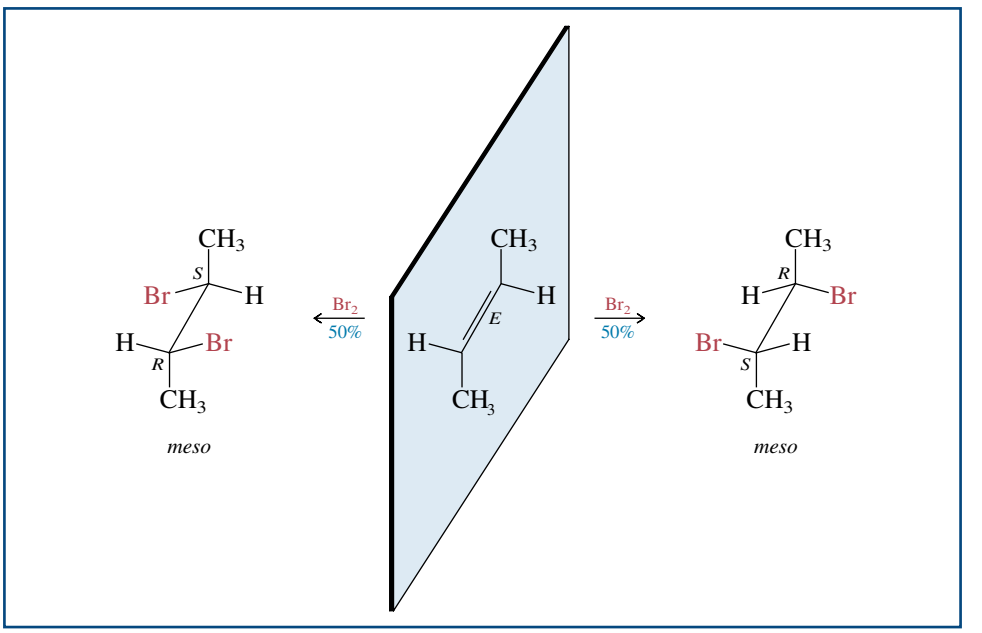


FIGURE 7.14 Anti addition of Br_2 to (*E*)-2-butene gives *meso*-2,3-dibromobutane.

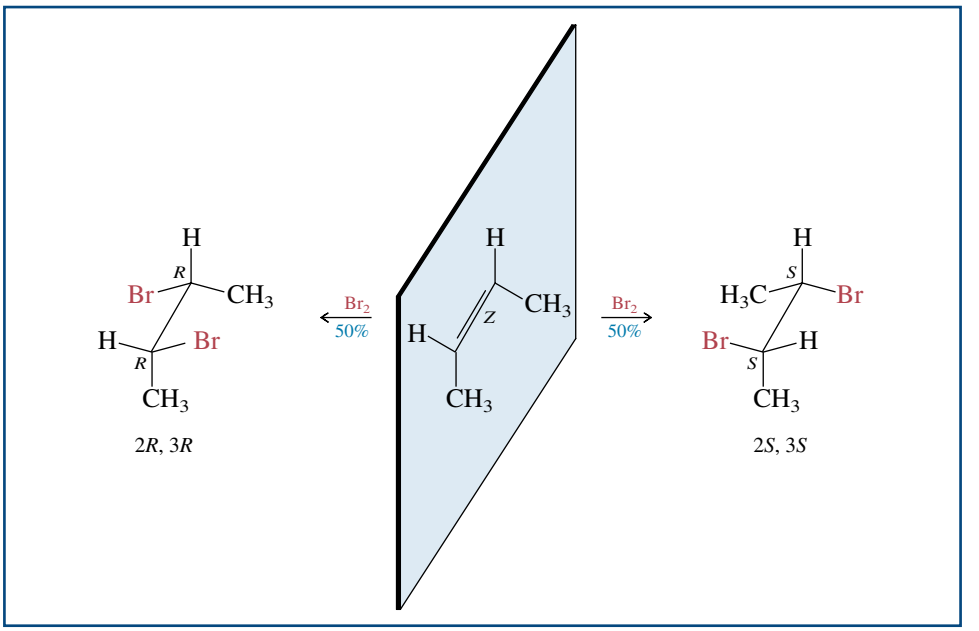
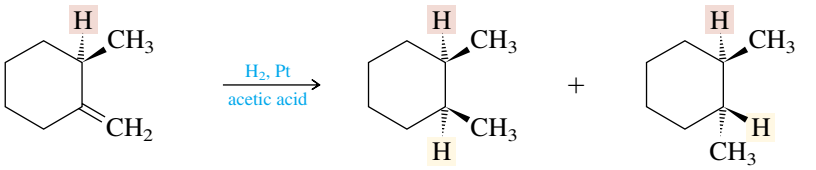


FIGURE 7.15 Anti addition of Br_2 to (*Z*)-2-butene gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-dibromobutane.

PROBLEM 7.17 Epoxidation of alkenes is a stereospecific syn addition. Which stereoisomer of 2-butene reacts with peroxyacetic acid to give *meso*-2,3-epoxybutane? Which one gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-epoxybutane?

A reaction that introduces a second stereogenic center into a starting material that already has one need not produce equal quantities of two possible diastereomers. Consider catalytic hydrogenation of 2-methyl(methylene)cyclohexane. As you might expect, both *cis*- and *trans*-1,2-dimethylcyclohexane are formed.



2-Methyl(methylene)cyclohexane

cis-1,2-Dimethylcyclohexane (68%)

trans-1,2-Dimethylcyclohexane (32%)

Make molecular models of the reactant and both products shown in the equation.

The relative amounts of the two products, however, are not equal; more *cis*-1,2-dimethylcyclohexane is formed than *trans*. The reason for this is that it is the less hindered face of the double bond that approaches the catalyst surface and is the face to which hydrogen is transferred. Hydrogenation of 2-methyl(methylene)cyclohexane occurs preferentially at the side of the double bond opposite that of the methyl group and leads to a faster rate of formation of the cis stereoisomer of the product.

PROBLEM 7.18 Could the fact that hydrogenation of 2-methyl(methylene)cyclohexane gives more *cis*-1,2-dimethylcyclohexane than *trans*- be explained on the basis of the relative stabilities of the two stereoisomeric products?

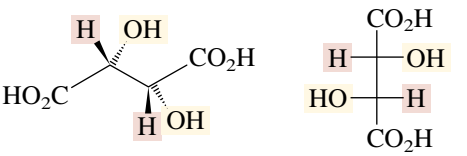
The hydrogenation of 2-methyl(methylene)cyclohexane is an example of a *stereoselective reaction,* meaning one in which stereoisomeric products are formed in unequal amounts from a single starting material (Section 5.11).

A common misconception is that a stereospecific reaction is simply one that is 100% stereoselective. The two terms though have precise definitions that are independent of one another. A stereospecific reaction is one which, when carried out with stereoisomeric starting materials, gives a product from one reactant that is a stereoisomer of the product from the other. A stereoselective reaction is one in which a single starting material gives a predominance of a single stereoisomer when two or more are possible. *Stereospecific* is more closely connected with features of the reaction than with the reactant. Thus terms such as syn *addition* and anti *elimination* describe the stereospecificity of reactions. *Stereoselective* is more closely connected with structural effects in the reactant as expressed in terms such as *addition to the less hindered side.* A stereospecific reaction can also be stereoselective. For example, syn addition describes stereospecificity in the catalytic hydrogenation of alkenes, whereas the preference for addition to the less hindered face of the double bond describes stereoselectivity.

Note that the terms *regioselective* and *regiospecific,* however, are defined in terms of each other. A regiospecific reaction is one that is 100% regioselective.

7.14 RESOLUTION OF ENANTIOMERS

The separation of a racemic mixture into its enantiomeric components is termed **resolution.** The first resolution, that of tartaric acid, was carried out by Louis Pasteur in 1848. Tartaric acid is a byproduct of wine making and is almost always found as its dextrorotatory 2*R*,3*R* stereoisomer, shown here in a perspective drawing and in a Fischer projection.



(2*R*,3*R*)-Tartaric acid (mp 170°C, $[\alpha]_D$ +12°)

PROBLEM 7.19 There are two other stereoisomeric tartaric acids. Write their Fischer projections, and specify the configuration at their stereogenic centers.

A description of Pasteur's work, as part of a broader discussion concerning crystal structure, can be found in the article "Molecules, Crystals, and Chirality" in the July 1997 issue of the *Journal of Chemical Education,* pp. 800–806.

Occasionally, an optically inactive sample of tartaric acid was obtained. Pasteur noticed that the sodium ammonium salt of optically inactive tartaric acid was a mixture of two mirror-image crystal forms. With microscope and tweezers, Pasteur carefully separated the two. He found that one kind of crystal (in aqueous solution) was dextrorotatory, whereas the mirror-image crystals rotated the plane of polarized light an equal amount but were levorotatory.

Although Pasteur was unable to provide a structural explanation—that had to wait for van't Hoff and Le Bel a quarter of a century later—he correctly deduced that the enantiomeric quality of the crystals was the result of enantiomeric molecules. The rare form of tartaric acid was optically inactive because it contained equal amounts of (+)-tartaric acid and (−)-tartaric acid. It had earlier been called *racemic acid* (from Latin *racemus,* "a bunch of grapes"), a name that subsequently gave rise to our present term for an equal mixture of enantiomers.

PROBLEM 7.20 Could the unusual, optically inactive form of tartaric acid studied by Pasteur have been *meso*-tartaric acid?

Pasteur's technique of separating enantiomers not only is laborious but requires that the crystal habits of enantiomers be distinguishable. This happens very rarely.

Consequently, alternative and more general approaches for resolving enantiomers have been developed. Most are based on a strategy of temporarily converting the enantiomers of a racemic mixture to diastereomeric derivatives, separating these diastereomers, then regenerating the enantiomeric starting materials.

Figure 7.16 illustrates this strategy. Say we have a mixture of enantiomers, which, for simplicity, we label as C(+) and C(−). Assume that C(+) and C(−) bear some functional group that can combine with a reagent P to yield adducts C(+)-P and C(−)-P. Now, if reagent P is chiral, and if only a single enantiomer of P, say, P(+), is added to a racemic mixture of C(+) and C(−), as shown in the first step of Figure 7.16, then the products of the reaction are C(+)-P(+) and C(−)-P(+). These products are not mirror images; they are diastereomers. Diastereomers can have different physical properties, which can serve as a means of separating them. The mixture of diastereomers is separated, usually by recrystallization from a suitable solvent. In the last step, an appropriate chemical transformation liberates the enantiomers and restores the resolving agent.

Whenever possible, the chemical reactions involved in the formation of diastereomers and their conversion to separate enantiomers are simple acid–base reactions. For example, naturally occurring (*S*)-(−)-malic acid is often used to resolve amines. One such amine that has been resolved in this way is 1-phenylethylamine. Amines are bases, and malic acid is an acid. Proton transfer from (*S*)-(−)-malic acid to a racemic mixture of (*R*)- and (*S*)-1-phenylethylamine gives a mixture of diastereomeric salts.

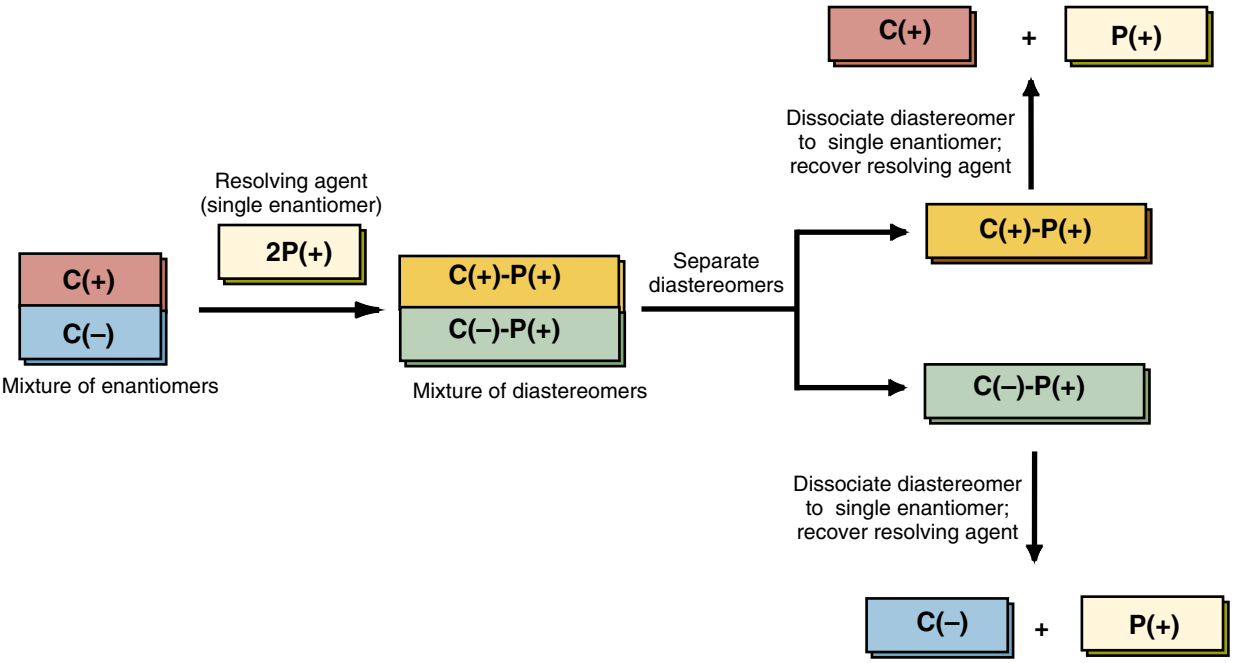
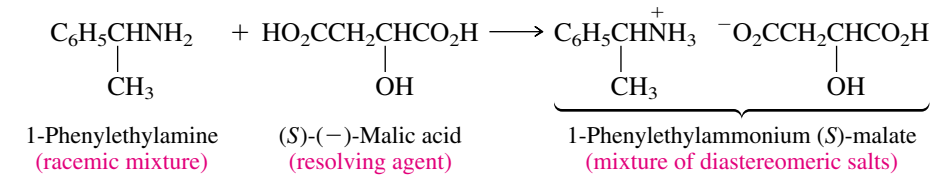
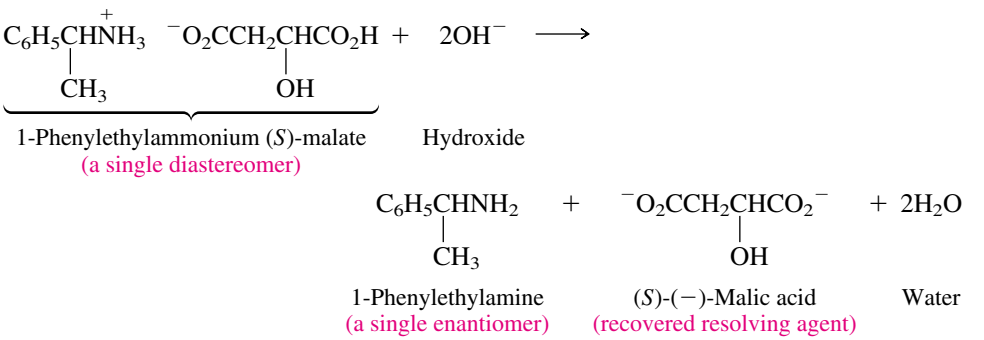


FIGURE 7.16 The general procedure followed in resolving a chiral substance into its enantiomers. Reaction with a single enantiomer of a chiral resolving agent P(+) converts the racemic mixture of enantiomers C(+) and C(−) to a mixture of diastereomers C(+)-P(+) and C(−)-P(+). The mixture of diastereomers is separated—by fractional crystallization, for example. A chemical reaction is then carried out to convert diastereomer C(+)-P(+) to C(+) and the resolving agent P(+). Likewise, diastereomer C(−)-P(+) is converted to C(−) and P(+). C(+) has been separated from C(−), and the resolving agent P(+) can be recovered for further use.



The diastereomeric salts are separated and the individual enantiomers of the amine liberated by treatment with a base:



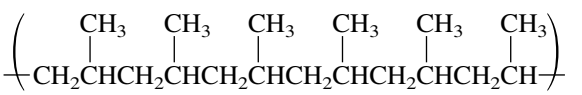
PROBLEM 7.21 In the resolution of 1-phenylethylamine using (−)-malic acid, the compound obtained by recrystallization of the mixture of diastereomeric salts is (*R*)-1-phenylethylammonium (*S*)-malate. The other component of the mixture is more soluble and remains in solution. What is the configuration of the more soluble salt?

This method is widely used for the resolution of chiral amines and carboxylic acids. Analogous methods based on the formation and separation of diastereomers have been developed for other functional groups; the precise approach depends on the kind of chemical reactivity associated with the functional groups present in the molecule.

The rapidly increasing demand for enantiomerically pure starting materials and intermediates in the pharmaceutical industry (see the boxed essay entitled *Chiral Drugs* in this chapter) has increased interest in developing methods for resolving racemic mixtures.

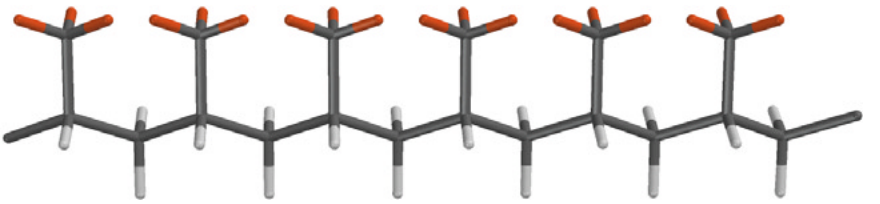
7.15 STEREOREGULAR POLYMERS

Before the development of the Ziegler–Natta catalyst systems (Section 6.21), polymerization of propene was not a reaction of much value. The reason for this has a stereochemical basis. Consider a section of *polypropylene:*



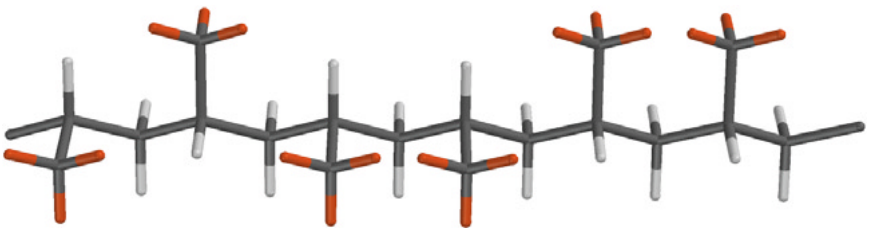
Representation of the polymer chain in an extended zigzag conformation, as shown in Figure 7.17, reveals several distinct structural possibilities differing with respect to the relative configurations of the carbons that bear the methyl groups.

One structure, represented in Figure 7.17*a,* has all the methyl groups oriented in the same direction with respect to the polymer chain. This stereochemical arrangement is said to be **isotactic.** Another form, shown in Figure 7.17*b,* has its methyl groups alternating front and back along the chain. This arrangement is described as **syndiotactic.**



(*a*) Isotactic polypropylene

(*b*) Syndiotactic polypropylene



(*c*) Atactic polypropylene

FIGURE 7.17 Polymers of propene. The main chain is shown in a zigzag conformation. Every other carbon bears a methyl substituent and is a stereogenic center. (*a*) All the methyl groups are on the same side of the carbon chain in isotactic polypropylene. (*b*) Methyl groups alternate from one side to the other in syndiotactic polypropylene. (*c*) The spatial orientation of the methyl groups is random in atactic polypropylene.

Both the isotactic and the syndiotactic forms of polypropylene are known as **stereoregular polymers,** because each is characterized by a precise stereochemistry at the carbon atom that bears the methyl group. There is a third possibility, shown in Figure 7.17*c*, which is described as **atactic.** Atactic polypropylene has a random orientation of its methyl groups; it is not a stereoregular polymer.

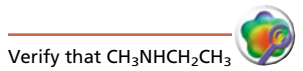
Polypropylene chains associate with one another because of attractive van der Waals forces. The extent of this association is relatively large for isotactic and syndiotactic polymers, because the stereoregularity of the polymer chains permits efficient packing. Atactic polypropylene, on the other hand, does not associate as strongly. It has a lower density and lower melting point than the stereoregular forms. The physical properties of stereoregular polypropylene are more useful for most purposes than those of atactic polypropylene.

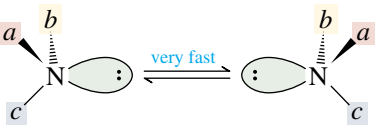
When propene is polymerized under free-radical conditions, the polypropylene that results is atactic. Catalysts of the Ziegler–Natta type, however, permit the preparation of either isotactic or syndiotactic polypropylene. We see here an example of how proper choice of experimental conditions can affect the stereochemical course of a chemical reaction to the extent that entirely new materials with unique properties result.

7.16 STEREOGENIC CENTERS OTHER THAN CARBON

Our discussion to this point has been limited to molecules in which the stereogenic center is carbon. Atoms other than carbon may also be stereogenic centers. Silicon, like carbon, has a tetrahedral arrangement of bonds when it bears four substituents. A large number of organosilicon compounds in which silicon bears four different groups have been resolved into their enantiomers.

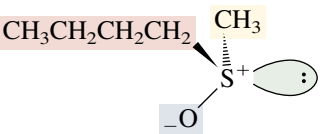
Trigonal pyramidal molecules are chiral if the central atom bears three different groups. If one is to resolve substances of this type, however, the pyramidal inversion that interconverts enantiomers must be slow at room temperature. Pyramidal inversion at nitrogen is so fast that attempts to resolve chiral amines fail because of their rapid racemization.


Verify that $CH_3NHCH_2CH_3$ is chiral by trying to superpose models of both enantiomers.



Phosphorus is in the same group of the periodic table as nitrogen, and tricoordinate phosphorus compounds (phosphines), like amines, are trigonal pyramidal. Phosphines, however, undergo pyramidal inversion much more slowly than amines, and a number of optically active phosphines have been prepared.

Tricoordinate sulfur compounds are chiral when sulfur bears three different substituents. The rate of pyramidal inversion at sulfur is rather slow. The most common compounds in which sulfur is a stereogenic center are sulfoxides such as:



(*S*)-(+)-Butyl methyl sulfoxide

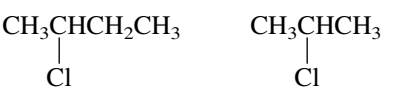
The absolute configuration at sulfur is specified by the Cahn–Ingold–Prelog method with the provision that the unshared electron pair is considered to be the lowest ranking substituent.

7.17 SUMMARY

A detailed flowchart describing a more finely divided set of subcategories of isomers appears in the February 1990 issue of the *Journal of Chemical Education.*

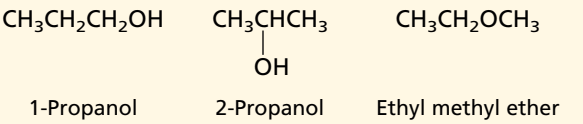
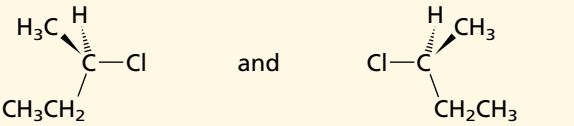
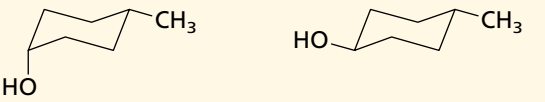
Chemistry in three dimensions is known as **stereochemistry.** At its most fundamental level, stereochemistry deals with molecular structure; at another level, it is concerned with chemical reactivity. Table 7.2 summarizes some basic definitions relating to molecular structure and stereochemistry.

Section 7.1 A molecule is **chiral** if it cannot be superposed on its mirror image. *Nonsuperposable mirror images* are **enantiomers** of one another. Molecules in which mirror images are superposable are achiral.



2-Chlorobutane (chiral) 2-Chloropropane (achiral)

TABLE 7.2 Classification of Isomers*

Definition	Example
1. *Constitutional isomers* are isomers that differ in the order in which their atoms are connected.	There are three constitutionally isomeric compounds of molecular formula C_3H_8O:  1-Propanol 2-Propanol Ethyl methyl ether
2. *Stereoisomers* are isomers that have the same constitution but differ in the arrangement of their atoms in space.	
(a) *Enantiomers* are stereoisomers that are related as an object and its nonsuperposable mirror image.	The two enantiomeric forms of 2-chlorobutane are  (*R*)-(−)-2-Chlorobutane (*S*)-(+)-2-Chlorobutane
(b) *Diastereomers* are stereoisomers that are not enantiomers.	The cis and trans isomers of 4-methylcyclohexanol are stereoisomers, but they are not related as an object and its mirror image; they are diastereomers.  *cis*-4-Methylcyclohexanol *trans*-4-Methylcyclohexanol

*Isomers are different compounds that have the same molecular formula. They may be either constitutional isomers or stereoisomers.

Section 7.2 The most common kind of chiral molecule contains a carbon atom that bears four different atoms of groups. Such an atom is called a **stereogenic center.** Table 7.2 shows the enantiomers of 2-chlorobutane. C-2 is a stereogenic center in 2-chlorobutane.

Section 7.3 A molecule that has a plane of symmetry or a center of symmetry is achiral. *cis*-4-Methylcyclohexanol (Table 7.2) has a plane of symmetry that bisects the molecule into two mirror-image halves and is achiral. The same can be said for *trans*-4-methylcyclohexanol.

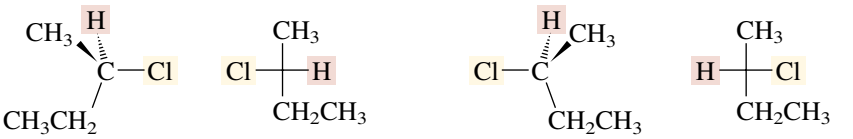
Section 7.4 **Optical activity,** or the degree to which a substance rotates the plane of polarized light, is a physical property used to characterize chiral substances. Enantiomers have equal and opposite **optical rotations.** To be optically active a substance must be chiral, and one enantiomer must be present in excess of the other. A **racemic mixture** is optically inactive and contains equal quantities of enantiomers.

Section 7.5 **Relative configuration** compares the arrangement of atoms in space to some reference. The prefix *cis* in *cis*-4-methylcyclohexanol, for example,

describes relative configuration by referencing the orientation of the CH_3 group to the OH. **Absolute configuration** is an exact description of the arrangement of atoms in space.

Section 7.6 Absolute configuration in chiral molecules is best specified using the prefixes *R* and *S* of the Cahn–Ingold–Prelog notational system. Substituents at a stereogenic center are ranked in order of decreasing precedence. If the three highest ranked substituents trace a clockwise path (highest→second highest→third highest) when the lowest ranked substituent is held away from us, the configuration is *R*. If the path is anticlockwise, the configuration is *S*. Table 7.2 shows the *R* and *S* enantiomers of 2-chlorobutane.

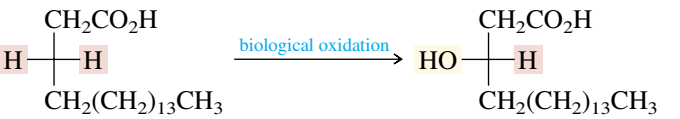
Section 7.7 A **Fischer projection** shows how a molecule would look if its bonds were projected onto a flat surface. Horizontal lines represent bonds coming toward you; vertical bonds point away from you. The projection is normally drawn so that the carbon chain is vertical, with the lowest numbered carbon at the top.



(*R*)-2-Chlorobutane (*S*)-2-Chlorobutane

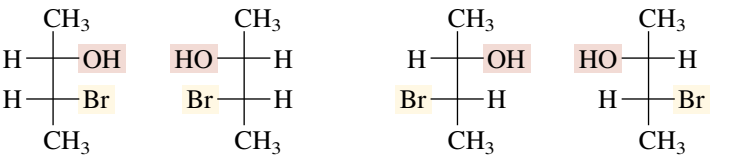
Section 7.8 Both enantiomers of the same substance are identical in most of their physical properties. The most prominent differences are biological ones, such as taste and odor, in which the substance interacts with a chiral receptor site in a living system. Enantiomers also have important consequences in medicine, in which the two enantiomeric forms of a drug can have much different effects on a patient.

Section 7.9 A chemical reaction can convert an achiral substance to a chiral one. If the product contains a single stereogenic center, it is formed as a racemic mixture. Optically active products can be formed from optically inactive starting materials only if some optically active agent is present. The best examples are biological processes in which enzymes catalyze the formation of only a single enantiomer.



Stearic acid (*S*)-3-Hydroxystearic acid

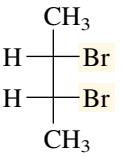
Section 7.10 When a molecule has two stereogenic centers and these two stereogenic centers are not equivalent, four stereoisomers are possible.



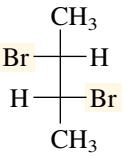
Enantiomers of *erythro*-3-bromo-2-butanol Enantiomers of *threo*-3-bromo-2-butanol

Stereoisomers that are not enantiomers are classified as **diastereomers.** Each enantiomer of *erythro*-3-bromo-2-butanol is a diastereomer of each enantiomer of *threo*-3-bromo-2-butanol.

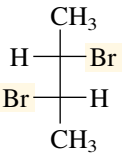
Section 7.11 Achiral molecules that contain stereogenic centers are called **meso forms.** Meso forms typically contain (but are not limited to) two equivalently substituted stereogenic centers. They are optically inactive.



meso-2,3-Dibromobutane



(2*R*,3*R*)-2,3-Dibromobutane



(2*S*,3*S*)-2,3-Dibromobutane

Section 7.12 For a particular constitution, the maximum number of stereoisomers is 2^n, where n is the number of structural units capable of stereochemical variation—usually this is the number of stereogenic centers, but can include *E* and *Z* double bonds as well. The number of stereoisomers is reduced to less than 2^n when there are meso forms.

Section 7.13 Addition reactions of alkenes may generate one (Section 7.9) or two (Section 7.13) stereogenic centers. When two stereogenic centers are produced, their relative stereochemistry depends on the configuration (*E* or *Z*) of the alkene and whether the addition is syn or anti.

Section 7.14 **Resolution** is the separation of a racemic mixture into its enantiomers. It is normally carried out by converting the mixture of enantiomers to a mixture of diastereomers, separating the diastereomers, then regenerating the enantiomers.

Section 7.15 Certain polymers such as polypropylene contain stereogenic centers, and the relative configurations of these centers affect the physical properties of the polymers. Like substituents appear on the same side of a zigzag carbon chain in an **isotactic** polymer, alternate along the chain in a **syndiotactic** polymer, and appear in a random manner in an **atactic** polymer. Isotactic and syndiotactic polymers are referred to as **stereoregular** polymers.

Section 7.16 Atoms other than carbon can be stereogenic centers. Examples include those based on tetracoordinate silicon and tricoordinate sulfur as the stereogenic atom. In principle, tricoordinate nitrogen can be a stereogenic center in compounds of the type N(*x, y, z*), where *x, y,* and *z* are different, but inversion of the nitrogen pyramid is so fast that racemization occurs virtually instantly at room temperature.

PROBLEMS

7.22 Which of the isomeric alcohols having the molecular formula $C_5H_{12}O$ are chiral? Which are achiral?

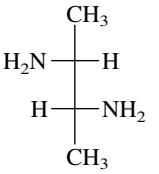
7.23 Write structural formulas or make molecular models for all the compounds that are trichloro derivatives of cyclopropane. (Don't forget to include stereoisomers.) Which are chiral? Which are achiral?

7.24 In each of the following pairs of compounds one is chiral and the other is achiral. Identify each compound as chiral or achiral, as appropriate.

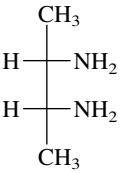
(a) $ClCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$ and $HOCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2OH$

(b) $CH_3CH{=}CHCH_2Br$ and $CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH{=}CH_2$

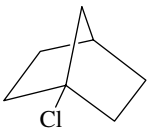
(c)



and



(d)



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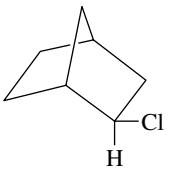
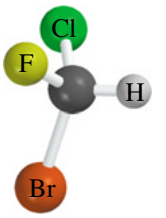
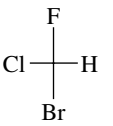
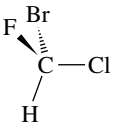


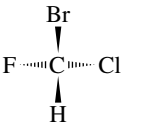
7.25 Compare 2,3-pentanediol and 2,4-pentanediol with respect to the number of stereoisomers possible for each constitution. Which stereoisomers are chiral? Which are achiral?

7.26 In 1996, it was determined that the absolute configuration of (−)-bromochlorofluoromethane is *R*. Which of the following is (are) (−)-BrClFCH?



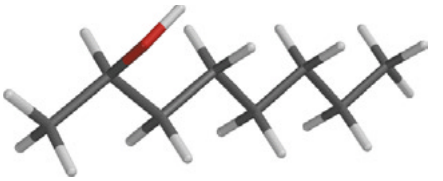




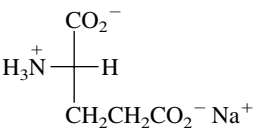


7.27 Specify the configuration at *R* or *S* in each of the following.

(a) (−)-2-Octanol

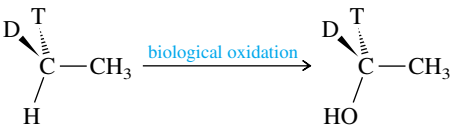


(b) Monosodium L-glutamate (only this stereoisomer is of any value as a flavor-enhancing agent)



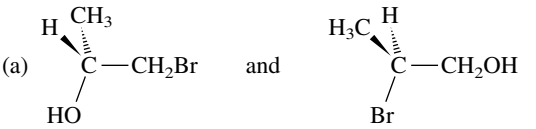
7.28 A subrule of the Cahn–Ingold–Prelog system specifies that higher mass number takes precedence over lower when distinguishing between isotopes.

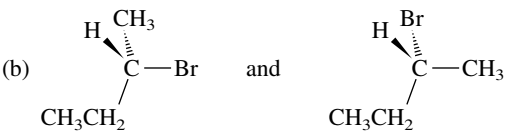
(a) Determine the absolute configurations of the reactant and product in the biological oxidation of isotopically labeled ethane described in Section 7.2.

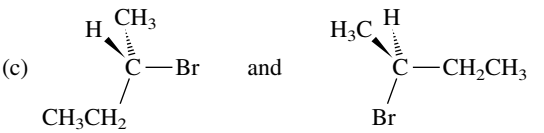


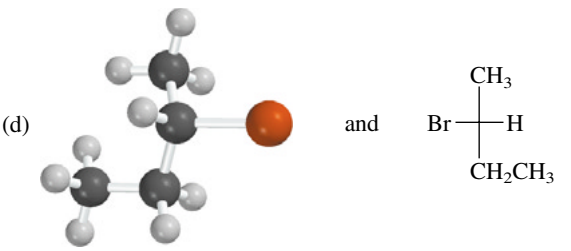
(b) Because OH becomes bonded to carbon at the same side from which H is lost, the oxidation proceeds with retention of configuration (Section 6.13). Compare this fact with the *R* and *S* configurations you determined in part (a) and reconcile any *apparent* conflicts.

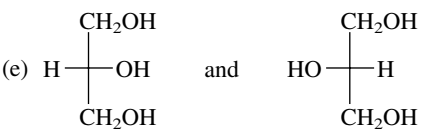
7.29 Identify the relationship in each of the following pairs. Do the drawings represent constitutional isomers or stereoisomers, or are they just different ways of drawing the same compound? If they are stereoisomers, are they enantiomers or diastereomers? (Molecular models may prove useful in this problem.)

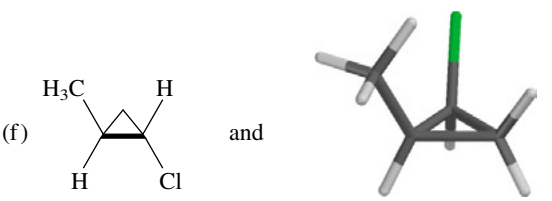


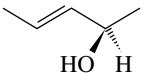
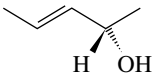


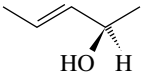
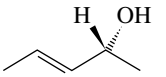


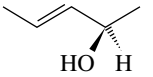
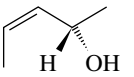


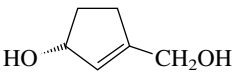
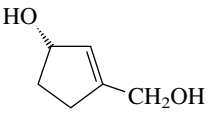


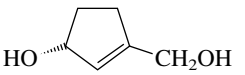
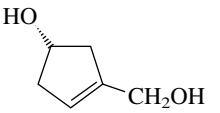


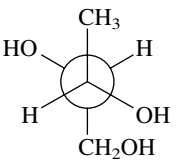
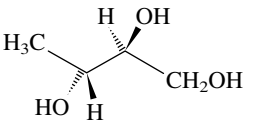
(g)  and 

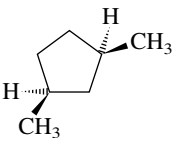
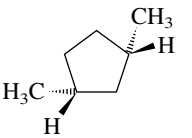
(h)  and 

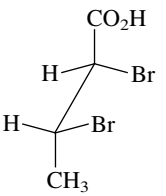
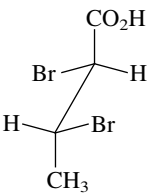
(i)  and 

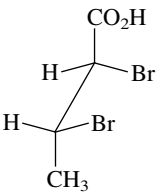
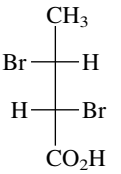
(j)  and 

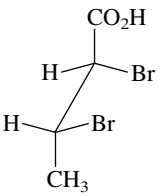
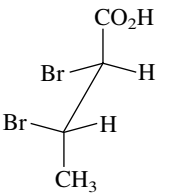
(k)  and 

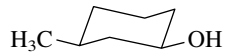
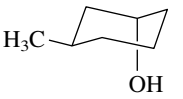
(l)  and 

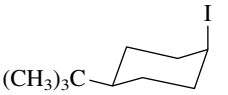
(m)  and 

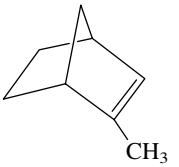
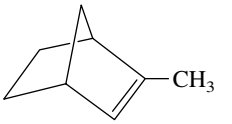
(n)  and 

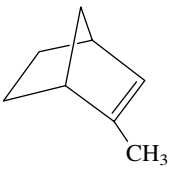
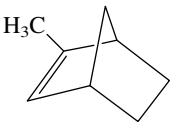
(o)  and 

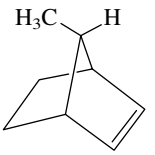
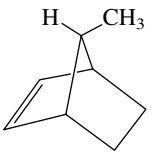
(p)  and 

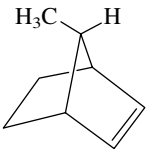
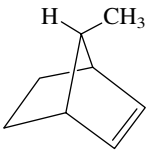
(q)  and 

(r)  and 

(s)  and 

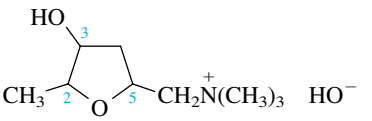
(t)  and 

(u)  and 

(v)  and 

7.30 Chemical degradation of chlorophyll gives a number of substances including *phytol.* The constitution of phytol is given by the name 3,7,11,15-tetramethyl-2-hexadecen-1-ol. How many stereoisomers have this constitution?

7.31 *Muscarine* is a poisonous substance present in the mushroom *Amanita muscaria.* Its structure is represented by the constitution shown.

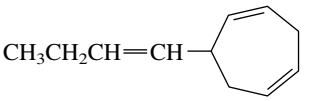


(a) Including muscarine, how many stereoisomers have this constitution?

(b) One of the substituents on the ring of muscarine is trans to the other two. How many of the stereoisomers satisfy this requirement?

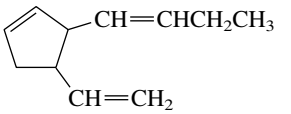
(c) Muscarine has the configuration 2*S*,3*R*,5*S*. Write a structural formula or build a molecular model of muscarine showing its correct stereochemistry.

7.32 *Ectocarpene* is a volatile, sperm cell-attracting material released by the eggs of the seaweed *Ectocarpus siliculosus.* Its constitution is



All the double bonds are cis, and the absolute configuration of the stereogenic center is *S*. Write a stereochemically accurate representation of ectocarpene.

7.33 *Multifidene* is a sperm cell-attracting substance released by the female of a species of brown algae *(Cutleria multifida).* The constitution of multifidene is



(a) How many stereoisomers are represented by this constitution?

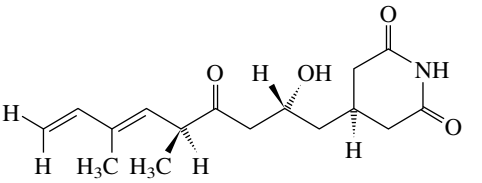
(b) Multifidene has a cis relationship between its alkenyl substituents. Given this information, how many stereoisomers are possible?

(c) The butenyl side chain has the *Z* configuration of its double bond. On the basis of all the data, how many stereoisomers are possible?

(d) Draw stereochemically accurate representations of all the stereoisomers that satisfy the structural requirements of multifidene.

(e) How are these stereoisomeric multifidenes related (enantiomers or diastereomers)?

7.34 *Streptimidone* is an antibiotic and has the structure shown. How many diastereomers of streptimidone are possible? How many enantiomers? Using the *E,Z* and *R,S* descriptors, specify all essential elements of stereochemistry of streptimidone.

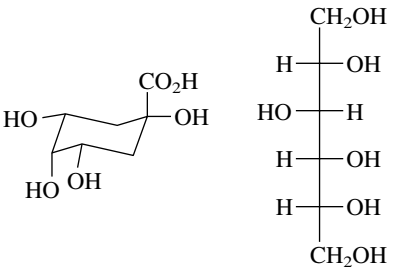


7.35 In Problem 4.26 you were asked to draw the preferred conformation of menthol on the basis of the information that menthol is the most stable stereoisomer of 2-isopropyl-5-methylcyclohexanol. We can now completely describe (−)-menthol structurally by noting that it has the *R* configuration at the hydroxyl-substituted carbon.

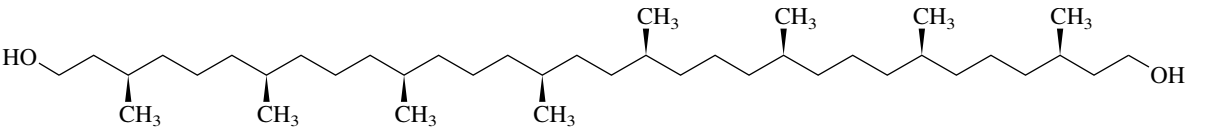
(a) Draw or construct a molecular model of the preferred conformation of (−)-menthol.

(b) (+)-Isomenthol has the same constitution as (−)-menthol. The configurations at C-1 and C-2 of (+)-isomenthol are the opposite of the corresponding stereogenic centers of (−)-menthol. Write the preferred conformation of (+)-isomenthol.

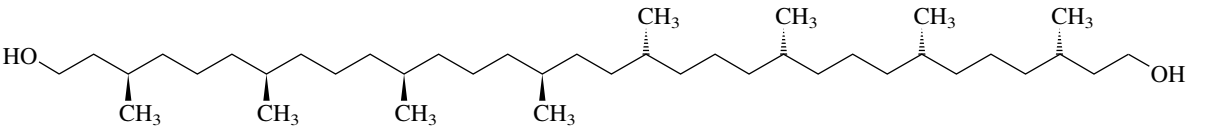
7.36 A certain natural product having $[\alpha]_D$ + 40.3° was isolated. Two structures have been independently proposed for this compound. Which one do you think is more likely to be correct? Why?



7.37 One of the principal substances obtained from archaea (one of the oldest forms of life on earth) is derived from a 40-carbon diol. Given the fact that this diol is optically active, is it compound A or is it compound B?



Compound A



Compound B

7.38 (a) An aqueous solution containing 10 g of optically pure fructose was diluted to 500 mL with water and placed in a polarimeter tube 20 cm long. The measured rotation was −5.20°. Calculate the specific rotation of fructose.

(b) If this solution were mixed with 500 mL of a solution containing 5 g of racemic fructose, what would be the specific rotation of the resulting fructose mixture? What would be its optical purity?

7.39 Write the organic products of each of the following reactions. If two stereoisomers are formed, show both. Label all stereogenic centers *R* or *S* as appropriate.

(a) 1-Butene and hydrogen iodide

(b) (*E*)-2-Pentene and bromine in carbon tetrachloride

(c) (*Z*)-2-Pentene and bromine in carbon tetrachloride

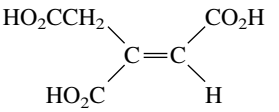
(d) 1-Butene and peroxyacetic acid in dichloromethane

(e) (*Z*)-2-Pentene and peroxyacetic acid in dichloromethane

(f) 1,5,5-Trimethylcyclopentene and hydrogen in the presence of platinum

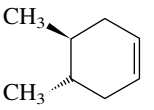
(g) 1,5,5-Trimethylcyclopentene and diborane in tetrahydrofuran followed by oxidation with hydrogen peroxide

7.40 The enzyme *aconitase* catalyzes the hydration of aconitic acid to two products: citric acid and isocitric acid. Isocitric acid is optically active; citric acid is not. What are the respective constitutions of citric acid and isocitric acid?

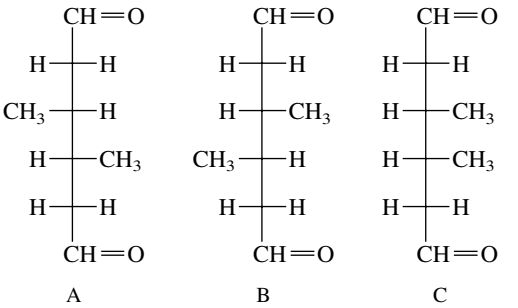


Aconitic acid

7.41 Consider the ozonolysis of *trans*-4,5-dimethylcyclohexene having the configuration shown.



Structures A, B, and C are three stereoisomeric forms of the reaction product.

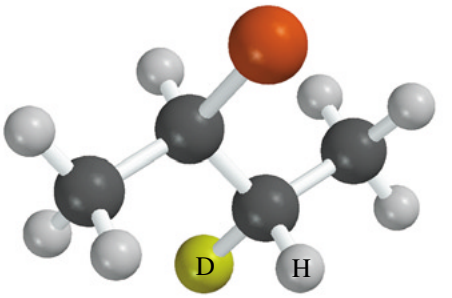


(a) Which, if any, of the compounds A, B, and C are chiral?

(b) What product is formed in the reaction?

(c) What product would be formed if the methyl groups were cis to each other in the starting alkene?

7.42 (a) On being heated with potassium ethoxide in ethanol (70°C), the deuterium-labeled alkyl bromide shown gave a mixture of 1-butene, *cis*-2-butene, and *trans*-2-butene. On the basis of your knowledge of the E2 mechanism, predict which alkene(s), if any, contained deuterium.

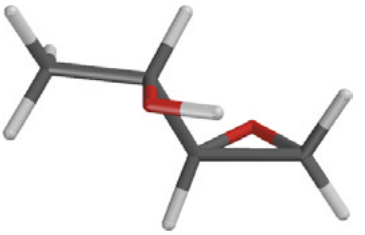


(b) The bromide shown in part (a) is the erythro diastereomer. How would the deuterium content of the alkenes formed by dehydrohalogenation of the threo diastereomer differ from those produced in part (a)?

7.43 A compound (C_6H_{10}) contains a five-membered ring. When Br_2 adds to it, two diastereomeric dibromides are formed. Suggest reasonable structures for the compound and the two dibromides.

7.44 When optically pure 2,3-dimethyl-2-pentanol was subjected to dehydration, a mixture of two alkenes was obtained. Hydrogenation of this alkene mixture gave 2,3-dimethylpentane, which was 50% optically pure. What were the two alkenes formed in the elimination reaction, and what were the relative amounts of each?

7.45 When (*R*)-3-buten-2-ol is treated with a peroxy acid, two stereoisomeric epoxides are formed in a 60:40 ratio. The minor stereoisomer has the structure shown.



(a) Write the structure of the major stereoisomer.

(b) What is the relationship between the two epoxides? Are they enantiomers or diastereomers?

(c) What four stereoisomeric products are formed when racemic 3-buten-2-ol is epoxidized under the same conditions? How much of each stereoisomer is formed?

7.46 Verify that dibromochloromethane is achiral by superposing models of its two mirror image forms. In the same way, verify that bromochlorofluoromethane is chiral.

7.47 Construct a molecular model of (*S*)-3-chlorocyclopentene.

7.48 Construct a molecular model corresponding to the Fischer projection of *meso*-2,3-dibromobutane. Convert this molecular model to a staggered conformation in which the bromines are anti to one another. Are the methyl groups anti or gauche to one another in this staggered conformation?

7.49 What alkene gives a racemic mixture of (2*R*,3*S*) and (2*S*,3*R*)-3-bromo-2-butanol on treatment with Br_2 in aqueous solution? (*Hint:* Make a molecular model of one of the enantiomeric 3-bromo-2-butanols, arrange it in a conformation in which the Br and OH groups are anti to one another, then disconnect them.)