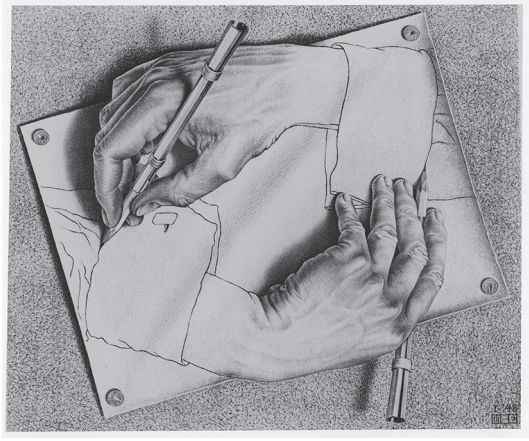
8 Stereochemistry



M. C. Escher, Drawing Hands, 1948

8.1 STEREOISOMERS

Molecules that have different arrangements in three-dimensional space are **stereoisomers**. Stereoisomers have different **configurations**. In Chapter 4, we considered the structures of geometric isomers —*E*,*Z* isomers—an important class of stereoisomers that have different configurations. Another type of stereoisomerism, which is based on *mirror image relationships* between molecules, is the subject of this chapter. The mirror image relationships of stereoisomers are not as easily visualized as the relation between geometric isomers, and a bit of practice is likely to be needed before we can "see" their relationship in three-dimensional space. This is a case where molecular models are very handy.

Changes in molecular configuration that occur in a reaction provide a valuable tool for probing many reaction mechanisms. Stereochemistry can also play an important role in organic synthesis since it is not an easy task to synthesize only a "right-handed" or "left-handed" molecule when both could potentially be formed in a chemical reaction. The chemical synthesis of molecules with precisely the right three-dimensional structure is often a huge experimental challenge; in practical terms, "chiral synthesis" is an essential component of virtually all drug synthesis.

A molecule's configuration also plays a major role in its biological function. We will see many examples of stereoisomerism in biological systems in this chapter and beyond.

8.2 MIRROR IMAGE OBJECTS, MIRROR IMAGE MOLECULES, AND CHIRALITY

We are all familiar with mirror image objects. Every object has a mirror image, but this reflected image need not be identical to the actual object. Thus, when we look into a mirror, we see someone who does not actually exist, namely, our mirror image.

A simple wooden chair looks exactly like its mirror image (Figure 8.1a). Similarly, the mirror images of a teacup or a hammer are identical to the objects themselves. When an object and its mirror image are identical, they are *superimposable*. Superimposable objects can be "placed" on each other so that each feature of one object precisely coincides in space with an equivalent feature in the mirror image object.

Some objects cannot be superimposed upon their mirror images: They are *nonsuperimposable*. One example is the sidearm chair shown in Figure 8.1b. When a chair with a "right-handed arm" is reflected in a mirror, it becomes a chair with a "left-handed arm" (Figure 8.1b). We can convince ourselves of this by imagining sitting in the chair or its mirror image. Or, we could stop by a classroom, which usually has chairs for both right- and left-handed persons, and do the experiment.

Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-800780-8.00008-5

Figure 8.1 Objects and Their Mirror Images
In (a), the chair and its mirror image are identical. They can be superimposed. In (b), the mirror image, side-arm chairs cannot be superimposed. One chair has a "right-handed" arm, and the other has a "left-handed" arm. (These particular chairs were designed by the renowned woodworker George Nakashima.)

Our hands are related as nonsuperimposable mirror images. We know that we cannot superimpose our hands, as is deftly shown by the M. C. Escher lithograph found at the beginning of this chapter and in Figure 8.2. An object that is not superimposable on its mirror image is **chiral** (Greek *chiron*, hand). Objects such as gloves and shoes also have a "handedness," and they are also chiral. An object that can be superimposed on its mirror image is **achiral**.

We can determine whether or not an object is chiral without trying to superimpose it on its mirror image. If an object has a *plane of symmetry*, it is not chiral. A plane of symmetry bisects an object so that one half is the mirror image of the other half. For example, a cup has a plane of symmetry that divides it so that one half is the mirror image of the other half. The chair in part (a) of Figure 8.3 is achiral because it has a plane of symmetry. *The presence or absence of a plane of symmetry tells us whether an object is chiral or achiral.*

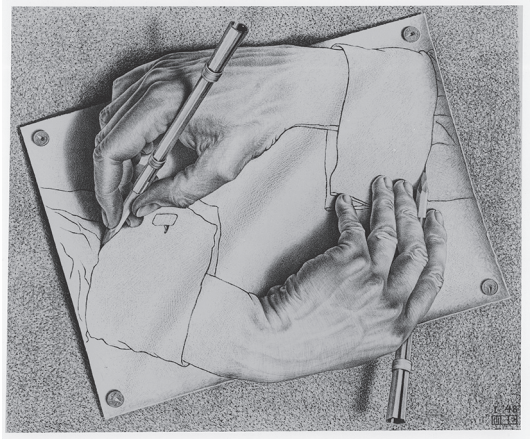


Figure 8.2 Nonsuperimosable Mirror Images
A left and a right hand are nonsuperimposable mirror images. (M.C. Escher's "Drawing Hands" © 2014 The M.C. Escher Company-The Netherlands. All rights reserved. www.mcescher.com)

Chiral Molecules

We can extend the concept of chirality from macroscopic objects to molecules. *A molecule is chiral if it contains at least one carbon atom attached to four different atoms or groups.* Such a carbon atom is a **stereogenic** center. A stereogenic center is sometimes called a **chiral center**, and the carbon atom is sometimes called a **chiral carbon** atom, although it is the molecule that is chiral, not a single carbon atom within it. Most molecules produced in living organisms are chiral, nearly all drugs are chiral, and the synthesis of chiral molecules in the laboratory is a significant part of organic synthesis.

The four atoms or groups at a stereogenic center can be arranged in two ways to give two stereoisomers. The stereoisomers of bromochlorofluoromethane provide an example. Bromochlorofluoromethane does not have a plane of symmetry. Figure 8.3 shows that it can exist as a pair of nonsuperimposable mirror image isomers. Therefore, bromochlorofluoromethane is chiral.

Figure 8.3 Nonsuperimosable Mirror Image Molecules
Bromochlorofluoromethane does not have a plane of symmetry. Therefore, it is chiral, and it exists as a pair of nonsuperimposable mirror image isomers. (a) Schematic diagram; (b) Ball-and-stick molecular models.

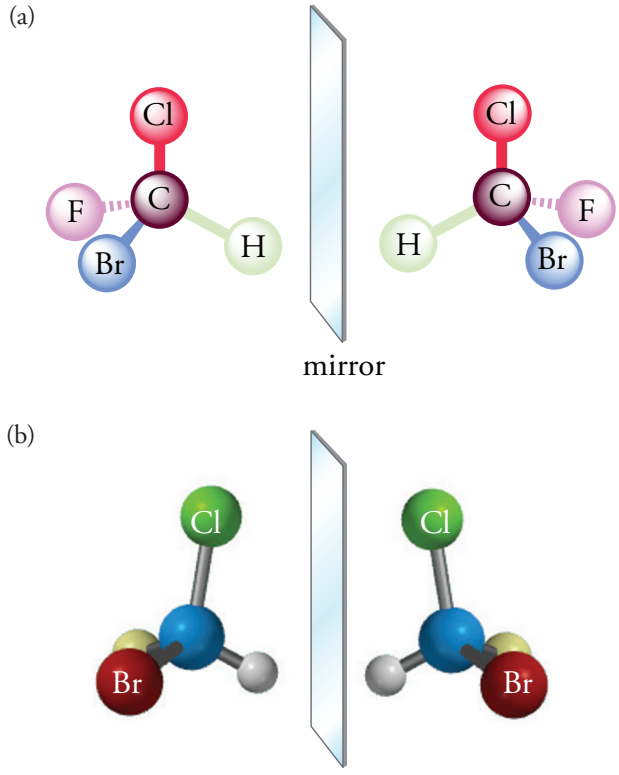


Figure 8.4 Planes of Symmetry in Dichloromethane
Dichloromethane, which has not one, but two planes of symmetry, can be superimposed on its mirror image. It is achiral.

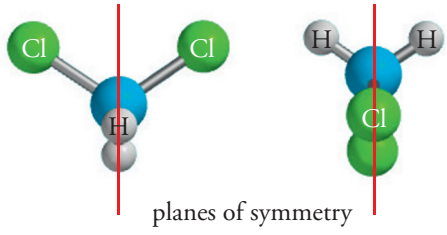
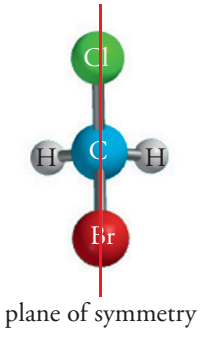
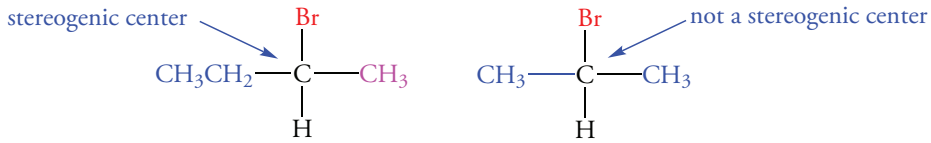


Figure 8.5 Plane of Symmetry in Bromochloromethane
Bromochloromethane has a plane of symmetry, and therefore, it can be superimposed on its mirror image. It is achiral.



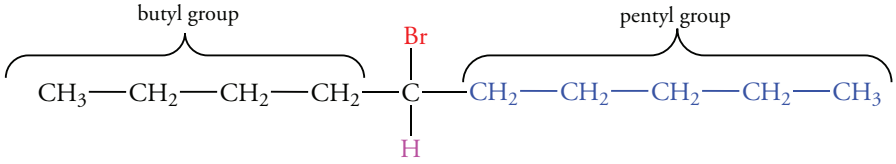
Mirror Image Isomers

Two stereoisomers related as nonsuperimposable mirror images are called **enantiomers** (Greek *enantios*, opposite + *meros*, part). We can tell that a substance is chiral and predict that two enantiomers exist by identifying the substituents on each carbon atom. A carbon atom with four different substituents is a stereogenic center, and a molecule with a stereogenic center is chiral. It can exist as either of a pair of enantiomers. For example, 2-bromobutane is chiral because C-2 is attached to four different groups (CH_3—, CH_3CH_2—, Br—, and H—). In contrast, no carbon in 2-bromopropane is bonded to four different groups; C-2 is bonded to two methyl groups. Thus, 2-bromopropane is not chiral (Figures 8.4 and 8.5).

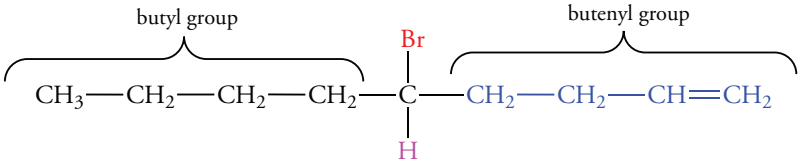


2-bromobutane (a chiral molecule) 2-bromopropane (an achiral molecule)

The existence of a stereogenic center in a complex molecule may not be immediately apparent. This situation occurs when the groups bonded to a chiral carbon atom differ at sites not immediately adjacent to the stereogenic center. The difference between a methyl group and an ethyl group is readily apparent in 2-bromobutane. However, in some molecules, the difference is less obvious. For example, 5-bromodecane and 5-bromo-1-nonene both have a stereogenic center.



5-bromodecane

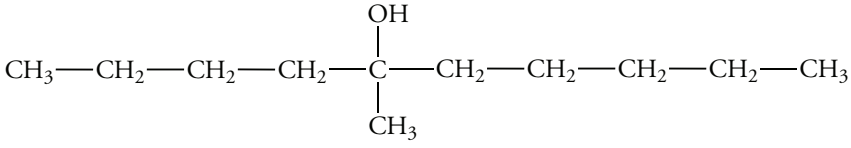


5-bromo-1-nonene

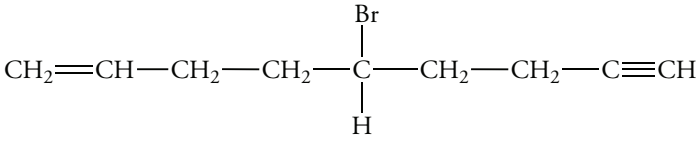
Problem 8.1

Which of the following molecules are chiral? Explain your answer.

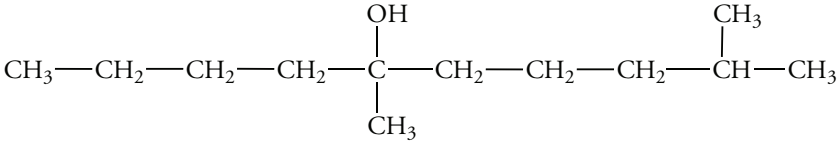
(a)



(b)

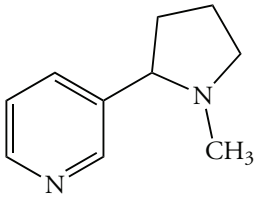


(c)



Problem 8.2

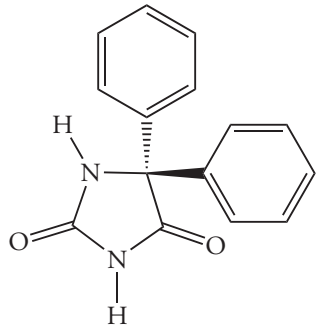
The structure of nicotine is shown below. Is nicotine chiral?



nicotine

Problem 8.3

Phenytoin has anticonvulsant activity. Is phenytoin chiral or achiral? Determine your answer by identifying the number of different groups bonded to its tetrahedral carbon atoms; then determine whether or not it has a plane of symmetry.



phenytoin

Sample Solution

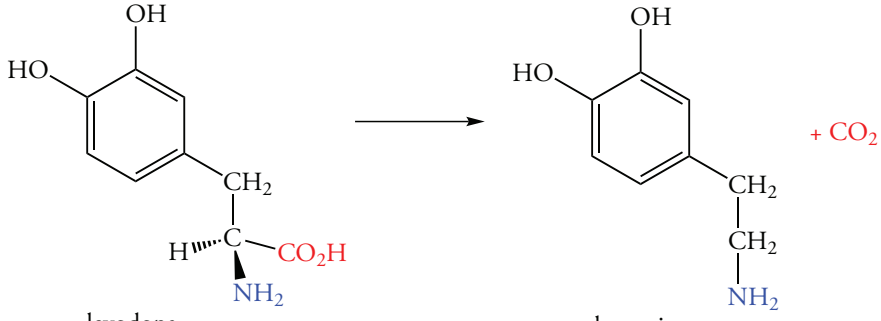
Phenytoin does not contain a carbon bonded to four different groups. It has a plane of symmetry that lies in the plane of the page. One of the benzene rings of phenytoin is above and the other below the symmetry plane. It is achiral.

Properties of Enantiomers

We can regard hands as analogous to the enantiomers of a chiral molecule. Let's consider the interaction of hands with a symmetrical object such as a pair of tweezers. The tweezers are symmetrical. They can be used equally well with either hand because there is no preferred way to pick up or manipulate a pair of tweezers. However, even if blindfolded, we could easily use our hands to distinguish right- and left-handed gloves. Our hands are "a chiral environment," and in this environment, mirror image gloves do not interact with hands in the same way. The right glove will fit only the right hand. *We can distinguish chiral objects only because we are chiral.*

Pairs of enantiomers have the same physical and chemical properties: they have that same heats of formation, density, melting point, and boiling point. They also have the same chemical properties, and undergo the same reactions in an achiral environment. However, enantiomers can be distinguished in a chiral environment. This difference is important in many processes in living cells. Only one of a pair of enantiomers fits into a specific site in a biological molecule such as an enzyme catalyst because the site on the enzyme that binds the enantiomer is chiral. The binding of this enantiomer is **stereospecific**.

An example of a stereospecific process is the conversion of the drug levodopa to dopamine, a neurotransmitter in the brain. Levodopa (or L-dopa), the precursor of dopamine, is administered to treat Parkinson's disease. Levodopa has one chiral carbon atom. Therefore, it exists as either of two enantiomers. Only the enantiomer with the configuration shown below is transformed into dopamine.



levodopa dopamine

The reaction occurs because a stereospecific decarboxylase catalyzes the loss of a carboxyl group by formation of carbon dioxide (decarboxylation). This enzyme has a chiral binding site for levodopa, but it does not bind the enantiomer of levodopa.

8.3 OPTICAL ACTIVITY

Although enantiomers have identical chemical properties in achiral environments, they differ in one important physical property: Enantiomers behave differently toward plane-polarized light. This difference allows us to distinguish a chiral molecule from its enantiomer in the laboratory.

Plane-Polarized Light

A beam of light consists of electromagnetic waves oscillating in an infinite number of planes at right angles to the direction of propagation of the light. When a light beam passes through a polarizing filter, it is converted to *plane-polarized light* whose electromagnetic waves oscillate in a single plane. We are familiar with this phenomenon in everyday life: Plane-polarized light can be produced by certain sunglasses, which reduce glare by acting as a polarizing filter. They partly block horizontally oscillating light reflecting off the surfaces of various objects. Some camera lenses also have polarizing filters to reduce glare in brightly lit photographs.

Plane-polarized light interacts with chiral molecules. This interaction can be measured by an instrument called a **polarimeter** (Figure 8.6). In a polarimeter, light with a single wavelength—that is, *monochromatic light*—passes through a polarizing filter. The polarized light then traverses a tube containing a solution of the compound to be examined. Plane-polarized light is not affected by achiral molecules. However, the plane of polarized light rotates when it is absorbed by chiral molecules. When the plane-polarized light leaves the sample tube, it passes through a second polarizing filter called an analyzer. The analyzer is rotated in either clockwise or counterclockwise direction to match the rotated polarization plane so that it passes through the filter with maximum intensity. An angle, α, is read off the analyzer. This angle is called the *observed optical rotation*, α_{obs}. It equals the angle by which the light has been rotated by the chiral compound. Because chiral molecules rotate plane-polarized light, they are **optically active**. Achiral molecules do not rotate plane-polarized light, so they are **optically inactive**.

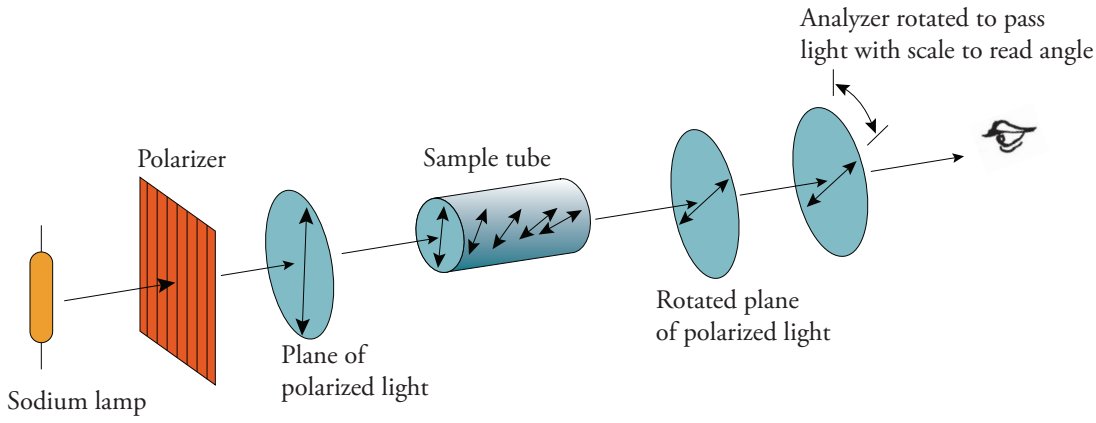


Figure 8.6 Schematic Diagram of a Polarimeter
Plane-polarized light is obtained by passing light through a polarizing filter. Any chiral compound in the sample tube rotates the plane-polarized light. The direction and magnitude of the rotation are determined by rotating the analyzer to allow the light to pass through with maximum brightness. In a modern instrument, this is all done electronically, but the basic principle is the same.

Specific Rotation

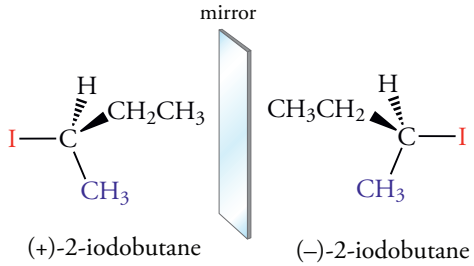
The amount of rotation observed in a polarimeter depends on the structure of the substance and on its concentration. The optical activity of a pure chiral substance is reported as its *specific rotation*, symbolized by $[\alpha]_D$. It is the number of degrees of rotation of a solution at a concentration measured in g mL^{-1} in a tube 1 dm (10 cm) long. The standard conditions selected for polarimetry measurements are 25 °C, and a wavelength of 589 nm. This yellow light is the D line of a sodium vapor lamp.

$$[\alpha]_D = \frac{\alpha_{obs}}{l \times c}$$

If a chiral substance rotates plane-polarized light to the right—that is, in a positive (+) or clockwise direction—the substance is *dextrorotatory* (Latin *dextra*, right). If a chiral substance rotates plane-polarized light to the left—in a negative (–) or counterclockwise direction—the substance is *levorotatory* (Latin

laevus, left). The enantiomers of a chiral substance—called dextrorotatory and levorotatory isomers—rotate polarized light the same number of degrees, but in opposite directions. Therefore, they are sometimes called **optical isomers**.

We often refer to an enantiomer by prefixing the sign of the optical rotation at 589 nm to the name of the compound. For example, one of the enantiomers of 2-iodobutane has $[\alpha]_D = -15.15$. It is called (–)-2-iodobutane. The other enantiomer is (+)-2-iodobutane, $[\alpha]_D = +15.15$.



(+)-2-iodobutane (–)-2-iodobutane

The (+) isomer is sometimes called the *d* form because it is dextrorotatory; the (–) isomer is sometimes called the *l* form because it is levorotatory. Earlier, we encountered levodopa, so named because it is levorotatory. It is also called L-dopa and (–)-dopa. The specific rotation of L-dopa is –13.1°. Table 8.1 lists the specific rotations of some common substances.

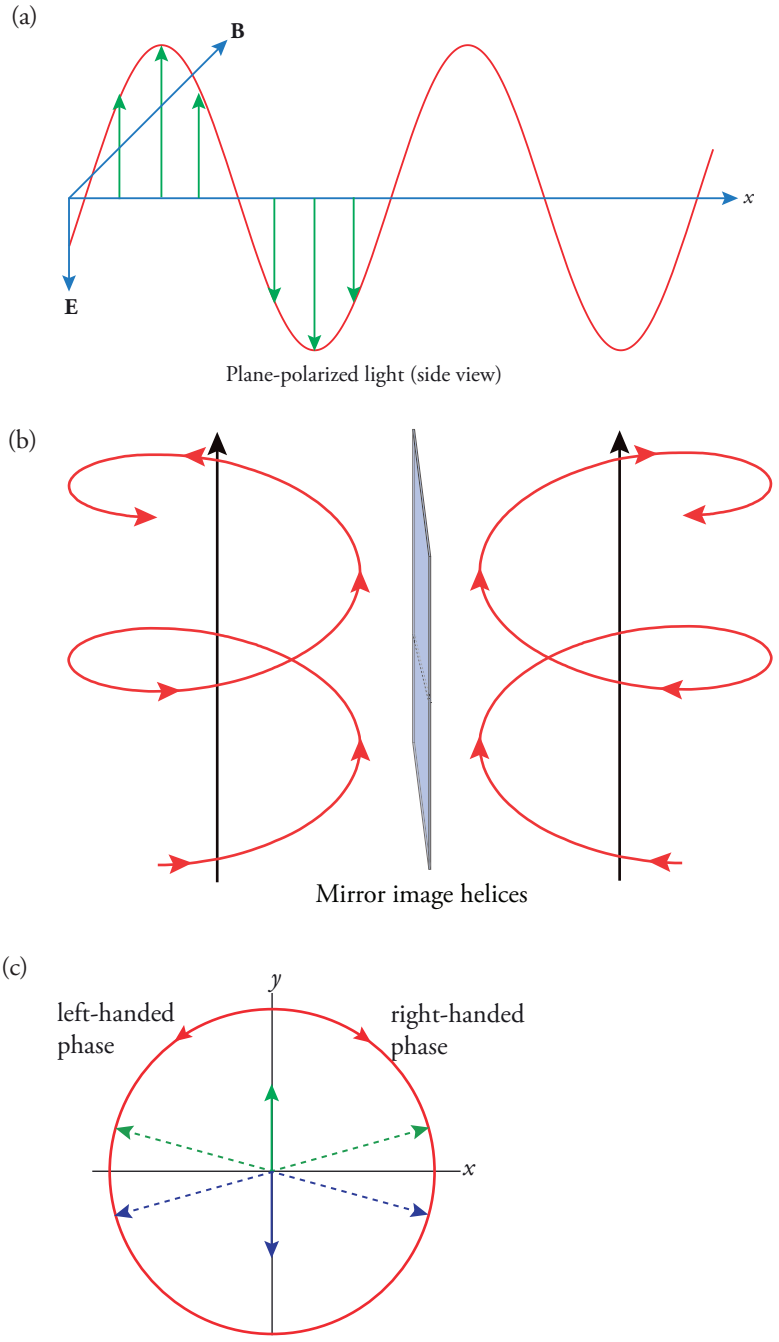
Table 8.1
Specific Rotations of Common Compounds

Compound	$[\alpha]_D$
Azidothymidine (AZT)	+99°
Cefotaxin (a cephalosporin)	+55°
Cholesterol	–31.5°
Cocaine	–16°
Codeine	–136°
Epinephrine (adrenaline)	–5.0°
Levodopa	–13.1°
Monosodium glutamate (MSG)	+25.5°
Morphine	–132°
Oxacillin (a penicillin)	+201°
Progesterone	+172°
Sucrose	+66°
Testosterone	+109°

Circularly Polarized Light and Optical Rotation

We have said that chiral molecules cannot be distinguished in a symmetric environment. In the next sentence, we said that chiral molecules interact differently with plane-polarized light. However, by definition, plane-polarized light has a plane of symmetry! Is there not a massive contradiction here? The answer is no because we can interpret plane-polarized light in terms of *circularly polarized light* (Figure 8.7). One form of circularly polarized light has a right-handed helical sense, and the other form has a left-handed helical sense. A helix is a chiral object, and right- and left-handed helices are related as mirror images. If we superimpose the two, we obtain plane-polarized light. So this helicity is "hiding" in plane-polarized light, which has inherent chiral components.

Figure 8.7
Schematic Diagrams of Plane- and Circularly Polarized Light
(a) In plane-polarized light, the electric field vectors of the light all oscillate in a single plane. (b) In circularly polarized light, the electric field vector can rotate in a right-handed (clockwise) or left-handed (counterclockwise) direction. (c) If right-handed and left-handed phases of circularly polarized light are superimposed, the electric field vectors in the $+x$ to $-x$ directions cancel, and the y-components are additive, and directed along the y-axis. The net result is plane-polarized light.



A chiral center is bonded to four different groups, and each of these bonds has an electric field. Therefore, the net electric field around a chiral center is chiral, and it absorbs one phase of circularly polarized light more than the other. As a result, the vectors no longer cancel, and the light is rotated in either a clockwise or counterclockwise direction.

Optical Purity

Most naturally occurring molecules that contain one stereogenic center exist as one enantiomer. Samples that contain only one enantiomeric form are **optically pure**. Naturally occurring cholesterol, for example, exists only as the (–) form. It rotates light in a counterclockwise direction. However, compounds synthesized in the laboratory may not all have the same handedness, and the reaction yields a mixture of two enantiomers.

What is the optical rotation of a mixture of enantiomers, and how is it related to the percentage of each enantiomer in the mixture? When plane-polarized light interacts with a single enantiomer of a chiral molecule, the plane is rotated in one direction. If the plane-polarized light interacts with the other enantiomer, the plane is rotated in an equal and opposite direction. If a solution contains equal amounts of two enantiomers, the clockwise and counterclockwise rotations resulting from all molecules

cancel, and there is no net rotation. Mixtures containing equal amounts of enantiomers are called **racemic mixtures**. A racemic mixture is represented in the name of a compound with a (±) prefix, as in (±)-2-iodobutane. The word "racemic" is derived from the Latin word *racemus*, a cluster of grapes. It is so named because racemic mixtures were first found in tartaric acid, which precipitates from many wines as they age. See Figure 8.13.

Now consider a circumstance in which the percent ratio of a mixture of enantiomers is not 50:50. The percent **enantiomeric excess** of the enantiomer present in the larger amount is calculated as follows.

% enantiomeric excess = % of one enantiomer – % of other enantiomer = optical purity

The percent enantiomeric excess is the **optical purity** of the sample. For example, a 60:40 ratio of (+)-2-iodobutane and (–)-2-iodobutane is 20% optically pure. This value indicates that the rotation of the (–) isomer (40% of the total) cancels the rotation of some of the (+) isomer (40% of the total). The remaining 20% of the sample, which is (+)-2-iodobutane, is responsible for the observed rotation, so the sample is 20% optically pure.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\%$$

Problem 8.4

What is $[\alpha]_D$ of the enantiomer of naturally occurring testosterone? (See Table 8.1.) What is the name of this enantiomer?

Problem 8.5

A sample of a solution of 1.5 g of cholic acid, a bile steroid, in 10 mL of alcohol is placed in a 10.0-cm sample tube. The observed rotation is +5.5. Calculate $[\alpha]_D$ for cholic acid.

Problem 8.6

A sample of epinephrine prepared in the laboratory has $\alpha_{obs} = -0.5°$. What is the optical purity of the sample? What is the percentage of each enantiomer in the sample? $[\alpha]_D$ for epinephrine is –5.0°.

Sample Solution

The specific rotation of epinephrine is –5.0°. We calculate the optical purity using the following equation.

$$\text{optical purity} = \frac{\text{observed rotation}}{\text{rotation of pure enantiomer}} \times 100\%$$

$$\text{optical purity} = \frac{-0.5}{-5.0} \times 100\% = 10\%$$

The enantiomeric excess is equal to the optical purity. The sum of the two enantiomers is 100%. Let the percent of the enantiomer with the negative optical rotation be x. The percent of the other enantiomer is $100 - x$. Use the following equation and substitute the algebraic quantities.

% enantiomeric excess = % of one enantiomer – % of other enantiomer = optical purity

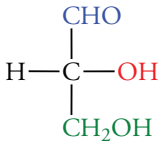
$$10\% = x - (100\% - x)$$

$$x = 55\%$$

Thus, the percentages of the two enantiomers are 55% and 45%.

8.4 FISCHER PROJECTION FORMULAS

Drawing molecules in three dimensions is time consuming. Furthermore, it is not easy to "read" the resulting perspective structural formulas, especially for compounds that contain several chiral centers (Section 8.6). However, the structural formula of a chiral substance can be conveniently drawn as a **Fischer projection**, which was introduced by the German chemist Emil Fischer more than a century ago. The configuration of a chiral substance in a Fischer projection formula is obtained by comparing it to the configuration of a *reference compound* whose common name is glyceraldehyde.



glyceraldehyde

Glyceraldehyde contains a carbon atom bonded to four different groups, so it can exist as either of two enantiomers (Figure 8.8). The enantiomers of glyceraldehyde in a Fischer projection are drawn according to the following conventions:

1. Arrange the carbon chain vertically with the most oxidized group (—CHO in glyceraldehyde) at the "top."
2. Place the carbon atom at the chiral center in the plane of the paper. It is C-2 in glyceraldehyde.
3. Because C-2 is bonded to four groups, the CHO group and the CH_2OH group extend behind the plane of the page, and the hydrogen atom and the hydroxyl group extend up and out of the plane.
4. Project these four groups onto a plane. The carbon atom at the chiral center is usually not shown in this convention. It is located at the point where the bond lines cross. The vertical lines project away from the viewer. The horizontal lines project toward the viewer.

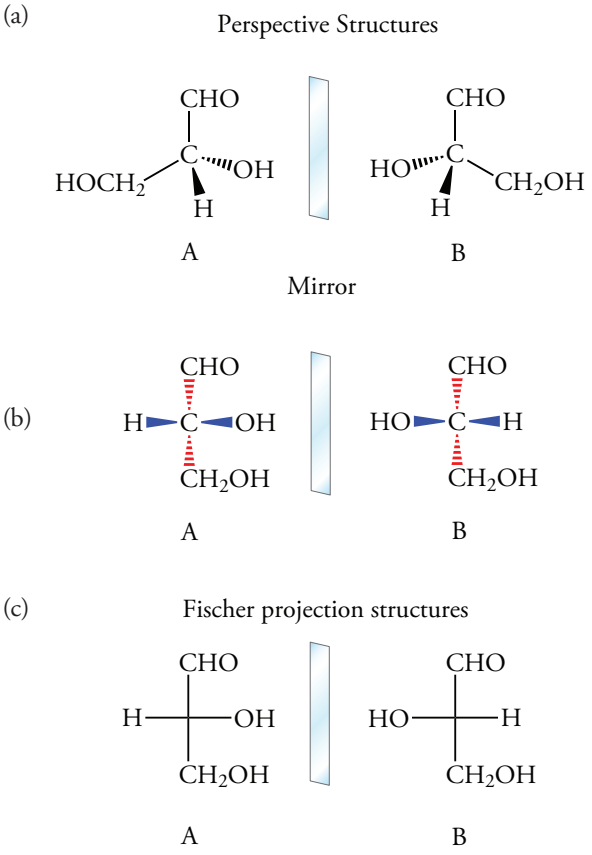
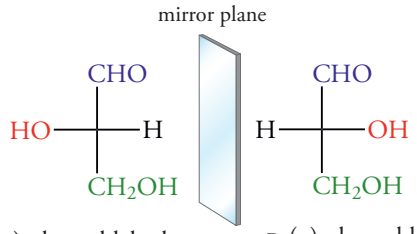


Figure 8.8 Fischer Projection Structures of Glyceraldehyde
(a) Perspective structures of glyceraldehyde. (b) Projection structures. (c) Fisher projection structures of the enantiomers glyceraldehyde. The chiral center is located at the point where the bond lines intersect. The carbon atom is not usually shown. The vertical lines extend away from the viewer, behind the plane of the page; horizontal lines extend toward the viewer, out of the plane of the page, as shown in part (b).

A Fischer projection formula is a two-dimensional representation. It might appear that if we lifted one formula out of the plane and rotated it 180° around the carbon backbone, we would obtain the structure of the enantiomer. However, if this were done for molecule A in Figure 8.8, the carbonyl group and the hydroxymethyl group, originally behind the plane, would be in front of the plane. These groups would not occupy identical positions with respect to the carbonyl group and hydroxymethyl group of molecule B, which are behind the plane. Therefore, to avoid the error of apparently achieving a two-dimensional equivalence of nonequivalent three-dimensional molecules, we *cannot* lift the two-dimensional representations out of the plane of the paper.

Fischer projection formulas can be drawn for any pair of enantiomers. These formulas imply that we know the configuration at the chiral carbon atom. However, the true configuration could not be determined by early chemists because there was no way to determine the arrangement of the atoms in space. Therefore, Fischer arbitrarily assigned a configuration to one member of the enantiomeric pair of

glyceraldehydes. The dextrorotatory enantiomer of glyceraldehyde, which rotates plane-polarized light in a clockwise direction (+13.5°), was assigned to the Fischer projection with the hydroxyl group on the right side. Fischer called the compound D-glyceraldehyde. The mirror image compound, (–)-glyceraldehyde, corresponds to the structure in which the hydroxyl group is on the left. It rotates plane-polarized light in a counterclockwise direction (–13.5°). Fischer called the compound L-glyceraldehyde.



L-(–)-glyceraldehyde
$[\alpha]_D = -13.5°$

D-(+)-glyceraldehyde
$[\alpha]_D = +13.5°$

Fischer projection structures

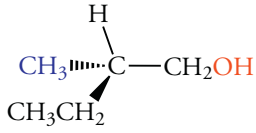
Problem 8.7

Write the Fischer projection formula of each of the following compounds.

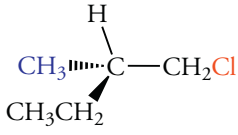
(a) D-lactic acid, $CH_3CH(OH)CO_2H$
(b) L-serine, $HOCH_2CH(NH_2)CO_2H$
(c) D-valine, $(CH_3)_2CHCH(NH_2)CO_2$

8.5 ABSOLUTE CONFIGURATION

We began this chapter by saying that the arrangement of atoms in space determines the configuration of a molecule. When we know the exact positions of these atoms in space, we know the molecule's **absolute configuration**. The absolute configuration of an enantiomer cannot be established by measuring the direction or magnitude of its optical rotation. Optical rotation depends on both the configuration and the identity of the four groups around the central carbon atom. One "left-handed" molecule could be levorotatory, whereas another "left-handed" molecule with different groups could be dextrorotatory. For example, in spite of the similarity of three of the groups (CH_3CH_2, CH_3, and H), the following structures of 2-methyl-1-butanol and l-chloro-2-methylbutane, which have the same configuration, have different directions of optical rotation.



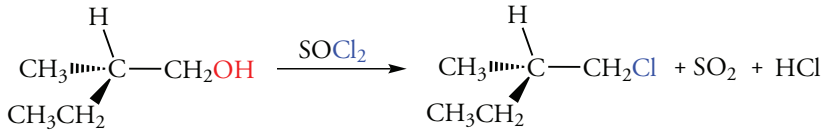
(–)-2-methyl-1-butanol
$[\alpha]_D = -5.8$



(+)-1-chloro-2-methylbutane
$[\alpha]_D = +1.7$

To determine the absolute configuration, we require a method that can specify the positions of all atoms in the molecule. One way to do this is by X-ray crystallography. The absolute configuration of an optically active substance was first determined in 1950. The arrangement of its atoms in space corresponds to the arrangement of atoms in (+)-glyceraldehyde arbitrarily assigned by Fischer. His original choice was correct! As a result, all configurations that had been deduced by using (+)-glyceraldehyde as the reference compound are also correct, and this includes all the amino acids isolated from proteins, all carbohydrates, and many other compounds.

The absolute configuration of a compound can be determined by comparing it to a reference compound of known absolute configuration. This structure proof sometimes requires an elaborate series of reactions. However, the principle is easily illustrated with the conversion of 2-methyl-l-butanol to l-chloro-2-methylbutane. Alcohols can be converted into chloroalkanes by thionyl chloride ($SOCl_2$). The reaction does not affect any of the bonds at the stereogenic center of 2-methyl-l-butanol. Hence, the configuration is unchanged. If the absolute configuration of the alcohol is known, the groups bonded to the stereogenic center in the chloroalkane must be arranged in the same configuration. If the absolute configuration of the alcohol were not known, we would still know that the haloalkane would have the same relative configuration.

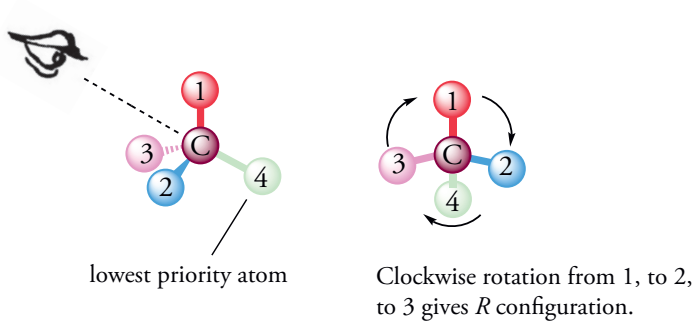


R,S Configurations: The Kahn–Ingold–Prelog System of Configurational Nomenclature

The configurations of some molecules, such as amino acids and carbohydrates, can easily be compared to reference compounds such as D-glyceraldehyde. But this procedure is not easily applied to molecules whose structures differ considerably from the reference compound. To circumvent this difficulty, R. S. Kahn, K. C. Ingold, and V. Prelog established a set of rules in 1964 that describe the absolute configuration of any chiral molecule.

The ***R,S* system** of configurational nomenclature for describing absolute configurations is related to the method we described in Chapter 6 to assign the *E,Z* configuration of alkenes. In the *R,S* system, the four groups bonded to each chiral carbon atom are ranked from highest to lowest priority. The highest priority group is assigned the number 1, the lowest priority group is assigned the number 4. Then, the molecule is oriented so that the bond from the carbon atom to the group of lowest priority is arranged directly along our line of sight pointing downward (Figure 8.9). When this has been done, the three higher priority groups point up and lie on the circumference of a circle. (It may help to imagine holding the lowest priority group in your hand like the stem of a flower as you examine the petals.) Consider the path taken as we trace the groups ranked 1–3. In Figure 8.9, this direction is clockwise. Therefore, the configuration is designated *R* (Latin *rectus*, right). If we trace a counterclockwise path from groups ranked 1–3, the configuration is designated *S* (Latin *sinister*, left). Once established, the configuration is designated by the symbol *R* or *S*, within parentheses, as a prefix to the name of the compound.

Figure 8.9
Kahn–Ingold–Prelog System of Configurational Nomenclature
Place the lowest priority atom or group away from your eye and view the chiral site along the axis of the carbon bond to the lowest priority group. (The diagram of the eye in this figure is from a drawing in the notebooks of Leonardo da Vinci.)



Priority Rules

The priority rules we defined in Chapter 5 for describing the configuration of geometric isomers also apply to *R,S* configurational nomenclature for chiral compounds.

1. Atoms: Rank the four atoms bonded to a chiral carbon atom in order of decreasing atomic number; the lower the atomic number, the lower the priority. Isotopes are ranked in order of decreasing mass. For example, ^{2}H (deuterium) > ^{1}H.

$$\underset{\text{highest priority}}{I} > Br > Cl > F > O > N > C > {}^{2}H > \underset{\text{lowest priority}}{{}^{1}H}$$

2. Groups of atoms: If a chiral atom is attached to two or more identical atoms, move down the chain until a difference is encountered. Then apply rule 1. Using this rule, we find that the priority of alkyl groups is

$$(CH_3)_3C— > (CH_3)_2CH— > CH_3CH_2— > CH_3—$$

3. Multiple bonds: If a group contains a double bond, both atoms are doubled. That is, a double bond is counted as two single bonds to each of the atoms of the double bond. The same principle is used for a triple bond. Thus, the order is

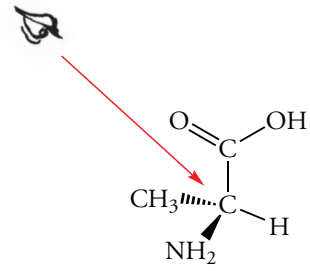
$$HC{\equiv}C\text{—} > CH_2{=}CH\text{—} > CH_3CH_2\text{—}$$

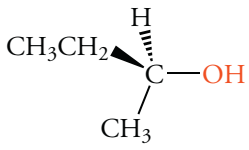
The priority order for common functional groups containing oxygen is

$$\text{—}CO_2H \text{ (carboxylic acid)} > \text{—}CHO \text{ (aldehyde)} > \text{—}CH_2OH \text{ (alcohol)}$$

We can use the *R*,*S* system to describe the configuration of the enantiomers of alanine, which has a chiral center bonded to a hydrogen atom, a methyl group, a carboxylic acid group, and an amino group (NH_2). A perspective drawing of the enantiomer of alanine isolated from proteins is shown below. It has an S configuration.

Look into the molecule toward the lowest priority group, which is hydrogen.



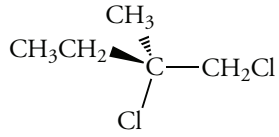


(*S*)-(+)2-butanol

We recall that the direction or magnitude of the optical rotation of a stereoisomer does not determine its absolute configuration. That is, a (+) optical rotation does *not* mean that a molecule has an *R* configuration. For example, the optical rotation of (*S*)-2-butanol is clockwise (+). This isomer is *S*-(+)-2-butanol.

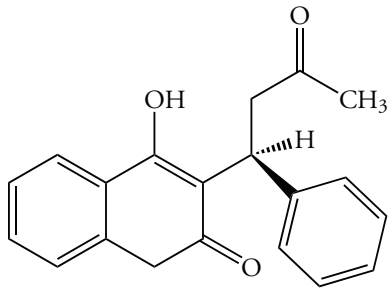
Problem 8.8

What is the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane?



Problem 8.9

Warfarin is an anticoagulant drug. Warfarin is used both to treat thromboembolic disease and, in larger doses, as a rat poison. Assign its configuration. (The C_6H_5 group, a *phenyl* group, represents a benzene ring bonded at the chiral center.) Assign the configuration of the following stereoisomer of 1,2-dichloro-2-methylbutane.

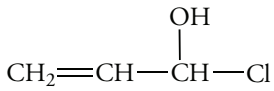


Sample Solution

Warfarin contains only one carbon atom that is attached to four different groups. That carbon atom is bonded to a hydrogen atom, a C_6H_5— group, a CH_2— group, and a fused ring system. The hydrogen atom has priority 4. Which has a higher priority, the benzene ring or the fused ring? The fused ring has a higher priority (1) than the benzene ring (2) because the first point of difference is an oxygen atom in the carbonyl group of the fused ring. Looking into the carbon–hydrogen bond at the chiral center, so that the hydrogen atom points away from us, we trace a counterclockwise path from group 1 to group 2 to group 3. Therefore, this enantiomer of warfarin has an *S* configuration.

Problem 8.10

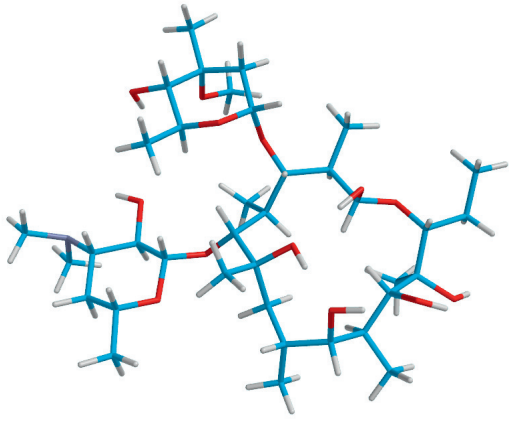
Reduction of (–)-3-buten-2-ol with hydrogen over a palladium catalyst gives (–)-2-butanol. Does the same sign of rotation show that the relative configurations of the two compounds are the same? Based on the mechanism of catalytic hydrogenation, what is the relative configuration of the two compounds? If (–)-3-buten-2-ol has the R configuration, what is the configuration of the product, (–)-2-butanol?



3-buten-2-ol

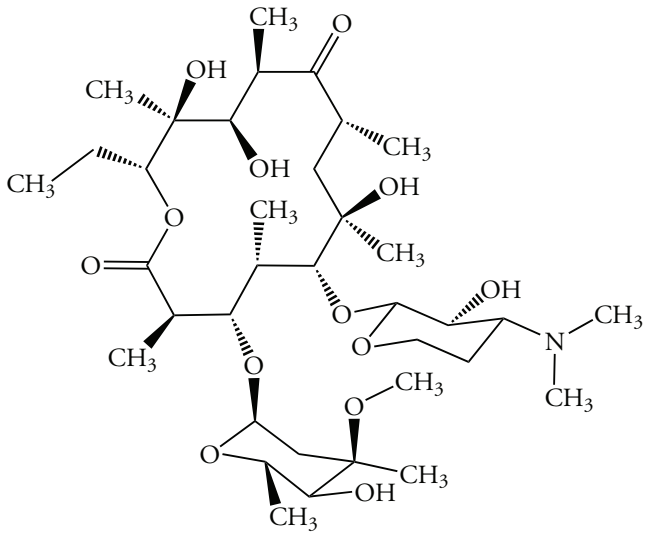
8.6 MOLECULES WITH TWO (OR MORE) STEREOGENIC CENTERS

So far, we have considered molecules that have only one stereogenic center. However, some compounds contain two or more stereogenic centers. For example, the antibiotic erythromycin, which is effective against many bacterial infections, contains 18 chiral centers (Figure 8.10). A molecule with one stereogenic center can exist as either of two enantiomers. How is the number of stereoisomers related to the number of stereogenic centers? What relationships exist between these isomers, and how are their optical rotations related? The answers to these questions depend on the relationship between the groups at each stereogenic center. Are the centers equivalent or nonequivalent? If the chiral carbon atoms are not bonded to identical sets of substituents, the stereogenic centers are **nonequivalent**. In contrast, if the stereogenic centers are bonded to identical sets of substituents, the centers are **equivalent**.



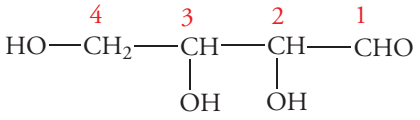
erythromycin A

Figure 8.10
Erythromycin—A Chiral Antibiotic
Erythromycin has 18 chiral centers. Each one is designated with dashed or solid wedge-shaped lines. The hydrogen atoms at the stereogenic centers have been omitted for clarity.



Nonequivalent Stereogenic Centers

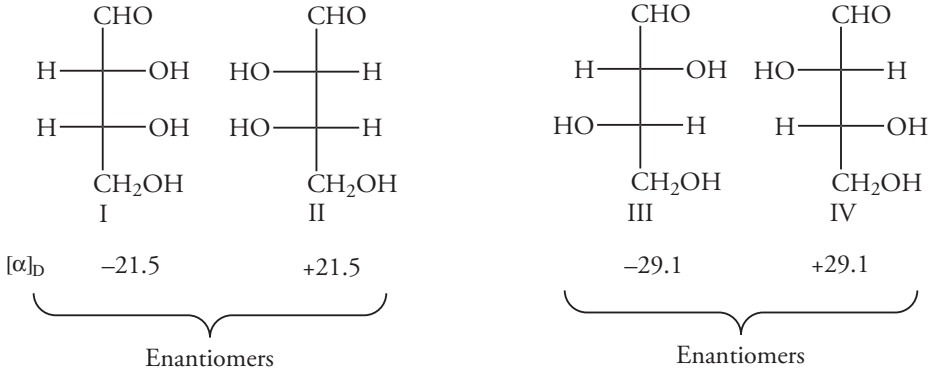
If a molecule contains two or more stereogenic centers, and if they are not bonded to identical groups, the stereogenic centers are nonequivalent. For n nonequivalent centers, the number of stereoisomers equals 2^n. The following example, 2,3,4-trihydroxybutanal, illustrates the general principle.



2,3,4-trihydroxybutanal

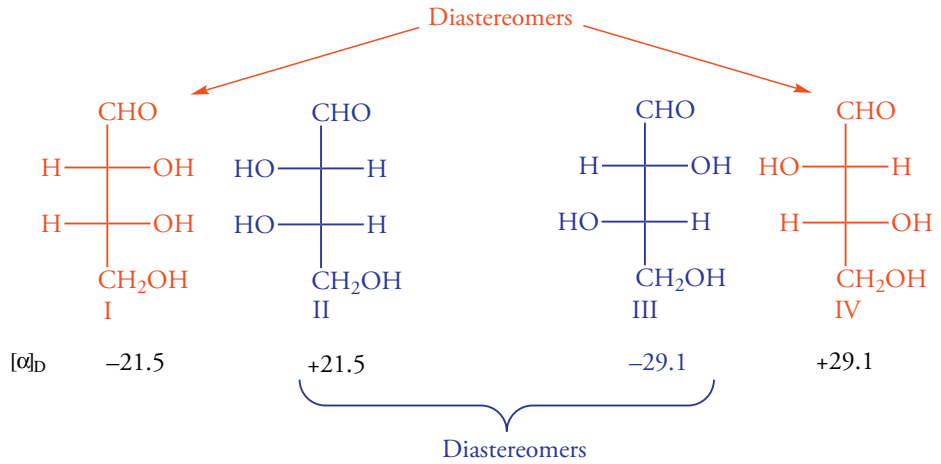
C-2 and C-3 are chiral. They are nonequivalent because they are not bonded to identical groups. Therefore, the configurations at C-2 and at C-3 can be *R* or *S*. Without even drawing the structures, we predict that the four stereoisomers calculated from the 2^n rule can be identified as (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). Figure 8.11 shows these configurations in Fischer projection formulas.

Figure 8.11
Enantiomers and Diastereomers
A molecule that contains two nonequivalent chiral centers, such as 2,3-4-trihydroxybutanal, can exist as four stereoisomers. They exist as two pairs of enantiomers. Stereoisomers that are not enantiomers are diastereomers.



The relationships between the stereoisomeric 2,3,4-trihydroxybutanals are established with mirror planes. Imagine a mirror placed between I and II. Structures I and II are nonsuperimposable mirror images; they are enantiomers. Structures III and IV are also nonsuperimposable mirror images. Like all enantiomers, they rotate plane-polarized light in equal and opposite directions.

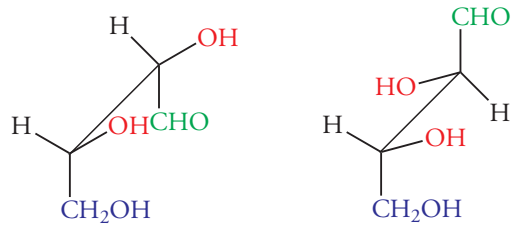
Structures I and III are stereoisomers, but they are not enantiomers. *Stereoisomers that are not enantiomers are called* ***diastereomers***. The pairs II and III, I and IV, and II and IV are diastereomers. In contrast to enantiomers, which have the same chemical and physical properties, diastereomers have different chemical and physical properties. For example, the enantiomers I and II both are liquids at room temperature and are very soluble in ethanol. The enantiomers III and IV both melt at 130 °C and are only slightly soluble in ethanol.



Nomenclature of Diastereomers

The name of a compound with two or more chiral centers contains the configuration of every chiral center. The configuration of each chiral center is indicated by a number that corresponds to its position in the carbon chain and the letter *R* or *S*. Commas separate the configurations. This designation immediately tells us about the relationship between stereoisomers without reference to three-dimensional structures or assignment of the priorities of the groups at the stereogenic centers. Let's consider the four stereoisomers labeled (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). The enantiomer of the 2*R*,3*R* compound must be the 2*S*,3*S* isomer, which has the opposite configuration at each chiral center. Compounds whose configurations differ at only one of the two chiral centers are diastereomers. For example, the 2*R*,3*R* compound is a diastereomer of the 2*S*,3*R* isomer.

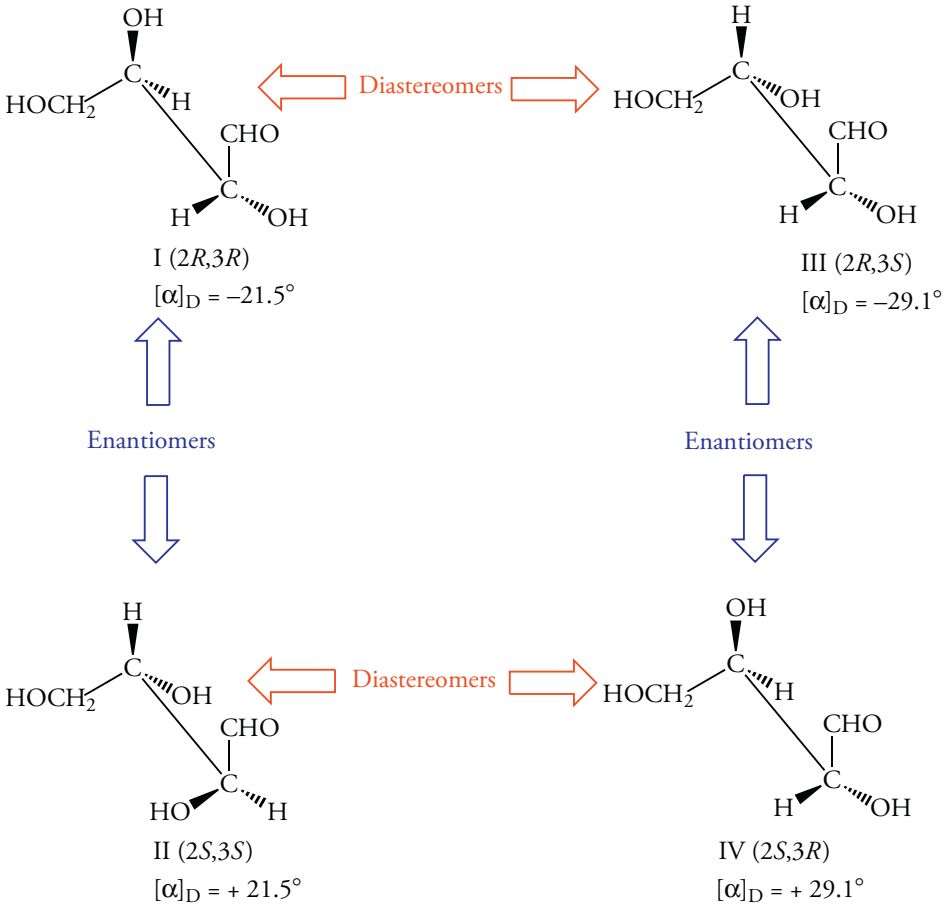
To assign the configurations of the 2,3,4-trihydroxybutanals shown in the Fischer projections in Figure 8.11, we rewrite the structures in three-dimensions. Consider structure I. The CHO and CH_2OH groups are behind the plane of the page. The H and OH groups are in front of the plane of the page. Note that the Fischer projection formula places the carbon chain in an eclipsed conformation. The configuration of each center can be established from this conformation. Their configurations can be also assigned from the more stable, staggered conformation that results from rotation around the C-2 to C-3 bond. Rotating groups around sigma bonds interconverts conformations, but it does *not* change the configuration at any chiral center.



eclipsed conformation staggered conformation

Converting the stereoisomers of 2,3,4-trihydroxybutanal into three-dimensional, staggered conformations gives the structures shown in Figure 8.12. Structure I has the configuration 2*R*,3*R*. Structure II is the mirror image of structure I. If a mirror were placed behind the plane of the page, you would see structure II. Because structures I and II are enantiomers I, we know that the configuration of structure I must be 2*S*,3*S*. The specific rotation of structure I is –21.5°, and the specific rotation of structure of structure II is +21.5°. The common names of structures I and II are (–)-erythrose and (+)-erythrose. The common names for structures III and IV are (–)-threose and (+)-threose. We will encounter erythrose and threose again in Chapter 25 when we discuss carbohydrates.

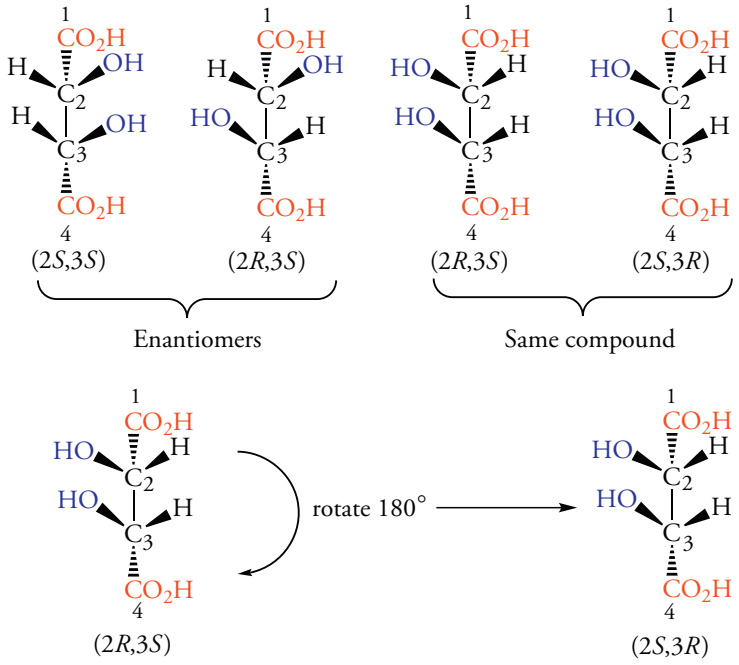
Figure 8.12
Configurations of Enantiomers and Diastereomers



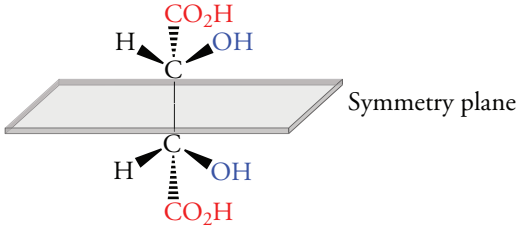
Equivalent Stereogenic Centers

We began our discussion of molecules with two or more stereogenic centers by noting that they chiral could be either equivalent or nonequivalent. Now let's consider compounds with equivalently substituted chiral centers. Examples of equivalent substituted chiral centers are shown in the eclipsed conformations of the tartaric acids (Figure 8.13). In each structure, C-2 and C-3 are connected to four different groups. However, only three stereoisomers exist. Of these, one is optically inactive! The structures labeled (2*S*,3*S*) and (2*R*,3*R*) are enantiomers; therefore, they are optically active. But look at the structures labeled (2*R*,3*S*) and (2*S*,3*R*). Although the structures are drawn as "mirror images," they are superimposable and, in fact, are identical. Thus, the two structures represent the same molecule. We can see this if we rotate the structure on the left in Figure 8.13 by 180° *in the plane of the page*. (Do not lift it out of the page!)

Figure 8.13
Configurations of Optically Active Tartaric Acids and Meso Compounds
Only three stereoisomers exist for tartaric acid because it has two equivalent chiral centers. Two of the stereoisomers are enantiomers. The third has a plane of symmetry, is optically inactive, and is called a *meso* compound, i.e., *meso*-tartaric acid.



Why is one of the stereoisomer of the tartaric acids optically inactive? The structures labeled (2*R*,3*S*) and (2*S*,3*R*) have two equivalent chiral carbon atoms, and each structure has a plane of symmetry. We recall from Section 8.2 that a structure with a plane of symmetry is achiral, and that it is superimposable on its mirror image. In the case of achiral tartaric acid, the plane of symmetry is between C-2 and C-3, so the top half of the molecule is the mirror image of the bottom half.



meso-tartaric acid

Compounds, such as tartaric acid, which have two or more chiral centers, but are nevertheless achiral, are called *meso* compounds (Greek *meso*, middle). *Meso* compounds are not optically active.

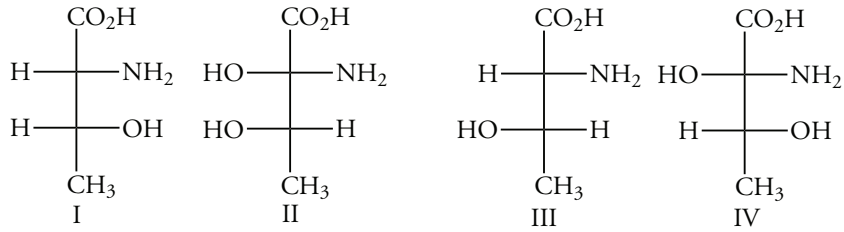
Problem 8.11

Threonine, an amino acid isolated from proteins, has the following condensed molecular formula. Write the Fischer projections of the possible stereoisomers. What is the configuration at each stereogenic center in each stereoisomer?

$$\overset{4}{CH_3}\overset{3}{CH}(OH)\overset{2}{CH}(NH_2)\overset{1}{CO_2H}$$

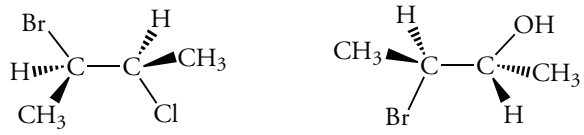
Sample Solution

C-2 and C-3 are each bonded to four different substituents. Therefore, threonine has two chiral centers. Because the chiral centers are nonequivalent, four diastereomers are possible. The Fischer projections are written by placing the carboxyl group at the top of the vertical chain. The amino and hydroxyl groups can be on the right or left sides of the projection formula. The structure of threonine isolated from proteins is given by the Fischer projection at the right. Its configuration is 2*S*,3*R*.



Problem 8.12

Determine the configuration at the stereogenic centers of each of the following structures.



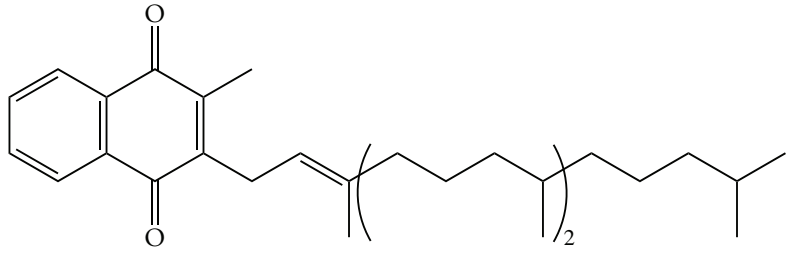
2-bromo-3-chlorobutane 3-bromo-2-butanol

Problem 8.13

Write the Fischer projection formulas of the stereoisomers of 2,3-dibromobutane. What relationship exists between the optical activities of these isomers?

Problem 8.14

Determine the number of chiral centers in vitamin K_1. How many stereoisomers are possible?



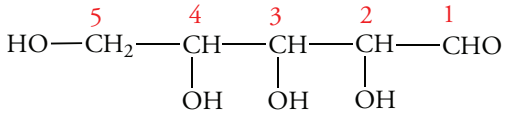
Sample Solution

The carbon atoms in the two rings are not chiral because neither one has a tetrahedral carbon atom. The long alkyl chain contains eight methylene units, none are chiral centers because a carbon atom in a methylene group is bonded to two hydrogen atoms. The tertiary carbon atom near the end of the alkyl chain, which has two methyl groups, is not chiral either.

Next, consider the positions in the middle of the alkyl chain that have methyl group branches. The methyl group on the left is bonded to a double-bonded carbon atom, which does not have four groups bonded to it; therefore, it is not chiral. The next two methyl groups are located on chiral centers. Because there are two chiral carbon atoms, $2^2 = 4$ stereoisomers are possible. These are the two carbons by the right hand of the parenthesis.

Problem 8.15

Using numbers and the symbols *R* and *S*, write the prefix designations of all of the possible stereoisomers of 2,3,4,5-tetrahydroxypentanal.



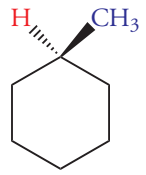
2,3,4,5-tetrahydroxypentanal

8.7 Cyclic Molecules with Stereogenic Centers

Many cyclic compounds have stereogenic centers. We assign their configurations in the same manner we described previously for acyclic compounds.

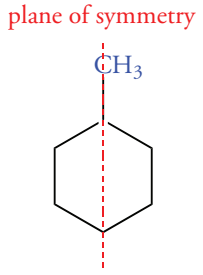
Cyclic Structures with One Stereogenic Center

When a stereogenic center is in a ring, we assign the priorities of the groups bonded to it by treating two "parts" of the ring as groups. First, we examine the atoms in the path around the ring in one direction. Then, we look at the atoms in the path around the ring in the opposite direction. Next, we apply priority rules 1 through 3 (Section 8.5). The structure of methylcyclohexane provides an example.



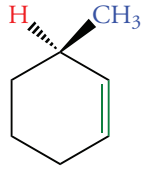
methylcyclohexane

The methyl group and the hydrogen atom at C-1 are two of the required four groups for a stereogenic center. What about the other two groups? C-2 and C-6 are equivalent methylene units by priority rule 1. We apply rule 2 and proceed to the next atom in each path and find that C-3 and C-5 are also equivalent methylene units. Finally, we encounter C-4 from either direction. Thus, C-l is bonded to two equivalent "groups" that are part of the ring itself. Methylcyclohexane has a plane of symmetry containing C-1 and C-4. Since methylcyclohexane has a plane of symmetry, it is achiral.



methylcyclohexane

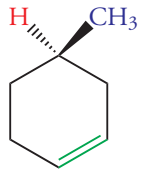
Now consider a compound in which the two paths around the ring are not equivalent. In 3-methylcyclohexene, a methyl group and a hydrogen atom are bonded to C-3. C-2 and C-4 are not equivalent by rule 3. As a result, C-3 of 3-methylcyclohexene is a stereogenic center. The structure of (*R*)-3-methylcyclohexene is shown below. We see that it does not have a plane of symmetry.



3-methylcyclohexene

What is the absolute configuration of this enantiomer of 4-methylcyclohexene? The lowest priority group is the hydrogen atom located behind the plane of the page. Thus, the arrangement of the other three higher priority groups is ideal to assign the configuration. The highest priority group, the sp^2-hybridized carbon atom, is located at the "4 o'clock" position. Priority group 2 is the methylene group of the C-4 atom because it is bonded to another carbon atom. It is located at the "8 o'clock" position. The methyl group is priority group 3 and is located at the "12 o'clock" position. The path traced by the three highest priority groups is clockwise, so the configuration of 4-methylcyclohexene in this structure is *R*.

As in acyclic compounds, differences in the groups can be at some distance from the stereogenic center. The difference in 4-methylcyclohexene is two carbon atoms away from the stereogenic center.



(*R*)-4-methylcyclohexene

Cyclic Structures with Two Stereogenic Centers: Disubstituted Cyclobutanes

As we found when we considered acyclic compounds containing two stereogenic centers, the number of stereoisomers of cyclic compounds depends on whether or not the centers are equivalent. This also true for cyclic compounds. First, we'll examine the isomeric *cis*- and *trans*-1-bromo-2-chlorocyclobutanes (Figure 8.14a). These compounds are diastereomers. The compounds in Figure 8.14 are arranged to demonstrate the mirror image relationship of the two *trans* enantiomers, whose configurations are 1*R*,2*R* and 1*S*,2*S*. There are also two enantiomeric *cis* isomers.

Now consider the consequences of the two equivalent stereogenic centers of 1,2-dibromocyclobutane (Figure 8.14b). There are still two enantiomeric *trans* compounds. However, the *cis* isomer has a plane of symmetry that passes through the C-l to C-2 bond, perpendicular to the plane of the ring. The 1*R*,2*S* and 1*S*,2*R* structures are identical and represent a single *meso* compound.

Cyclic Structures with Two Stereogenic Centers: Dimethyl Cyclohexanes

The relationship between the chiral cyclohexane compounds that we originally called geometric isomers follows from the above discussion of the disubstituted cyclobutanes. Cyclohexane exists in a chair conformation. However, for the purposes of determining stereochemical relationships, a planar structure gives the right answers since we can project the six-membered ring onto a plane without altering the configuration of a chiral center.

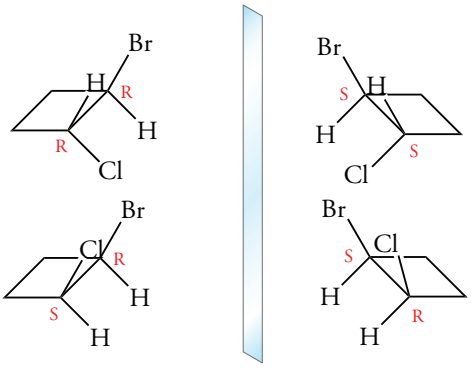
In this section, we will examine only dimethyl cyclohexanes. First, let's examine *cis*- and *trans*-1,4-dimethylcyclohexane (Figure 8.15). These compounds have no stereogenic centers because a symmetry plane passes through C-l and C-4 and cuts through both methyl groups. This plane is more easily seen in the planar projection of these compounds.

cis- and *trans*-1,3-Dimethylcyclohexane each have two stereogenic centers. Because the centers are equivalent, only three stereoisomers exist (Figure 8.16). *cis*-l,3-Dimethylcyclohexane, a *meso* compound, has a symmetry plane that passes through C-2 and C-5. The symmetry plane is easily seen in the planar projection structure. *trans*-l,3-Dimethylcyclohexane has two stereogenic centers and no plane of symmetry. Thus, it exists as two enantiomers.

The *cis*- and *trans*-1,2-dimethylcyclohexanes have two stereogenic centers. The *trans* isomer does not have a plane of symmetry. Thus, it exists as two enantiomers (Figure 8.17). The *cis* isomer is a *meso* compound, but for reasons that are not straightforward. The two chair conformations rapidly interconvert, and they have equal energy. They are enantiomers. Hence, there is no net optical rotation (Figure 8.18). (If chair–chair interconversion were slow—which it is not—the two enantiomers could in principle be separated.)

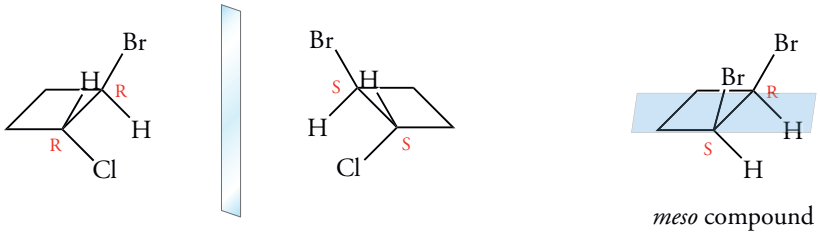
Figure 8.14
Diastereomers of 1,2-Disubstituted Cyclobutanes

(a) A 1,2-disubstituted cyclobutane with two nonequivalent chiral centers has four diastereomers. (b) However, a 1,2-disubstituted cyclobutane with two equivalent chiral centers has only three diastereomers, one of which is a *meso* compound.



Mirror

(a) Diastereomers of 1-bromo-2-chlorocyclobutane

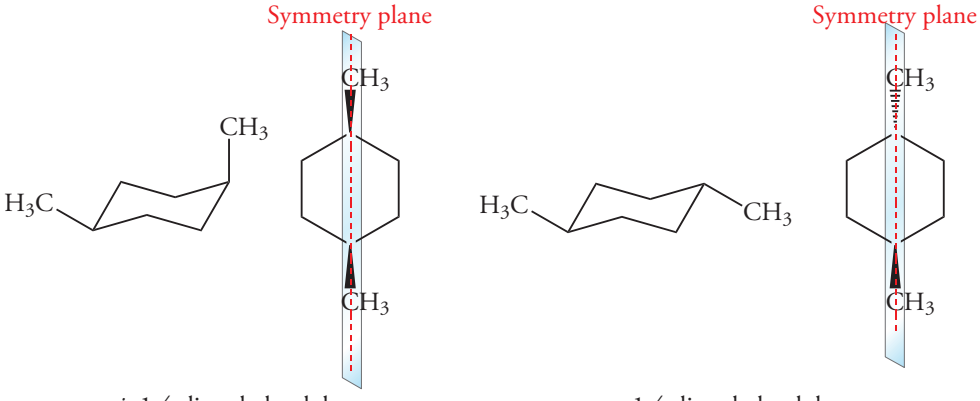


meso compound

(b) Diastereomers of 1,2-dibromocyclobutane

Figure 8.15
Stereoisomers of 1,4-Dimethylcyclohexane

The *cis* and *trans* isomers of 1,4-dimethylcyclohexane are achiral because each has a plane of symmetry.



cis-1,4-dimethylcyclohexane

trans-1,4-dimethylcyclohexane

Figure 8.16
Diastereomers of 1,3-Dimethylcyclohexane
cis-1,3-Dimethylcyclohexane is a *meso* compound. It is achiral because it has a plane of symmetry. *trans*-1,3-Dimethylcyclohexane exists as a pair of enantiomers.

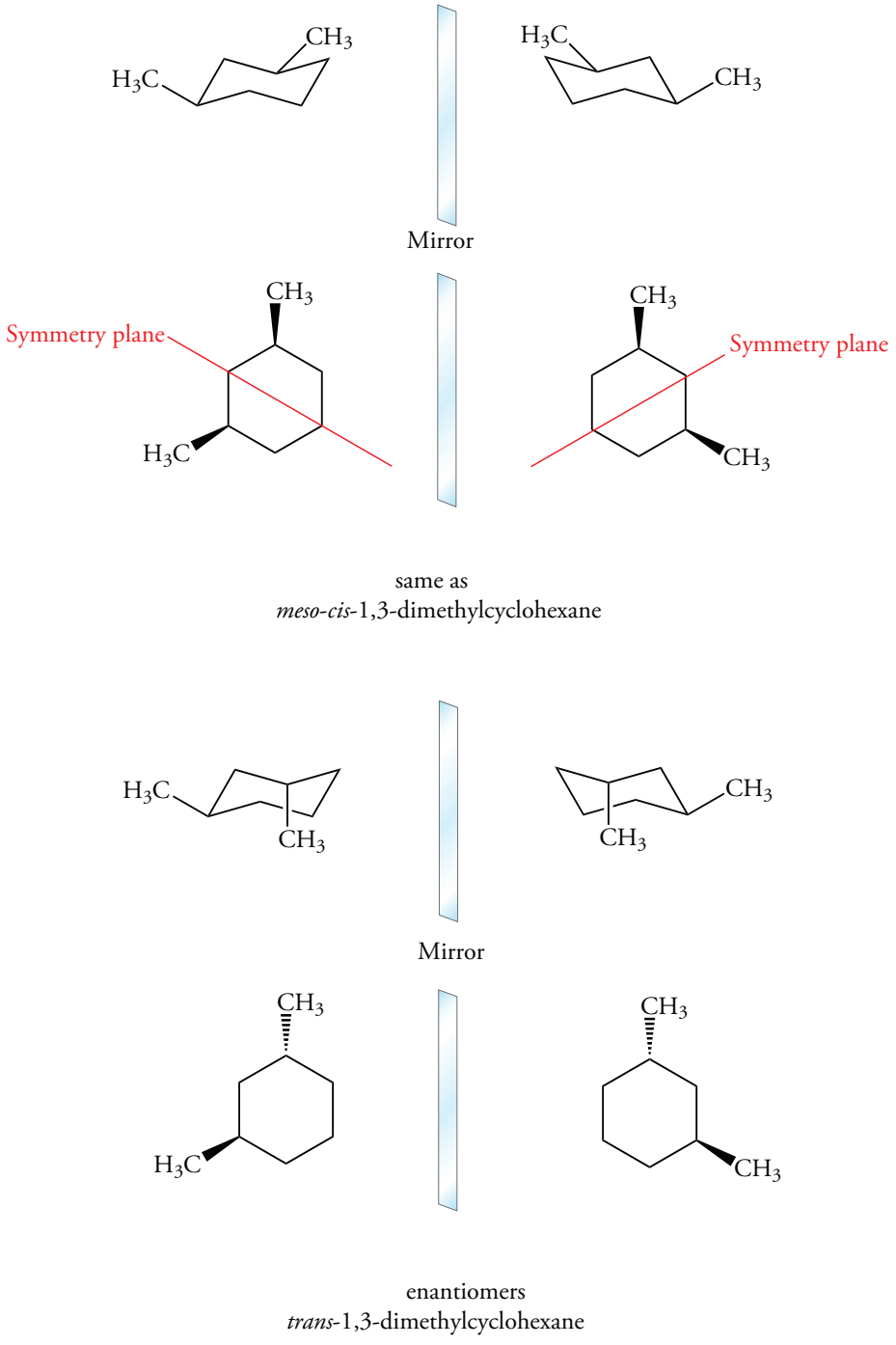


Figure 8.17
Enantiomers of *trans*-1,2-Dimethylcyclohexane
trans-1,2-Dimethylcyclohexane exists as a pair of enantiomers. There is no a plane of symmetry.

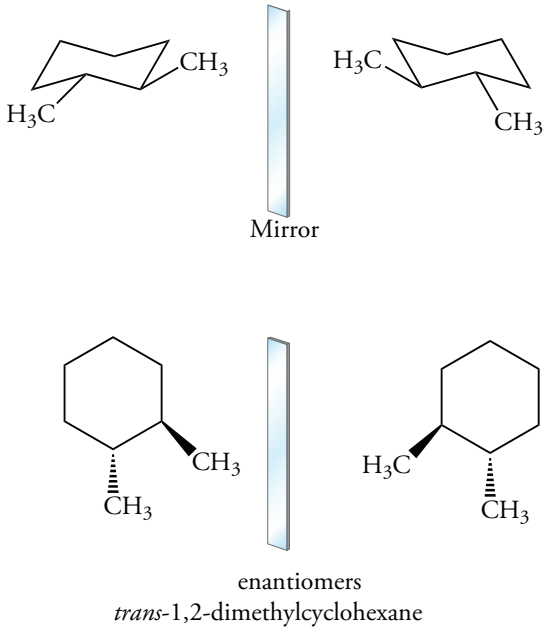
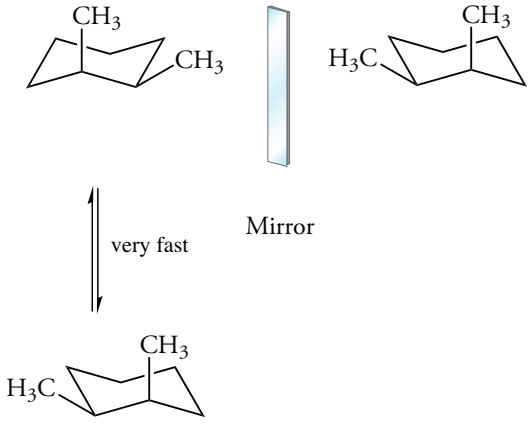
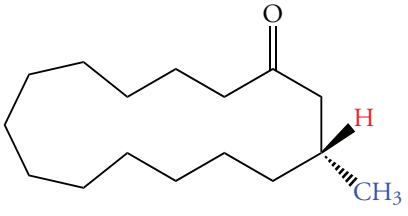


Figure 8.18
***cis*-1,2-Dimethylcyclohexane**
The mirror images of *cis*-1,2-dimethylcyclohexane are not superimposable. However, chair–chair interconversion is very fast, so the enantiomers cannot be separated.



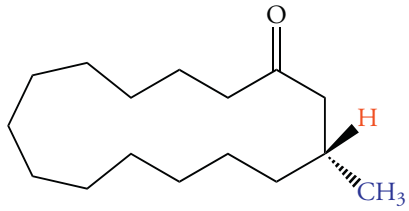
Problem 8.16
What is the absolute configuration of muscone, a compound used in perfumes to provide a musk odor?



muscone

Sample Solution

The stereogenic center is at the branch containing the methyl group. The lowest priority group is a hydrogen atom that points above the plane of the page at the branching carbon atom. The methylene carbon atoms of the ring attached to the branching point both have higher priorities than the methyl group, which is priority (3). The methylene portion of the ring that contains the carbonyl carbon atom has a higher priority than the other methylene portion of the ring. Looking into the C—H from behind the plane of the page, and into the C—H bond, and tracing the other three groups, we move in a clockwise direction. Therefore, muscone has an *R* configuration.



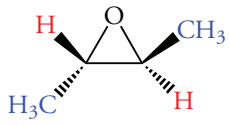
(*R*)-muscone

Problem 8.17

Write the structures of (1*R*,2*S*)- and (1*S*,2*S*)-1-bromo-2-chlorocyclopropane. Which is a *cis* and which is a *trans* isomer? Are the structures enantiomers or diastereomers?

Problem 8.18

Determine the configuration of each stereogenic center in the following *trans*-2,3-dimethyloxirane. Write a structure of its enantiomer.

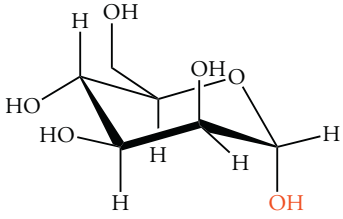


trans-1,2-dimethyloxirane

Chirality and Our Senses of Taste and Smell

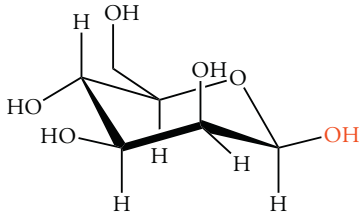
Our senses are sensitive to the configuration of molecules. Both the sense of taste and the sense of smell result from changes induced in a sensory receptor when it binds a specific small molecule (ligand). Ligand binding causes a conformational change that triggers a sequence of events culminating in transmission of a nerve impulse to the brain by sensory neurons. The brain interprets the input from sensory neurons as the "odor" of, say, spearmint.

Diastereomers interact with highly specific sensory receptors. For example, D-mannose, a carbohydrate, exists in two diastereomeric forms that differ in the configuration of a hydroxyl group at one center. The two isomers are designated α and β. The α form tastes sweet, but the β form tastes bitter.



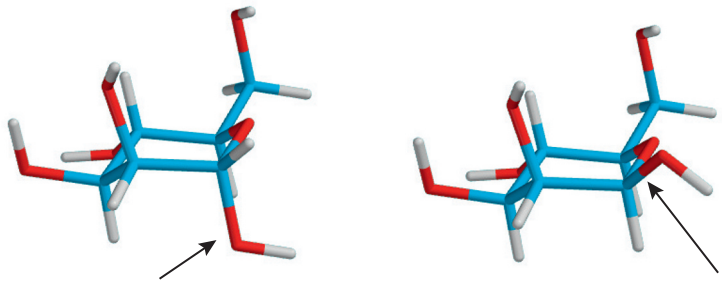
α-D-mannose

(The hydroxy group is axial in the α isomer.)



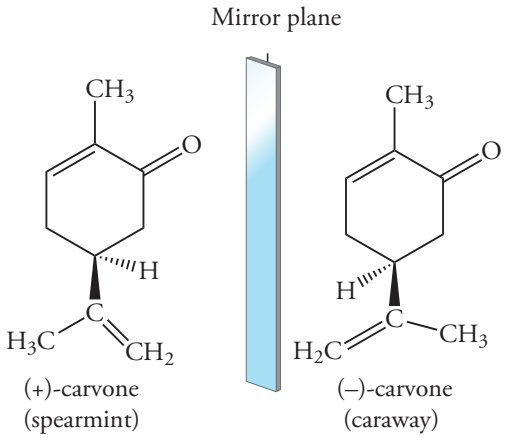
β-D-mannose

(The hydroxy group is equatorial in the β isomer.)



α-D-mannose (axial hydroxyl group) β-D-mannose (equatorial hydroxyl group)

Sensory receptors also readily distinguish enantiomers. The specificity of response is similar to the relationship between our hands and how they fit into gloves. Because sensory receptors are chiral, they interact stereospecifically with only one of a pair of enantiomers. The two enantiomeric forms of carvone have very different odors. (+)-Carvone is present in spearmint oil, imparting its odor. In contrast, its enantiomer, (–)-carvone, is present in caraway seed. It has the familiar odor associated with rye bread.



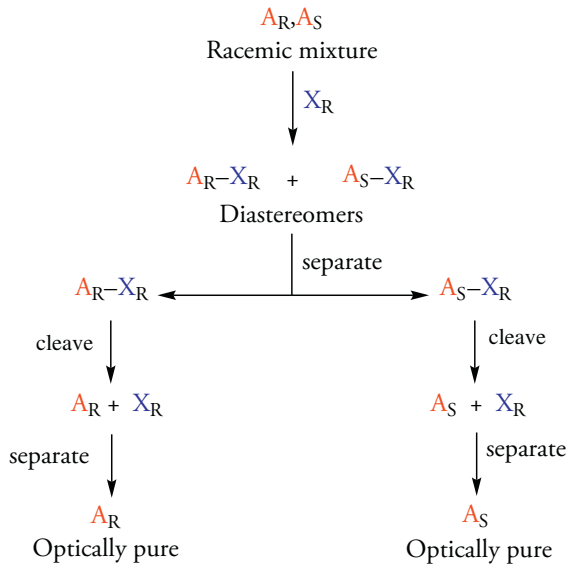
(+)-carvone (spearmint) (–)-carvone (caraway)

8.8 SEPARATION OF ENANTIOMERS

General Principles

Substances with stereogenic centers are invariably found in nature as a single enantiomer. However, as we noted in Section 8.3, compounds with stereogenic centers prepared in the laboratory from achiral starting materials are racemic. We can separate the racemic mixture into pure samples of each enantiomer by indirect methods. Because enantiomers have the same physical properties, such as boiling point or solubility, they cannot be separated by distillation or crystallization. However, enantiomers can be separated by reacting the racemic mixture with another optically pure compound to produce a mixture of diastereomers (Figure 8.19). Because diastereomers have different physical properties, they can often be separated on the basis of solubility differences. Then, each enantiomer is recovered from its diastereomeric derivative by another chemical reaction. The entire process is called **resolution** of enantiomers. The optically pure compound used to form the diastereomeric mixture is called the **resolving agent**.

Figure 8.19
General Method for Resolving Enantiomers

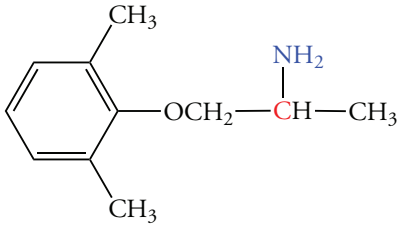


The racemic mixture to be resolved in Figure 8.19 is designated A_R,A_S. The optically active compound selected as the resolving agent is represented X_R. The choice of X_R over X_S is arbitrary in this discussion. The choice we make in the laboratory is based on the configuration of the available resolving agent. The diastereomeric compounds made from the racemic mixture are A_R–X_R and A_S–X_R. After the diastereomers are separated, one or the other or both can be reacted to liberate the pure enantiomers. In practice, only one of the enantiomers is easily obtained. For example, the least soluble diastereomer may crystallize from solution and yield one of the enantiomers in the subsequent step. Because some of the less soluble diastereomer remains in solution with the more soluble diastereomer, it is difficult to obtain the second enantiomer in optically pure form.

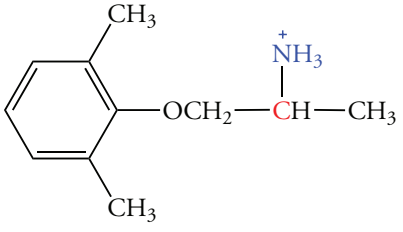
Chiral Chromatography

The method for resolving enantiomers we discussed above illustrates the general principle that the key to the separation of enantiomers is the formation of diastereomers. This can be achieved by **chiral chromatography**, a process in which the column itself contains a chiral ligand. Chiral chromatography depends upon a partition between compounds in the moving phase—the solution of enantiomers passing through the column—and a stationary phase, the chiral column material itself. When a solution of enantiomers passes through the column, the enantiomers bind to the column with different affinities because an (*R*-ligand/*R*-enantiomer) interaction differs from an (*R*-ligand/*S*-enantiomer) interaction.

We will examine the separation of the enantiomers of mexiletine, an antiarrhythmic drug that acts by blocking sodium channels. (–)-*R*-mexiletine is far more potent than its enantiomer, but for a long time, mexiletine has been administered as a racemic mixture. In many cases, if one enantiomer of a drug is effective therapeutically, its enantiomer is either inactive or toxic. Thus, the purification of drug enantiomers is pharmacologically important.



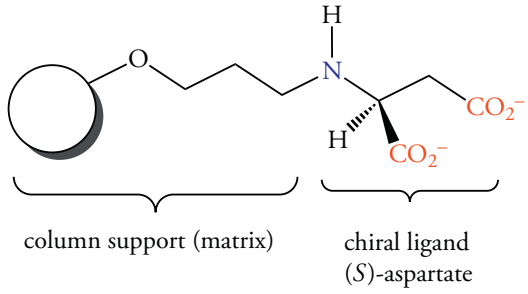
(±)-mexiletine (an antiarrhythmic drug)



conjugate acid of mexiletine (pH 7)

Enantiomers can be separated by high-performance liquid chromatography in which the column material, or matrix, is covalently bonded to a chiral ligand. In this case, the chiral ligand is (*S*)-aspartic acid, an inexpensive, readily available amino acid. At pH 7, the carboxylic acid group of aspartic acid exists as its conjugate base, a carboxylate anion. The amino group is bonded to the column matrix.

At pH 7, the carboxylic acid group of aspartic acid exists as its conjugate base, a carboxylate anion. It is called (*S*)-aspartate. The column matrix itself—covalently bound to (*S*)-aspartate—is the resolving agent.



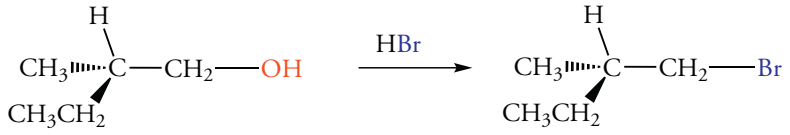
Mexiletine contains an amino group, and at pH 7, it exists as its conjugate acid; that is the amino group is a protonated ammonium ion. When a solution of (±)-mexiletine at pH 7 passes through a column whose chiral ligand is (*S*)-aspartate, ion pairs between the chiral column matrix and the (+) and (–) forms of mexiletine form transiently. The ion pairs are diastereomers, and the mexiletine enantiomers do not have the same affinity for the column. It turns out that (–)-(*R*)-mexiletine binds to the column with lower affinity than its enantiomer, and it emerges from the column (elutes) first. A complete separation of enantiomers is the result.

8.9 CHEMICAL REACTIONS AT STEREOGENIC CENTERS

In this section, we consider some reactions of chiral molecules, which are often highly valuable in the study of reaction mechanisms. They are also of great importance in the study of enzymatic catalysis, since virtually all enzymes react with chiral molecules.

Reactions of Chiral Molecules That Do Not Occur at the Stereogenic Center

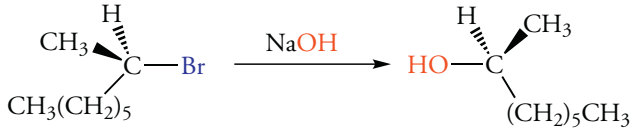
If a reaction of a chiral compound does not form or cleave any bonds to the stereogenic center, then the configuration of the product is the same as that of the reactant. Therefore, we can establish the absolute configuration of particular molecules using reference molecules of known absolute configuration. For example, 2-methyl-l-butanol is converted to 1-bromo-2-methylbutane by HBr. The reaction does not occur at the stereogenic center. Therefore, the *S*-2-methyl-l-butanol yields S-1-bromo-2-methylbutane.



(*S*)-2-methyl-1-butanol (*S*)-1-bromo-2-methylbutanet

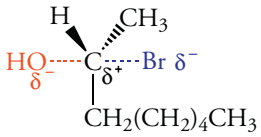
Preview: Stereochemistry of a Substitution Reaction at a Stereogenic Center

In coming chapters, we will devote considerable attention to substitution reactions at sp^3-hybridized carbon atoms. The stereochemical changes that occur in these reactions provide a powerful probe of the reaction mechanisms. For example, the reaction shown below occurs at the stereogenic center of a chiral compound and yields a chiral product. Treating (*R*)-2-bromooctane with sodium hydroxide yields (*S*)-2-octanol. In this reaction, the stereochemistry of the reactant and product are opposite, so the reaction occurs with **inversion of configuration** at the stereogenic site of the substitution reaction.



(*R*)-2-bromooctane (*S*)-2-octanol

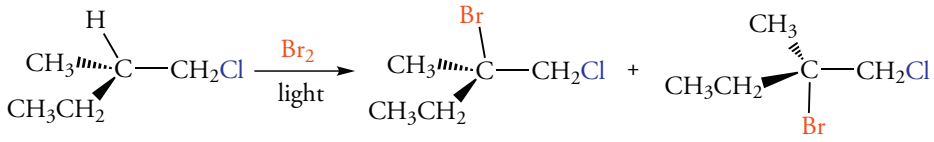
We can account for inversion of configuration by imagining that the hydroxide ion attacks (*R*)-2-bromooctane at the carbon atom from the side opposite the C—Br bond axis. Thus, it is reasonable to propose a linear transition state in which the stereogenic center has partial bonds to both the hydroxide and the bromide ions.



Transition state for inversion of configuration

Stereochemistry of a Free Radical Reaction

A substitution reaction at a stereogenic center can lead to a racemic mixture of products. For example, in the free radical reaction of bromine with (*S*)-1-chloro-2-methylbutane, a bromine atom replaces a hydrogen atom at the tertiary stereogenic center to give a racemic mixture of (*R*)- and (*S*)-2-bromo-l-chloro-2-methylbutane.



(*S*)-1-chloro-2-methylbutane

This experimental result indicates that the free radical intermediate produced in the course of the reaction is achiral. The radical is planar (Figure 8.20). Therefore, reaction of the radical with bromine can occur with equal probability from above or below the plane, giving a 50:50 mixture of enantiomers.

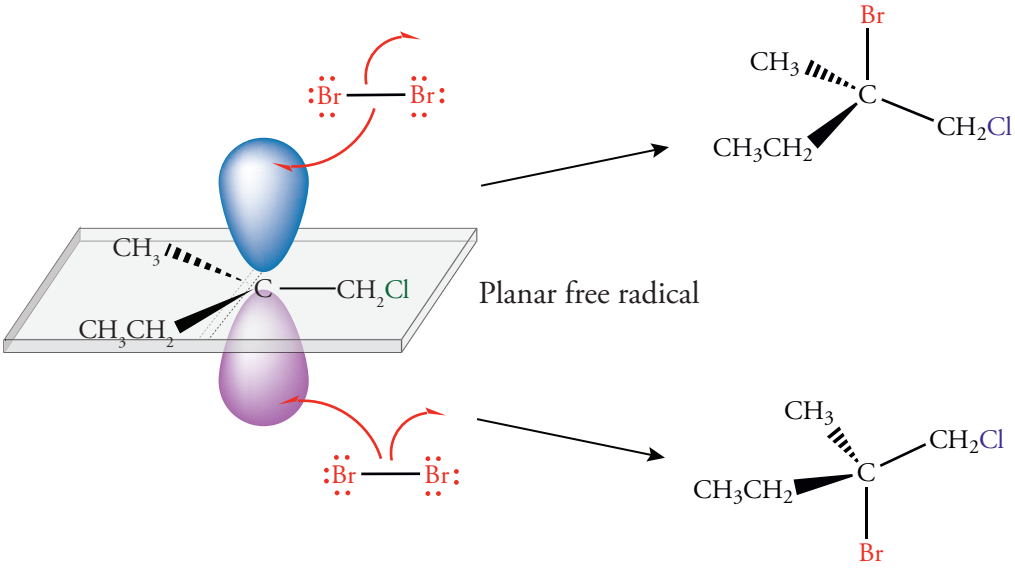


Figure 8.20
Free Radical Reaction at a Stereogenic Center

A free radical intermediate is achiral because it has a plane of symmetry. A bromine molecule can therefore attack with equal probability from above or below the plane to give a 50:50 mixture of enantiomers. The 2p orbital is half-occupied, and there is a 50% probability of finding an electron above or below the nodal plane of the orbital.

Problem 8.19

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure of the 2-bromo-1-chlorobutane formed. Determine the configuration(s) of the stereogenic center(s). Is the product optically active?

Problem 8.20

Based on the data for the conversion of (*R*)-2-bromooctane into (*S*)-2-octanol using NaOH, predict the product of the reaction of (*S*)-2-bromooctane with NaOH.

Sample Solution

Nucleophilic attack at the side opposite the bond of the displaced leaving group from (*S*)-2-bromooctane gives a product with inversion of configuration. Thus, the enantiomeric *R* compound should react likewise and gives an inverted product, (*S*)-2-octanol.

8.10 REACTIONS THAT PRODUCE STEREOGENIC CENTERS

We have studied several reactions that yield products with stereogenic centers from compounds with no stereogenic centers. What prediction can we make about the configuration of the product? The reaction of an achiral radical described previously shows that chiral products cannot form from the reaction of achiral reactants. Molecules with stereogenic centers can form, however, the enantiomers form in equal amounts.

Stereochemistry of Markovnikov Addition to Alkenes

Let's examine the stereochemistry of the addition of HBr to 1-butene to give 2-bromobutane. We know that this is Markovnikov addition. A proton adds to 1-butene at C-1 to give a secondary carbocation. It is achiral because it has a plane of symmetry (Figure 8.21). The carbocation is attacked by the nucleophilic bromide ion with equal probability from the top or bottom side of the planar intermediate. Attack at the top gives the *S* enantiomer, attack at the bottom gives the R enantiomer, and a racemic mixture results.

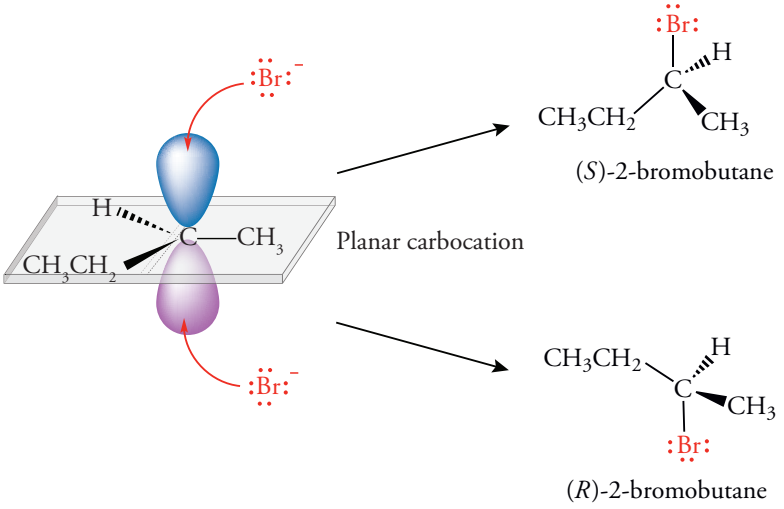
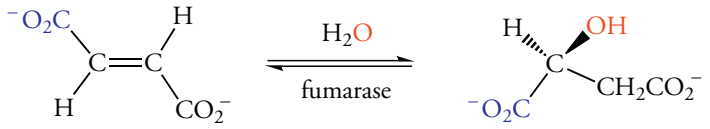


Figure 8.21
Stereochemistry of Markovnikov Addition of HBr to 1-Butene
A proton adds to the double bond of 1-butene to give an intermediate secondary carbocation. It is achiral because it has a plane of symmetry. Bromide ion can attack with equal probability from the top or the bottom to give a racemic mixture.

Biochemical processes are catalyzed by enzymes that have multiple stereogenic centers and are therefore chiral. Enzymes provide a chiral environment in which to form stereogenic centers. As a consequence, only one enantiomer forms from an enzyme-catalyzed reaction, even if the reactant is achiral. For example, fumaric acid reacts with water in an addition reaction catalyzed by the enzyme fumarase in the citric acid cycle to give only (*S*)-malic acid. We show the carboxylic acids as their conjugate bases because they are ionized at pH 7. These ionic compounds are called "fumarate" and "malate." This reaction converts fumarate to (*S*)-malate.



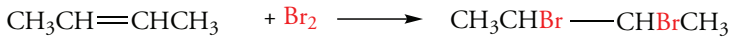
fumarate
(the conjugate base of fumaric acid)

(*S*)-malate
(the conjugate base of (*S*)-malic acid)

Only one enantiomer forms in the reaction, and only the *trans* geometric isomer reacts in the presence of fumarase. The *cis* unsaturated isomer is not converted to a hydrated product by fumarase. In fact, it does not bind to the enzyme at all.

Stereochemistry of Alkene Bromination

We recall that the reaction of bromine with an alkene gives a product with bromine atoms on adjacent carbon atoms (Section 6.6). For example, 2-butene reacts with bromine to give 2,3-dibromobutane. Two equivalently substituted stereogenic centers form in this reaction. There are three stereoisomers for such compounds, a pair of enantiomers and a *meso* compound. Which products would we predict based on the reaction mechanism we discussed in Section 7.6? Put another way, how do the observed products support the proposed mechanism of the reaction?



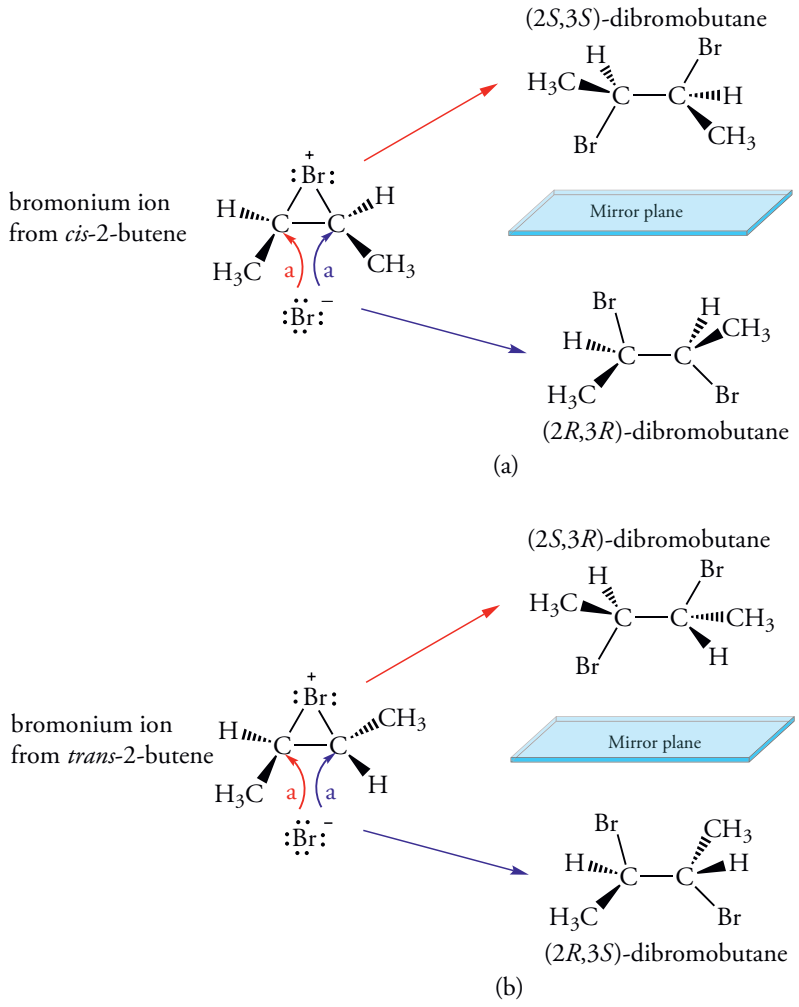
The configuration of the addition product depends on the configuration of the 2-butene, which can be *cis*- or *trans*-, and on the stereochemistry of the *anti* addition reaction that occurs in the second step. Bromine adds to *cis*-2-butene to give a mixture of the enantiomeric (2*R*,3*R*)- and (2*S*,3*S*)-dibromobutanes (Figure 8.22a). Although the bromonium ion could form by attack equally well on the top or bottom, let's examine the intermediate obtained from attack on the top. (The intermediate obtained from attack on the bottom is the same because it is achiral.) Subsequent attack of bromide ion can occur at either the right or the left carbon atom. Attack at the right carbon atom gives the 2*R*,3*R* isomer. Attack at the left carbon atom gives the 2*S*,3*S* isomer. Both paths of attack are equally probable, and a racemic mixture results.

Now let's consider the consequences of formation of the cyclic bromonium ion derived from *trans*-2-butene followed by nucleophilic attack by bromide ion (Figure 8.22b). The bromonium ion results from attack on the top. Bromide ion attacks equally well at the right and left carbon atoms, giving the 2*S*,3*R* and 2*R*,3*S* structures, respectively. This pattern corresponds to two equivalently substituted chiral carbon atoms in a molecule with a plane of symmetry; thus, this isomer corresponds to a single *meso* compound.

We now can confidently accept the mechanism for addition of bromine to alkenes because it agrees with the experimental facts. We have again found that achiral reactants—in this case either *cis*- or *trans*-2-butene and bromine—always form optically inactive products. Remember: the products have two stereogenic centers; the reaction produces either a racemic mixture or a *meso* compound.

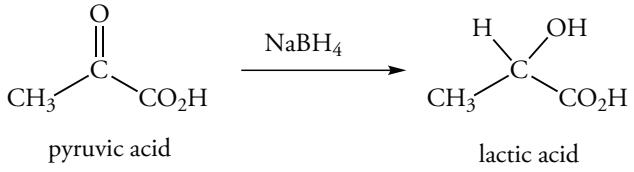
Figure 8.22
Stereochemistry of Bromine Addition to Alkenes

The reaction of bromine with an alkene produces a bromonium ion intermediate. This intermediate reacts with bromide ion in a process that results in net *anti* addition of bromine. The stereochemical consequences for adding bromine to *cis*-2-butene and *trans*-2-butene are different. *cis*-2-Butene yields a pair of enantiomers; *trans*-2-butene yields a *meso* compound.



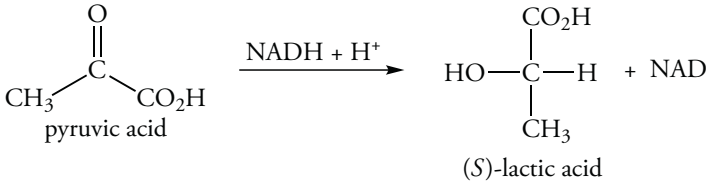
Problem 8.21

Sodium borohydride ($NaBH_4$) reacts with the C-2 carbonyl carbon atom of pyruvic acid to give lactic acid. What is the optical rotation of the product(s)?



Problem 8.22

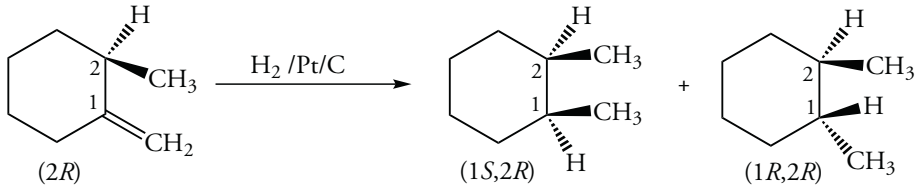
Reduction of pyruvic acid by NADH using the liver enzyme lactate dehydrogenase yields exclusively (*S*)-lactic acid. Write the Fischer projection of this product. Why does only a single product form?



8.11 REACTIONS THAT FORM DIASTEREOMERS

In the previous section, we discussed the formation of compounds with one or two stereogenic centers from achiral reactants. Now, we'll see what happens when a second stereogenic center forms in a chiral molecule. Diastereomers could result. A molecule with one stereogenic site, designated A_R, that forms a second stereogenic site at B within the molecule could give A_RB_R and A_RB_S. We recall that a single enantiomer results when a stereogenic center forms in a molecule in a chiral environment, such that provided by an enzyme. Similarly, a chiral site in a molecule should affect the stereochemistry of the second site when diastereomers form.

In the hydrogenation of an alkene using a transition metal catalyst, the planar molecule binds to the surface of the metal. If the alkene is achiral, the "side" presented to the surface of the metal is not important. The alkene can be hydrogenated from the "top" or "bottom" to give the hydrogenated product. If the alkene contains a chiral carbon atom near the double bond, however, two products are possible. Consider the catalytic hydrogenation of (*R*)-2-methylmethylenecyclohexane. Two stereoisomers, 1*S*,2*R* and 1*R*,2*R*, form, but in unequal amounts. Approximately 70% of the product is the *cis* isomer (1*S*,2*R*).



Because the alkene is chiral, there is a difference between the steric environment of the two faces of the double bond. The methyl group above the plane decreases the probability of hydrogenation from that face of the double bond. Hydrogenation from the less hindered bottom side "pushes" the newly formed methyl group up, and the *cis* isomer results. The two stereoisomers form in unequal amounts as a consequence of the chiral center. The reaction is **stereoselective**.

Similar observations show that one enantiomer reacts with an achiral reagent to give unequal amounts of diastereomeric products. The relative yields of the diastereomers often depend on the structure of the existing stereogenic center and its proximity to the newly formed stereogenic center. Many stereogenic centers are present in an enzyme catalyst. They create a chiral environment, which leads to high stereoselectivity. Usually, only one diastereomer forms in enzyme-catalyzed reactions.

Problem 8.23

Write the structure of the oxirane (epoxide) that forms when (*Z*)-2-butene reacts with *m*-chloroperbenzoic acid. Assign the configurations of the stereogenic centers.

Problem 8.24

Free radical chlorination of (*S*)-2-bromobutane yields a mixture of compounds with chlorine substituted at any of the four carbon atoms. Write the structure(s) of the 2-bromo-3-chlorobutane formed. Assign the configuration of the stereogenic center(s). Is the product optically active?

Problem 8.25

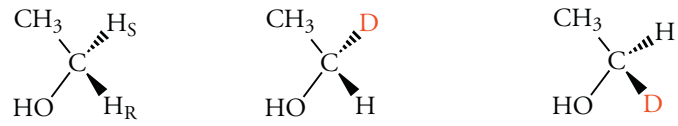
Based on the percent composition of the products for the hydrogenation of 2-methyl-methylenecyclohexane, predict the product(s) of the hydrogenation of 2-*tert*-butylmethylenecyclohexane.

Sample Solution

The 2-*tert*-butyl group on the "top" of the molecule decreases the probability of hydrogenation from that face. Hydrogenation tends to occur from the less hindered side and "pushes" the newly formed methyl group up. The methyl and *tert*-butyl groups are *cis*. The *cis*/*trans* ratio is larger than the 70:30 obtained from 2-methylmethylenecyclohexane because the larger *tert*-butyl group hinders attack by hydrogen more than the smaller methyl group.

8.12 PROCHIRAL CENTERS

We have seen some examples of biochemical reactions in which an enzyme stereospecifically distinguishes between enantiomers. Enzymes can also distinguish between apparently equivalent groups in achiral substrates. Under such circumstances, the enzyme can generate a chiral center at an atom of an achiral reactant. An atomic center that can become chiral as a result of a stereospecific reaction is called **prochiral**. The methylene group of ethanol provides a simple example. Because the methylene carbon atom is bonded to two hydrogen atoms, it is not a chiral center. Now assume that an enzyme-catalyzed reaction substitutes a deuterium atom for one hydrogen atom. Two enantiomers result. The hydrogen atoms are **enantiotopic** because they are in mirror image environments. We designate these hydrogens H_R and H_S. For example, enantiomeric compounds form if deuterium replaces one hydrogen atom at C-1.

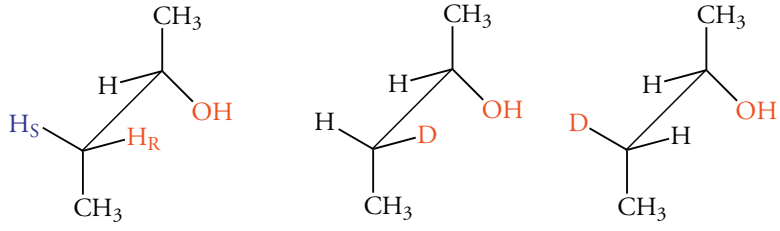


ethanol (*S*)-1-deuteroethanol (*R*)-1-deuteroethanol

Enantiotopic atoms or groups are designated *pro-R* and *pro-S*. The hydrogen atom behind the page, as shown above, is designated *pro-S* because replacing it with deuterium gives the *S* enantiomer. The hydrogen atom in front of the page is designated *pro-R* because replacing it with deuterium gives the *R* enantiomer. A prochiral center cannot be converted into a single chiral compound by a symmetrical (achiral) reagent. However, the enzymes that catalyze biochemical reactions are chiral. Therefore, enzymes can distinguish between the enantiotopic groups of a prochiral center. Enzymes have specific binding sites into which substrates fit. For a molecule such as ethanol, when the CH_3— and OH— groups "fit" into the enzyme binding site, the prochiral hydrogen atoms are located in different environments of the chiral enzyme. A reaction might occur at one prochiral hydrogen atom, for example, and not at the other.

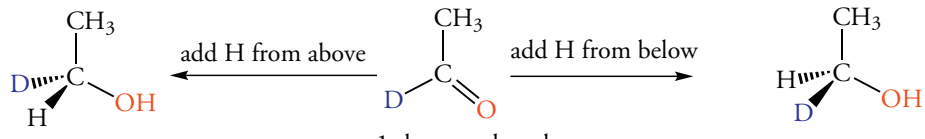
The concept of prochirality is also important in describing the biochemical reactions of molecules that already have one or more chiral centers. Formation of a second chiral center at an achiral site could lead to a mixture of diastereomers. The two equivalent groups at the achiral site are **diastereotopic**.

The hydrogen atoms at C-3 of (*R*)-2-butanol are diastereotopic. We can replace either one of them by deuterium. Replacing the C-3 hydrogen atom on the right in the structure gives the *R* configuration. That hydrogen atom is *pro-R*. The diastereomeric 2*R*,3*S* compound results from replacing the C-3 hydrogen atom on the left, which is *pro-S*.



(*R*)-2-butanol (2*R*,3*R*) (2*R*,3*S*)

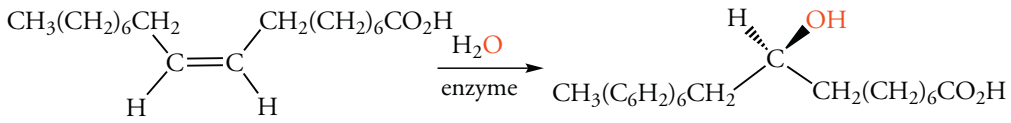
Next we consider a reaction at an sp^2-hybridized carbon atom as it is converted into a product with an sp^3-hybridized carbon atom. Although the trigonal carbon atom of a carbonyl group is not a stereogenic center, reducing that group to an alcohol gives a new stereogenic center. Consider the formation of a C—H bond in the reduction of ethanal that has been deuterated at C-l. Bond formation at one face gives one enantiomer; formation of a C—H bond at the opposite face gives the other enantiomer.



(*R*)-1-deuteroethanol 1-deuteroethanol (*S*)-1-deuteroethanol

To describe the addition reactions at the two possible faces of planar parts of a molecule, we must be able to distinguish the faces. To do this, consider the sequence of groups bonded to the trigonal atom. If, when viewed from one face, the groups are in a clockwise sequence when arranged by *R*,*S* priority rules, that face is designated *re*. If the sequence of groups is counterclockwise, the face is designated *si*. Viewing ethanal-l-d from above the page as shown above, the face is *si* because the order of the groups O > CH_3 > D is counterclockwise. If a hydrogen adds to the *si* face, pushing the deuterium down, the product is (*R*)-1-deuteroethanol.

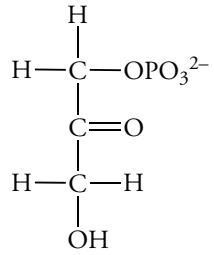
Many biochemical reductions occur at sp^2-hybridized carbon atoms. These reactions yield a single enantiomer. For example, the hydration of oleic acid yields exclusively (*R*)-10-hydroxystearic acid.



oleic acid (*R*)-10-hydroxystearic acid

Problem 8.26

The structure of dihydroxyacetone phosphate, an intermediate in glycolysis, is shown below. Identify the prochiral hydrogen atoms and label them as H_R and H_S.



dihydroxyacetone phosphate

Problem 8.27

In the addition of water to oleic acid in the above example, is the face to which oxygen adds *si* or *re*?

Exercises

Chirality

8.1 Which of the following isomeric methylheptanes has a chiral center?

(a) 2-methylheptane (b) 3-methylheptane (c) 4-methylheptane

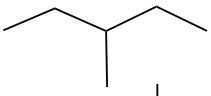
8.2 Which of the following isomeric bromohexanes has a chiral center?

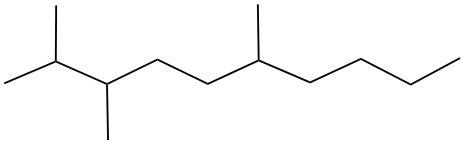
(a) 1-bromohexane (b) 2-bromohexane (c) 3-bromohexane

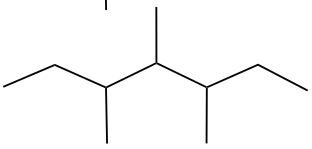
8.3 Which of the compounds with molecular formula $C_5H_{11}Cl$ has a chiral center?

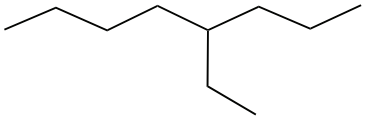
8.4 Which of the compounds with molecular formula $C_3H_5Cl_2$ has a chiral center?

8.5 Which of the following isomeric methylheptanes has a chiral center?

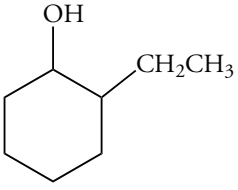
(a) 

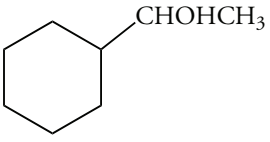
(b) 

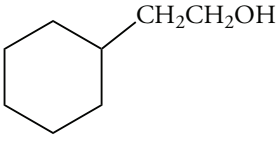
(c) 

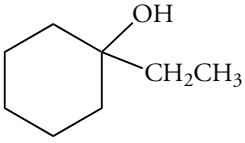
(d) 

8.6 How many chiral centers does each of the following cyclic compounds have?

(a) 

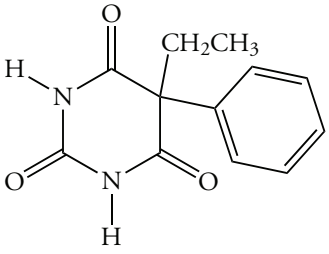
(b) 

(a) 

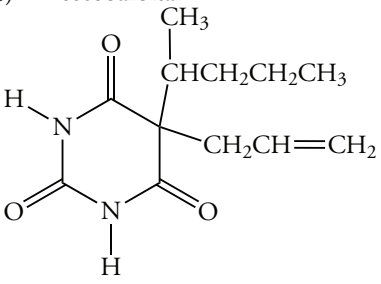
(d) 

8.7 How many chiral centers does each of the following barbiturates have?

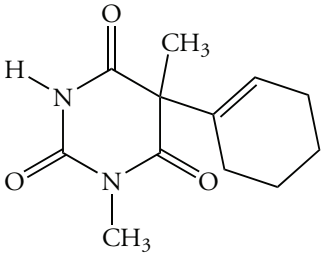
(a) phenobarbital



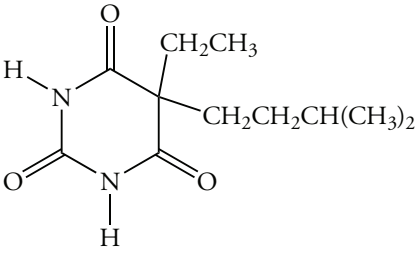
(b) secobarbital



(c) hexobarbital

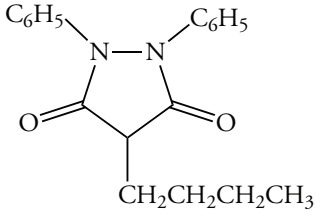


(d) amobarbital

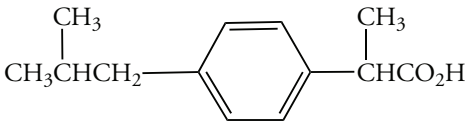


8.8 How many chiral centers does each of the following drugs have?

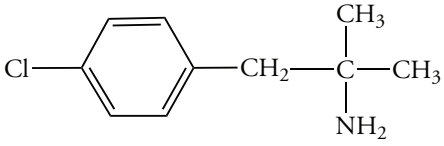
(a) phenylbutazone, used to treat gout



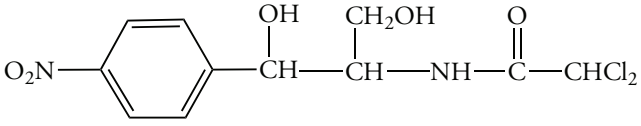
(b) ibuprofen, an analgesic



(c) chlorphentermine, a nervous system stimulent

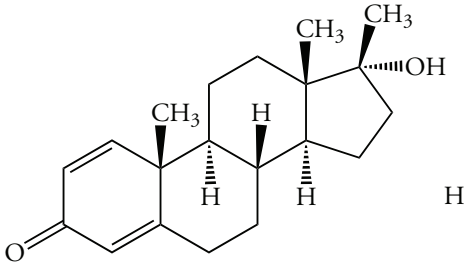


(d) chloramphenicol, an antibiotic

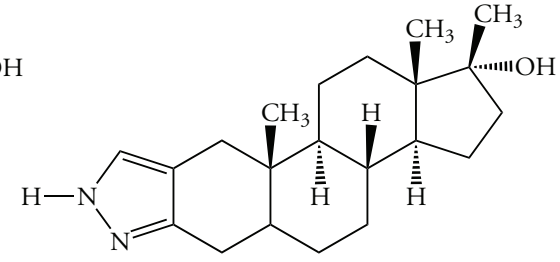


8.9 How many chiral carbon atoms are in each of the following synthetic anabolic steroids?

(a) Dianabol

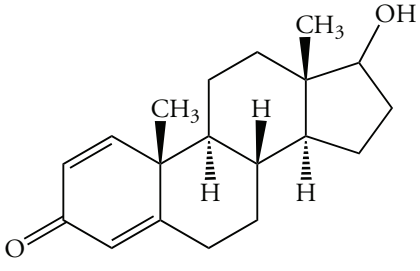


(b) stanozolol

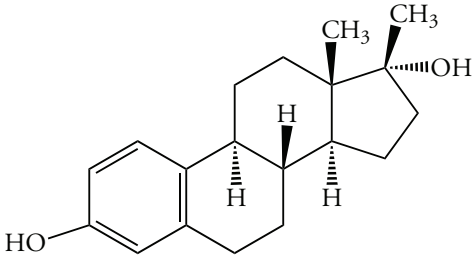


8.10 Determine the number of chiral centers in the male sex hormone testosterone and in the female sex hormone estradiol.

(a) testosterone



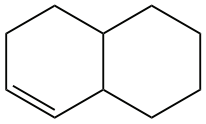
(b) estradiol



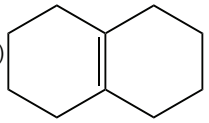
Plane of Symmetry

8.11 Determine whether each of the following compounds has a plane of symmetry.

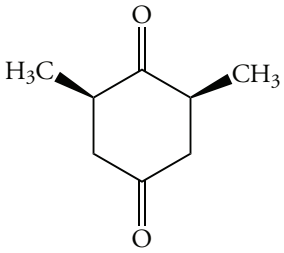
(a)



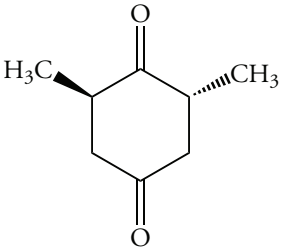
(b)



(c)

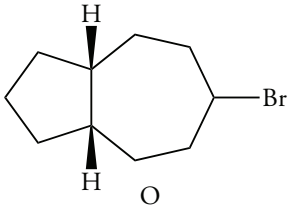


(d)

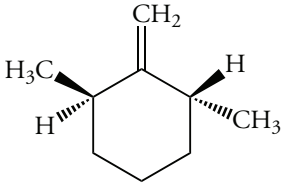


8.12 Determine whether each of the following compounds has a plane of symmetry.

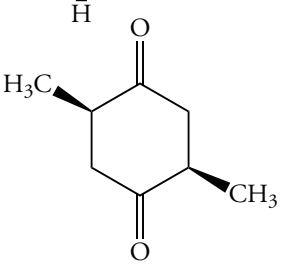
(a)



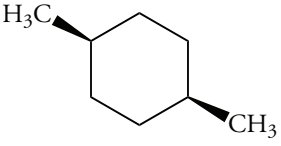
(b)



(c)



(d)



Optical Activity

8.13 Lactic acid in the blood has a specific rotation of +2.6°. A sample of lactic acid obtained from sour milk has a specific rotation of –2.6°. How do these compounds differ?

8.14 Optically pure (*S*)-(+)-citronellol from citronella oil has a specific rotation of +5.3°. An enantiomer of optically pure (*S*)-(+)-citronellol is obtained from geranium oil. What is its specific rotation?

8.15 The configuration of naturally occurring monosodium glutamate, MSG, which has a specific rotation of +24° is *S*. Is the assignment of configuration based upon the sign of the optical rotation correct?

8.16 Carvone obtained from spearmint oil is the (*R*)-(–) enantiomer. Explain the meaning of both terms within parentheses.

8.17 A solution of 3 g of menthol in 50 mL of ethanol is prepared and a sample is placed in a 10-cm tube. The optical rotation is +3.0. What is the specific rotation of menthol?

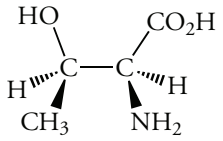
8.18 The specific rotation of (*R*)-2-bromobutane in ethanol is –23.1°. A solution of the compound in a 1-dm tube has $[\alpha]_D$ = 55°. What is the concentration of the compound in grams per 100 mL?

8.19 The specific rotation of (+)-2-butanol as a pure liquid is +13.9°. A synthetic sample of 2-butanol has an optical rotation of –4.5°. What is the composition of the sample?

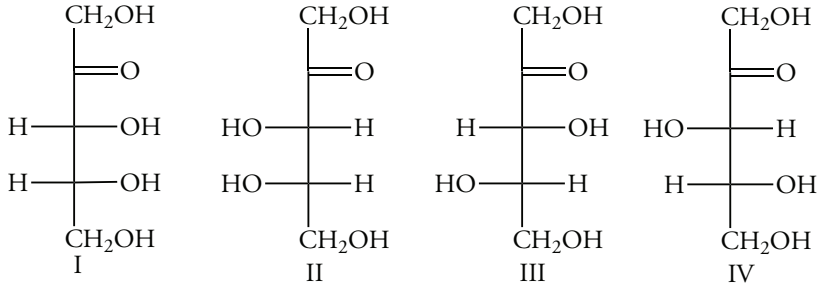
8.20 The specific rotation of the *S* enantiomer of MSG, a flavor enhancer, is +24°. What is the optical purity of a synthetic sample whose α_{obs} is +6°? What are the percentages of the two enantiomers in the sample?

Fischer Projection Formulas

8.21 Draw the Fischer projection formula of the following enantiomer of naturally occurring threonine which is isolated from proteins. Also, draw the Fischer projection formula for the other diastereomers.



8.22 What stereochemical relationship exists between any and all pairs of the following structures of carbohydrates?



Priority Rules

8.23 Arrange the groups in each of the following sets in order of increasing priority.

(a) —OH, —SH, —SCH_3, —OCH_3

(b) —CH_2Br, —CH_2Cl, —Cl, —Br

(c) —CH_2—CH=CH_2, —CH_2—O—CH_3, — CH_2—C≡CH, —C≡C—CH_3

(d) —CH_2CH_3, —CH_2OH, —CH_2CH_2Cl, —OCH_3

8.24 Arrange the groups in each of the following sets in order of increasing priority.

(a) —C(=O)—CH_3 < —C(=O)—OH < —O—C(=O)—CH_3

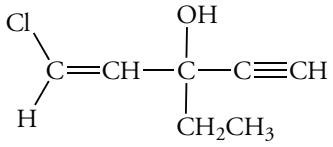
(b) —C(=O)—NH_2 < —NH—C(=O)—CH_3 < —O—C(=O)—CH_3

(c) —C(=O)—Cl < —O—C(=O)—CH_2Br < —S—C(=O)—CH_3

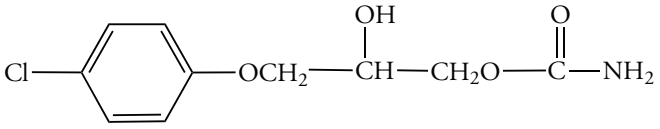
(d) —C≡CH < —C≡N < —N≡C

8.25 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority.

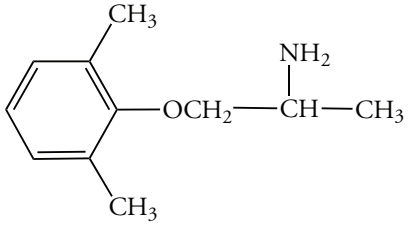
(a) ethchlorvynol, a sedative-hypnotic



(b) chlorphenesin carbamate, a muscle relaxant

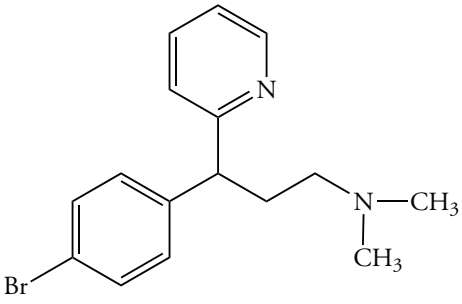


(c) mexiletine, an antiarrhythmic

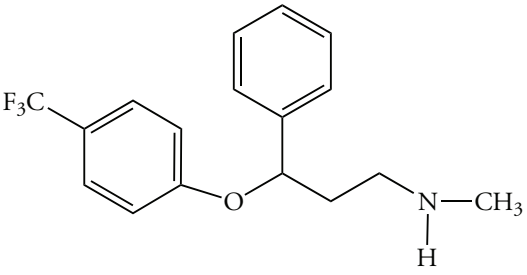


8.26 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority.

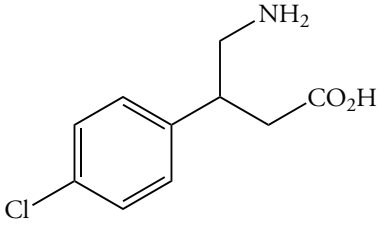
(a) brompheniramine, an antihistamine



(b) fluoxetine, an antidepressant



(c) baclophen, an antispastic



R,S Configuration

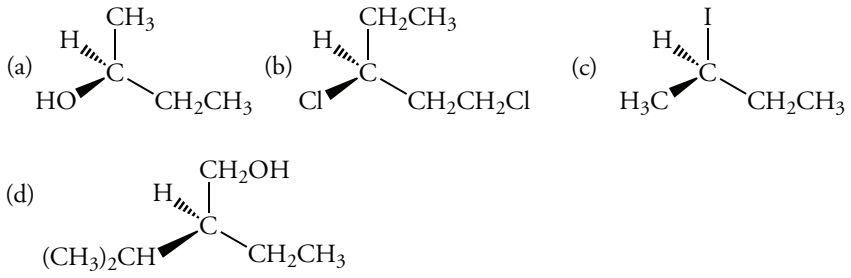
8.27 Draw the structure of each of the following compounds.

(a) (*R*)-2-chloropentane (b) (*R*)-3-chloro-1-pentene (c) (*S*)-3-chloro-2-methylpentane

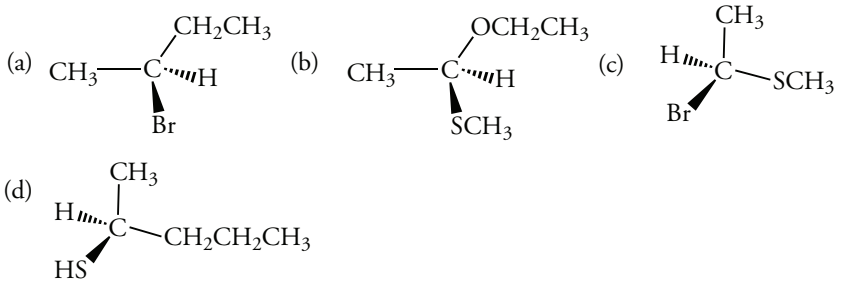
8.28 Draw the structure of each of the following compounds.

(a) (*S*)-2-bromo-2-phenylbutane (b) (*S*)-3-bromo-1-hexyne (c) (*R*)-2-bromo-2-chlorobutane

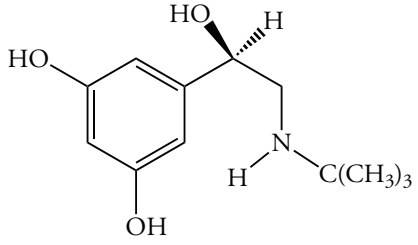
8.29 Assign the configuration of each of the following compounds.



8.30 Assign the configuration of each of the following compounds.

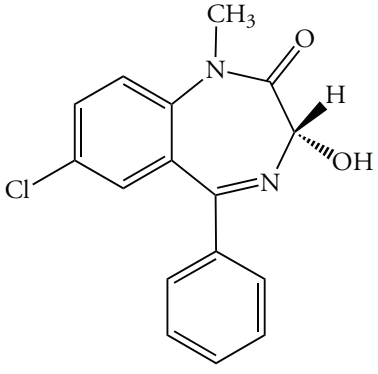


8.31 Assign the configuration of terbutaline, a drug used to treat bronchial asthma.



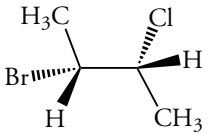
terbutaline

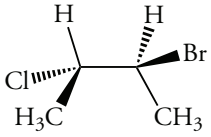
8.32 Assign the configuration of the following hydroxylated metabolite of diazepam, a sedative.

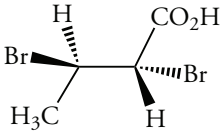


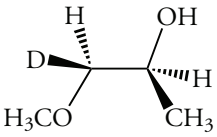
Diastereomers

8.33 Assign the configuration of each of the following compounds.

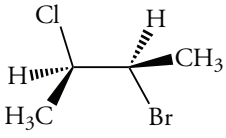
(a) 

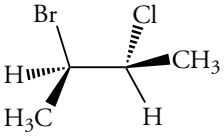
(b) 

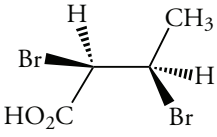
(c) 

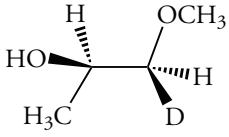
(d) 

8.34 Assign the configuration of each of the following compounds.

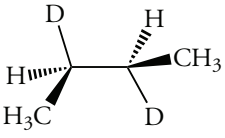
(a) 

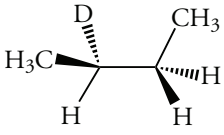
(b) 

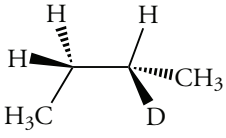
(c) 

(d) 

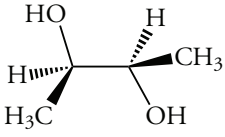
8.35 Assign the configuration of each of the following compounds.

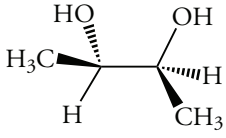
(a) 

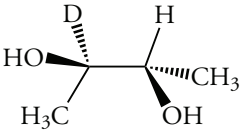
(b) 

(c) 

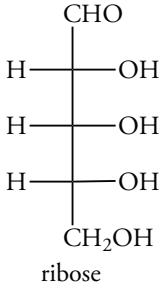
8.36 Assign the configuration of each stereogenic center in the following structures. Based on the assignment, determine if the structure is *meso*.

(a) 

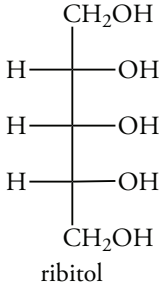
(b) 

(c) 

8.37 Ribose is optically active, but ribitol, its reduction product, is optically inactive. Why?

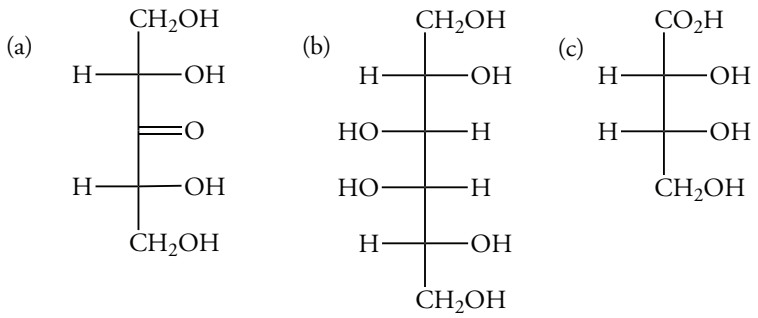


ribose

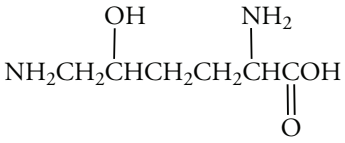


ribitol

8.38 Which of the following carbohydrate derivatives are *meso* compounds?

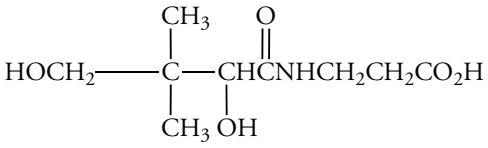


8.39 5-Hydroxylysine is an amino acid isolated from collagen. Determine the number of possible stereoisomers.



5-hydroxylysine

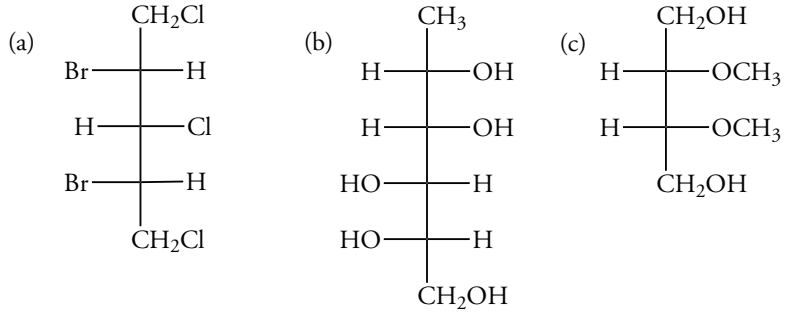
8.40 Consider the structure of pantothenic acid (vitamin B_3) and determine the number of possible stereoisomers.



pantothenic acid

8.41 There are four isomeric 2,3-dichloropentanes, but only three isomeric 2,4-dichloropentanes. Explain why.

8.42 Which of the following structures are *meso* compounds?



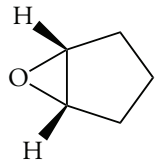
Cyclic Compounds

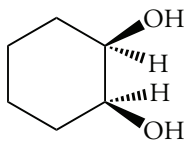
8.43 Which of the following compounds has a plane of symmetry?

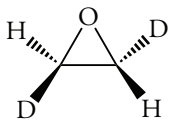
(a) *cis*-l,2-dibromocyclobutane (b) *trans*-l,2-dibromocyclobutane

(c) *cis*-l,3-dibromocyclobutane (d) *trans*-l,3-dibromocyclobutane

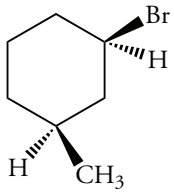
8.44 Which of the following structures has a plane of symmetry?

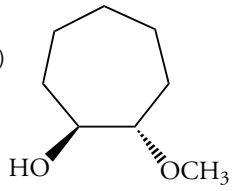
(a) 

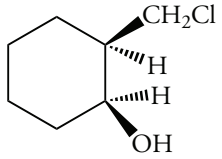
(b) 

(c) 

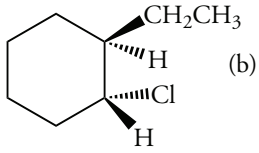
8.45 Assign the configuration of each stereogenic center in the following structures.

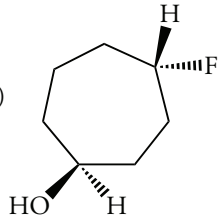
(a) 

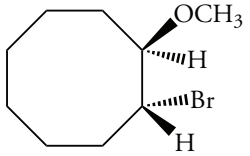
(b) 

(c) 

8.46 Assign the configuration of each stereogenic center in the following structures.

(a) 

(b) 

(c) 

Resolution of Enantiomers

8.47 Reaction of a racemic mixture of A_R,A_S with a resolving agent X_R yields diastereomers. The A_R–X_R isomer is less soluble than A_R–A_S. Consequently, the A_S isomer is obtained optically pure. Describe the experimental results if X_S were available as a resolving agent.

8.48 Resolution of a racemic mixture yields one enantiomer with $[\alpha]_D = +44°$ and another enantiomer with $[\alpha]_D = -33°$. One enantiomer is optically pure. Which one? What is the optical purity of the other enantiomer?

Reactions of Chiral Compounds

8.49 (*R*)-(–)-Lactic acid is converted into a methyl ester when it reacts with methanol. What is the configuration of the ester? Can you predict its sign of rotation?

$$CH_3\overset{\overset{\displaystyle OH}{|}}{C}H{-}CO_2H + CH_3OH \longrightarrow CH_3\overset{\overset{\displaystyle OH}{|}}{C}H{-}CO_2CH_3 + H_2O$$

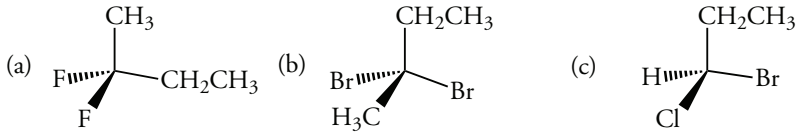
8.50 Free radical chlorination of (*S*)-2-bromobutane gives a mixture of compounds resulting from attack at any of the four nonequivalent carbon–hydrogen bonds. The products of reaction at C-l and C-4 are both optically active. Explain why.

8.51 Free radical chlorination of (*S*)-2-fluorobutane gives a 31% yield of 2-chloro-2-fluorobutane. What is the expected stereochemistry of the product?

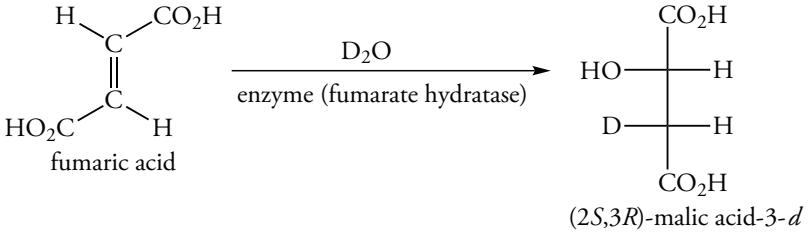
8.52 Free radical chlorination of (*S*)-2-bromobutane at the C-2 atom gives an optically inactive product, but reaction at C-3 gives an optically active product. Explain why.

Prochiral Centers

8.53 Consider the atoms in each of the following structures and indicate which are prochiral. Which have enantiotopic groups? Which have diastereotopic groups?

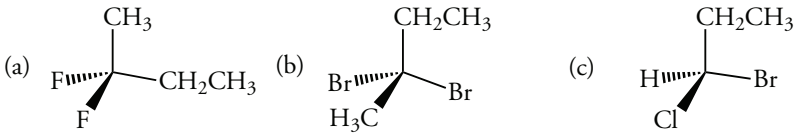


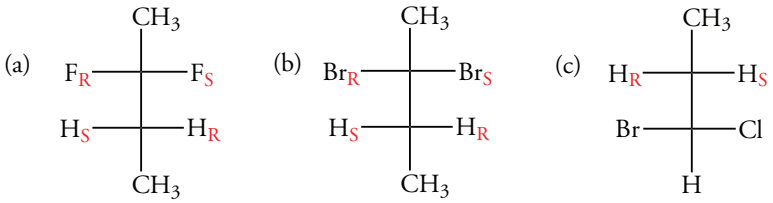
8.54 Addition of water to fumaric acid yields (*S*)-malic acid as part of the citric acid cycle. When D_2O is used, the product is (2*S*,3*R*)-malic acid-3-d. Is the addition reaction *syn* or *anti*? Are the two carbon atoms of the double bond equivalent or not?



8.53 Consider the atoms in each of the following structures and indicate which are prochiral. Which have enantiotopic groups? Which have diastereotopic groups?

Answer: (a) The two fluorine atoms are prochiral, as are the hydrogen atoms of the methylene group. Each of these atoms is enantiotopic.
(b) The two bromine atoms are prochiral, as are the hydrogen atoms of the methylene group. Each of these atoms is enantiotopic.
(c) The two hydrogen atoms of the methylene group are prochiral. They are diastereotopic because the C-1 atom is chiral.





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Answer: Draw a three-dimensional representation of the Fischer projection and rotate about the C-2 to C-3 bond to obtain a staggered conformation placing the deuterium and the hydroxyl group in an *anti* arrangement assuming that an *anti* addition reaction occurred. In this conformation, the two —CO_2H groups are arranged as if the addition reaction occurred by an *anti* periplanar transition state. Thus, the addition is indeed *anti*.