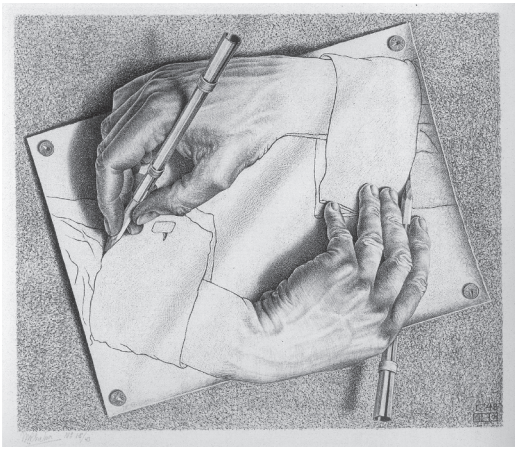
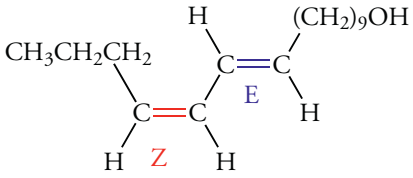
6 STEREOCHEMISTRY



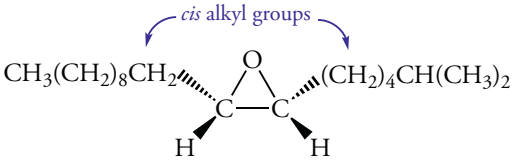
M. C. Escher, Drawing Hands, 1948

6.1 CONFIGURATION OF MOLECULES

In Chapters 3 and 4 we considered the structures of geometric isomers, which are one of a general class of stereoisomers. **Stereoisomers** have the same connectivity—the same sequence of bonded atoms—but different arrangements of the atoms in space. The different three-dimensional arrangements of atoms in space determine their configurations. Geometric isomers have different configurations. The **configuration** of a molecule plays a major role in its biological properties. Stereoisomers often have entirely different biological properties. Geometric isomers invariably elicit different responses in organisms. For example, bombykol, the sex attractant of the male silk-worm moth, has a (Z)/(E) arrangement about the double bonds at C-10 and C-12. It is 10^9 to 10^{13} times more potent than the other three possible geometric isomers. Disparlure, the sex attractant of the female gypsy moth, is biologically active only if the alkyl groups bonded to the three-membered ring are in a *cis* configuration.



bombykol



disparlure

Geometric isomerism is only one type of stereoisomerism. Another type of stereoisomerism is the result of the minor image relationships between molecules, the subject of this chapter. These molecules differ in configuration about an sp^3-hybridized, "tetrahedral carbon" atom bearing four different groups of atoms, which is called a **stereogenic center**. This phenomenon is not as easily visualized as geometric isomers, but its consequences are even more vital to life processes.

6.2 MIRROR IMAGES AND CHIRALITY

The fact that we live in a three-dimensional world has important personal consequences. In the simple act of looking into a mirror, you see someone who does not actually exist—namely, your mirror image. Every object has a mirror image, but this reflected image need not be identical to the actual object. Let's consider a few common three-dimensional objects. A simple wooden chair looks exactly like its mirror image (Figure 6.1). When an object and its mirror image exactly match, we say that they are **superimposable**. Superimposable objects can be "placed" on each other so that each three-dimensional feature of one object coincides with an equivalent three-dimensional feature in the mirror image.

Now let's consider some objects and their mirror images that are not identical. These are said to be **nonsuperimposable**. One example is the side-arm chair found in many classrooms. When a chair with a "right-handed arm" is reflected in a mirror, it becomes a chair with a "left-handed arm" (Figure 6.1). We can convince ourselves of this by imagining sitting in the chair or its mirror image, or we could stop by a classroom and do the experiment ourselves.

Principles of Organic Chemistry. http://dx.doi.org/10.1016/B978-0-12-802444-7.00006-9

Figure 6.1 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, the other has a "left-handed" arm. (These chairs were designed by 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 in the lithograph found at the beginning of this chapter and in Figure 6.2. 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. 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 6.1 it 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.*

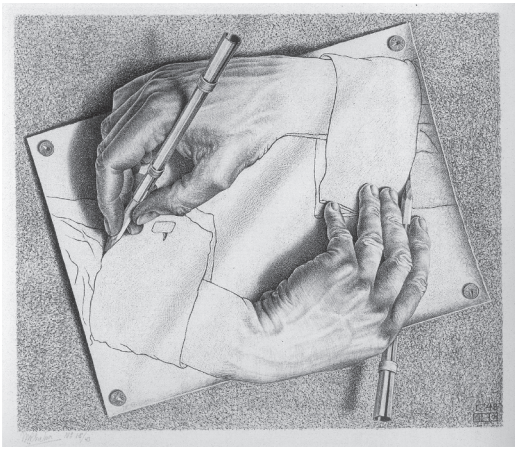


Figure 6.2 Chiral Hands
M.C. Escher's "Drawing Hands" show the relationship between a pair of hands. If you lay your hands on a surface such as a piece of paper you will find the same arrangement. (M.C. Escher's "Drawing Hands" © 2014 The M.C. Escher Company-The Netherlands. All rights reserved.)

M.C. Escher, Drawing Hands, 1948

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 6.3 shows that it can exist as a pair of nonsuperimposable mirror image isomers. Therefore, bromochlorofluoromethane is chiral. In contrast, neither dichloromethane (Figure 6.4) nor bromochloromethane (Figure 6.5) have a plane of symmetry. Neither is chiral.

Figure 6.3
Nonsuperimposable 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.

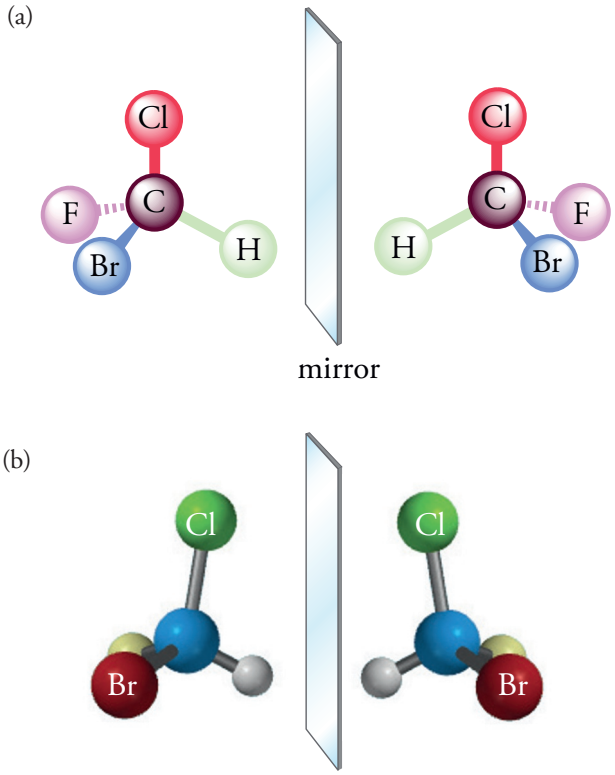


Figure 6.4
Planes of Symmetry in Dichloromethane
Dichloromethane, which has not one, but two planes of symmetry can be superimposed on its mirror image. It is achiral.

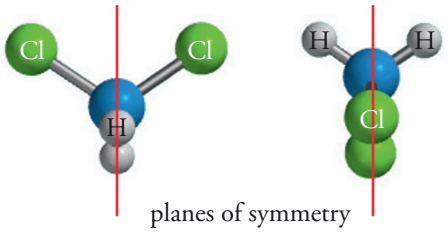
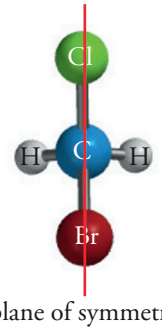
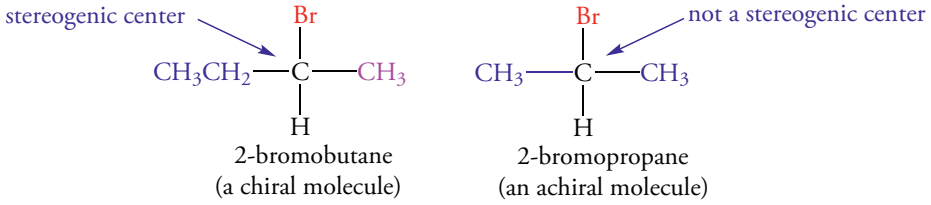


Figure 6.5
Plane of Symmetry in Bromochloromethane
Bromochloromethane has a plane of symmetry, and therefore it can be superimposed on its mirror image. It is achiral.



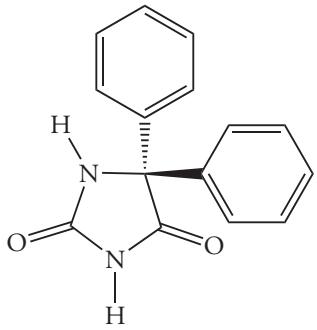
Mirror Image Isomers Are Enantiomers

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.



Problem 6.1

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.



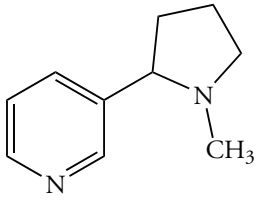
phenytoin

Solution

Phenytoin has only one sp^3-hybridized carbon atom. It is bonded to a nitrogen atom, a carbonyl group, and two phenyl groups. Because the sp^3-hybridized carbon atom is attached to two identical phenyl groups, it is not a stereogenic center, and as a result the molecule is achiral. Phenytoin has a plane of symmetry that lies in the plane of the page. The phenyl groups of phenytoin lie above and below the symmetry plane. Note that the other atoms of phenytoin are bisected by this plane.

Problem 6.2

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



nicotine

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**.

6.3 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 6.6). 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**.

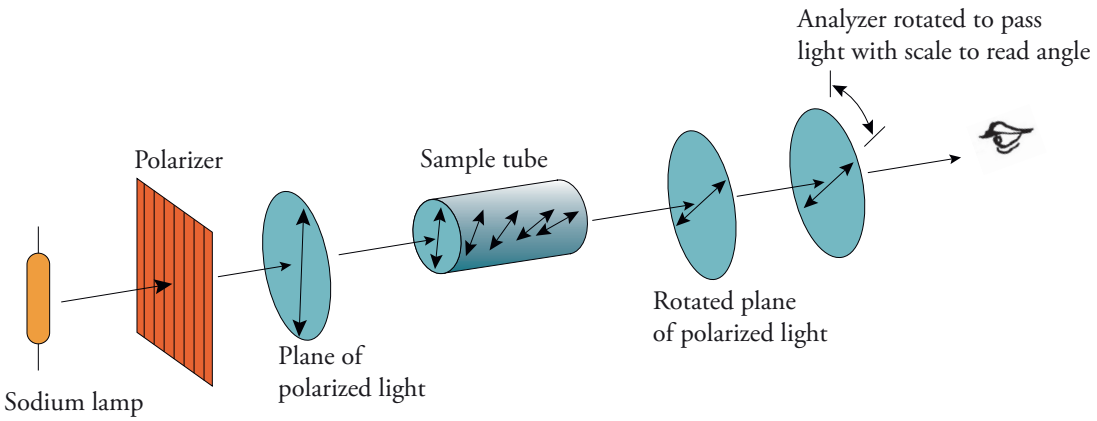


Figure 6.6
Schematic Diagram of a Polarimeter
Plane-polarized light is obtained by passing light through a polarizing filter. Any chiral compound in the sample tube rotates the plane-polarized light. The direction and magnitude of the rotation are determined by rotating the analyzer to allow the light to pass through with maximum brightness. In a modern instrument this is all done electronically, but the basic principle is the same.

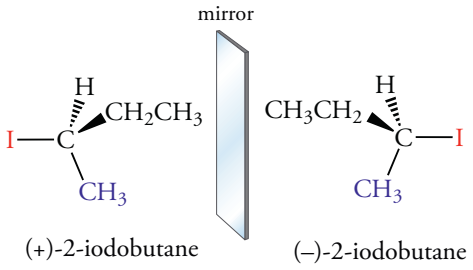
Specific Rotation

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, $[\alpha]_D = +15.15$.



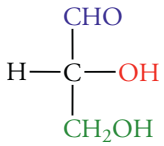
The (+) isomer is sometimes called the *d* form because it is dextrorotatory; the (–) isomer is sometimes called the *l* form because it is levorotatory. Earlier, we encountered levodopa, so named because it is levorotatory. It is also called L-dopa and (–)-dopa. The specific rotation of L-dopa is –13.1°. Table 6.1 lists the specific rotations of some common substances.

Table 6.1
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°

6.4 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 6.6). 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 6.7). 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.

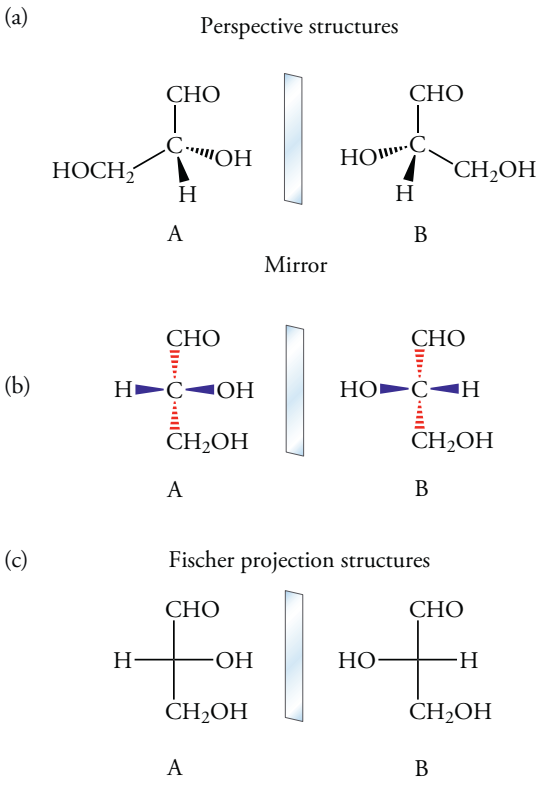
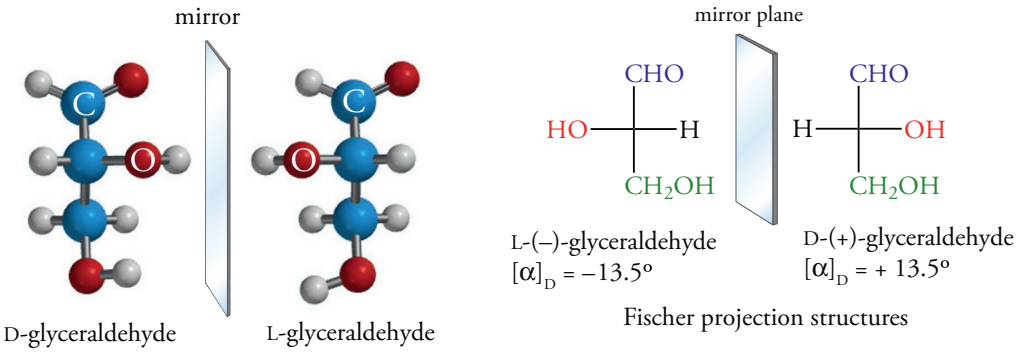


Figure 6.7
Fischer Projection Structures of Glyceraldehyde
(a) Perspective structures of glyceraldehyde. (b) Projection structures. (c) Fisher projection structures of the enantiomers glyceraldehyde. The chiral center is located at the point where the bond lines intersect. The carbon atom is not usually 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 6.7, 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.**



6.5 ABSOLUTE CONFIGURATION

The configuration of the stereogenic center of some molecules, such as amino acids and carbohydrates, can easily be compared to that of 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. Cahn, K.C. Ingold, and V. Prelog established a set of rules that define the **absolute configuration** of any stereogenic center. The configuration is designated by placing the symbol R or S within parentheses in front of the name of the compound.

R,S Configurations: The Cahn-Ingold-Prelog System of Configurational Nomenclature

The R,S system of configurational nomenclature for describing absolute configurations is related to the method we introduced in Section 4.3 to describe the positions of groups in geometric isomers of alkenes. In the R,S system, the four groups bonded to each stereogenic carbon atom are arranged from highest to lowest priority. The highest priority group is assigned the number 1, the lowest priority group the number 4. Then the molecule is oriented so that the bond from the carbon atom to the group of lowest priority is arranged directly along our line of sight (Figure 6.8). When this has been done, the three highest priority groups point toward us 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 then examine the petals.) Consider the path taken as we trace the groups ranked 1 to 3. In Figure 6.8 this direction is clockwise. Therefore, the configuration is designated R (Latin, *rectus*, right). If we trace a counterclockwise path from groups ranked 1 to 3, the configuration is designated S (Latin, *sinister*, left).

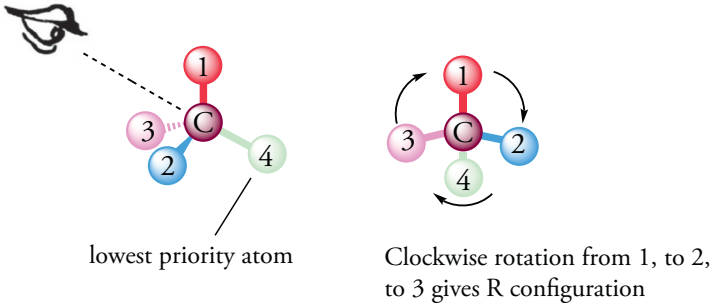


Figure 6.8
Cahn-Ingold-Prelog System of Configurational Nomenclature
Place the lowest priority atom or group away from your eye, and view the chiral site along the axis of the carbon-bond to the lowest priority group. (The diagram of the eye in this figure is from a drawing in the notebooks of Leonardo da Vinci.)

Priority Rules

The priority rules we defined in Chapter 4 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.

$$I > Br > CI > F > O > N > C > {}^{2}H > {}^{1}H$$

Highest priority — Lowest priority

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

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

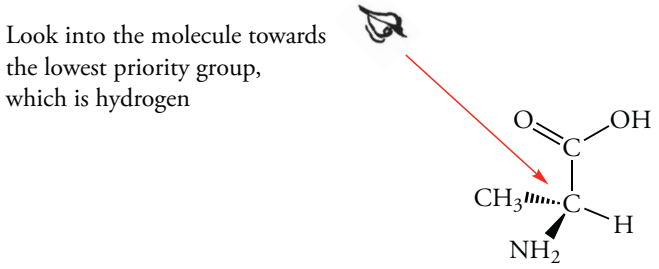
3. *Multiple bonds:* If a group contains a double bond, both atoms are doubled. That is, a double bond is counted as two single bonds to each of the atoms of the double bond. The same principle is used for a triple bond. Thus, the order is

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

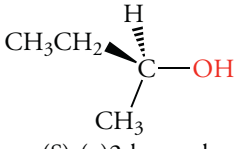
The priority order for common functional groups containing oxygen is

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

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.



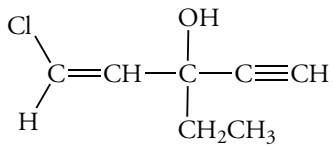
We recall that the direction or magnitude of the optical rotation of a stereoisomer does not determine its absolute configuration. That is, a (+) optical rotation does *not* mean that a molecule has an R configuration. For example, the optical rotation of (S)-2-butanol is clockwise, (+). This isomer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



(S)-(+)2-butanol

Problem 6.3

Arrange the groups at the stereogenic center of ethchlorvynol, a sedative-hypnotic, in order from low to high priority.

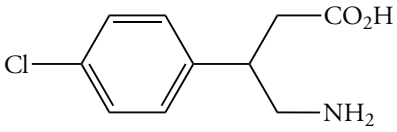


Solution

The stereogenic center has three bonds to carbon atoms and one to an oxygen atom. Because oxygen has a higher atomic number than carbon, the —OH group has the highest priority. The priorities of the other three groups are determined by going to the next atom in the chain. In each case the next atom is carbon. However, there are different numbers of carbon-carbon bonds. The ethyl group has the lowest priority, followed by the —CH=CHCl group and the —C≡CH group in order of increasing priority. Thus, the groups around the stereogenic carbon atom increase in priority in the order —CH_2CH_3 < —CH=CHCl < —C≡CH < —OH.

Problem 6.4

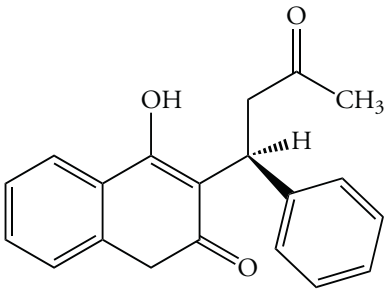
Arrange the groups at the stereogenic center of baclofen, an antispastic drug, in order from low to high priority.



baclofen

Problem 6.5

Warfarin is an anticoagulant drug. Warfarin is used both to treat thromboembolic disease and, in larger doses, as a rat poison. Assign its configuration.

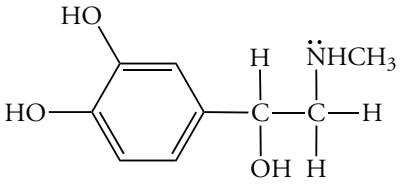


Solution

Warfarin contains only one carbon atom that is attached to four different groups. That stereogenic carbon atom is attached to a hydrogen atom, a —C_6H_5 group (a phenyl group), and two other more complex groups. The lowest priority group is the hydrogen atom. The remaining three groups are linked through carbon atoms. One of them, the methylene group at the 12 o'clock position, has the next lowest priority (3) because it is attached to two hydrogen atoms. Next, we assign the priorities of the phenyl group and the ring system to the left. Both groups are attached to the stereogenic carbon atom by a carbon atom with a single and a double bond. Therefore, we must move to the next atom. When we do this in the complex ring, we find a carbon atom bonded to oxygen, which has a higher priority than the carbon atom bonded to hydrogen at the equivalent position in the phenyl ring. Therefore, the complex ring has a higher priority (1) than phenyl (2). Looking into the carbon-hydrogen bond at the stereogenic carbon atom, so that the hydrogen atom points away from us, we trace a counterclockwise path from group 1 to group 2 to group 3. This enantiomer of warfarin has the S configuration.

Problem 6.6

What is the configuration of epinephrine, commonly known as adrenaline?



epinephrine

6.6 MOLECULES WITH MULTIPLE STEREOGENIC CENTERS

Many compounds contain several stereogenic centers. For example, the antibiotic erythromycin contains 18 stereogenic centers! (Figure 6.9) How is the number of stereoisomers in a molecule with two or more stereogenic centers related to the number of stereogenic carbon atoms? The chirality of a molecule with two or more stereogenic centers depends on whether the centers are equivalent or *nonequivalent.* The term nonequivalent means that the stereogenic carbon atoms are not bonded to identical sets of substituents.

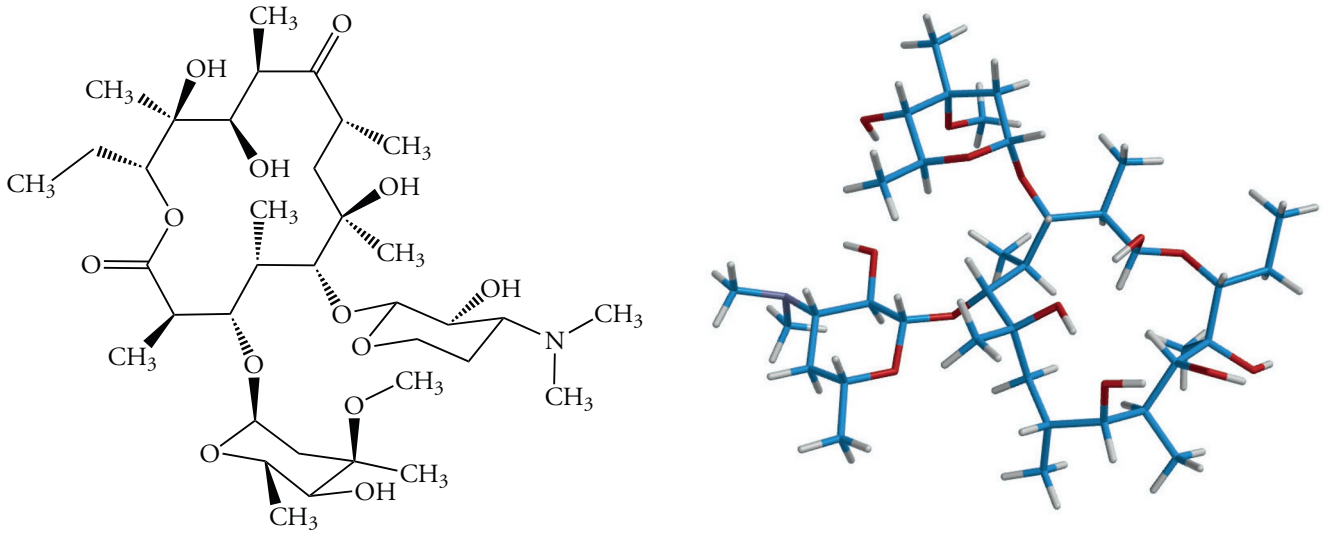
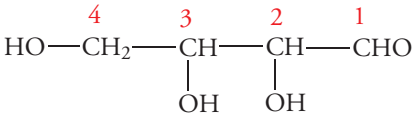


Figure 6.9
Erythromycin—A Chiral Antibiotic

Erythromycin A 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

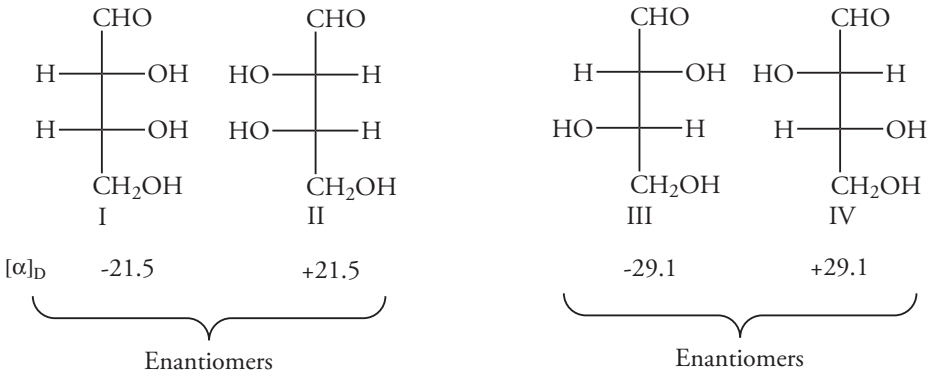
If a molecule contains two or more stereogenic centers, and if they are not bonded to identical groups, the stereogenic centers are **nonequivalent**. For *n* nonequivalent centers, the number of stereoisomers equals 2^n. The following example, 2,3,4-trihydroxybutanal, illustrates the general principle.



2,3,4-trihydroxybutanal

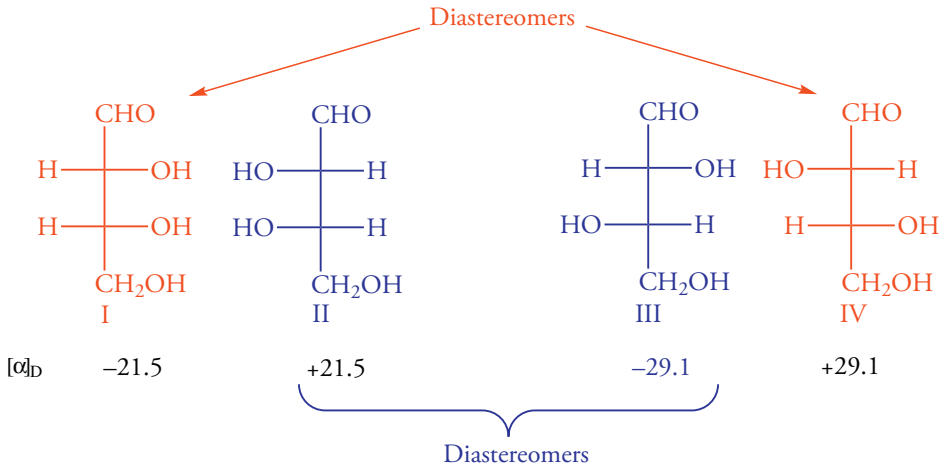
C-2 and C-3 are chiral. They are nonequivalent because they are not bonded to identical groups. Therefore, the configurations at C-2 and at C-3 can be R or S. Without even drawing the structures, we predict that the four stereoisomers calculated from the 2^n rule can be identified as (2R,3R), (2S,3S), (2R,3S), and (2S,3R). Figure 6.10 shows these configurations in Fischer projection formulas.

Figure 6.10
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 stereogenic centers must indicate the configuration of every center. The configuration of each stereogenic carbon atom is indicated by a number, which corresponds to its position in the carbon chain, and the letter R or S, separated by commas. Figure 6.10 shows the structures of the four stereoisomers of 2,3,4-trihydroxybutanol. Each structure has two stereogenic carbon atoms: C-2 and C-3. Each of these stereogenic carbon atoms can be R or S. Thus, the four possibilities are (2R,3R), (2S.3S), (2S,3R), and (2R,3S), The enantiomer of the (2R,3R) compound is the (2S,3S) isomer, which has the opposite configuration at each stereogenic center Compounds whose configurations differ at only one of the two stereogenic centers are diastereomers. For example, the (2R.3R) compound is diastereomer of the (2S,3R) isomer.

Achiral Diastereomers

Compounds that have two or more equivalent stereogenic centers, but are nevertheless achiral, are called **meso compounds** (Greek, *meso*, middle). Meso compounds are not optically active. Let's consider compounds with two equivalently substituted stereogenic centers, as in the tartaric shown

in Figure 6.11. In each structure, the C-2 and C-3 atoms are connected to four different groups. But instead of the four diastereomers that would exist if the stereogenic centers were nonequivalent, only three stereoisomers exist, and one is optically inactive. The compounds labeled (2S,3S) and (2R,3R) are enantiomers. Therefore, they are optically active. But look at the structures labeled (2R,3S) and (2S,3R). Although the structures are drawn as "mirror images," these mirror images are, in fact, superimposable and are identical. To show that this is so, rotate one structure 180° in the plane of the paper: the resulting structure is superimposable on the original structure. Thus the two structures represent the same molecule, which is not optically active. The structures labeled (2R,3S) and (2S,3R) have two equivalent stereogenic carbon atoms. Each of these structures has a plane of symmetry. We recall from Section 6.2 that a structure with a plane of symmetry is achiral and that it is superimposable on it mirror image. In the case of the tartaric acid, the plane of symmetry between the C-2 and C-3 atoms on the top half of the molecule is the mirror image of the bottom half.

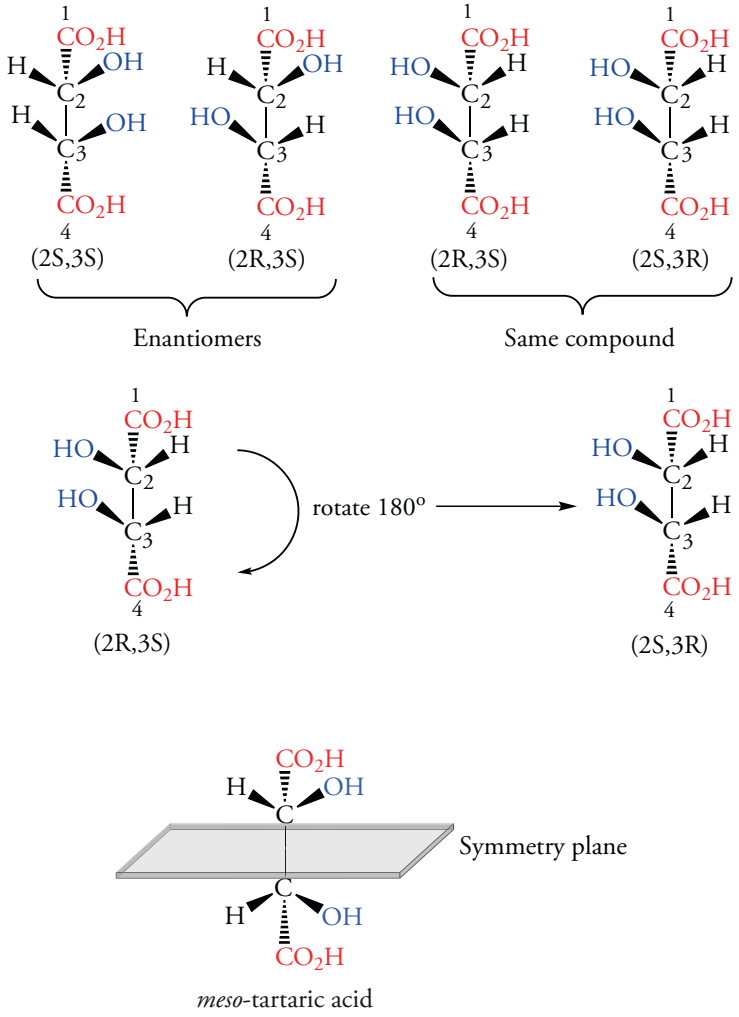


Figure 6.11
Configurations of Optically Active Tartaric Acids and Meso Compounds
Only three stereoisomers exist for tartaric acid because it has two equivalent chiral centers. Two of the stereoisomers are enantiomers. The third has a plane of symmetry, is optically inactive, and is called a *meso* compound; that is, *meso*-tartaric acid.

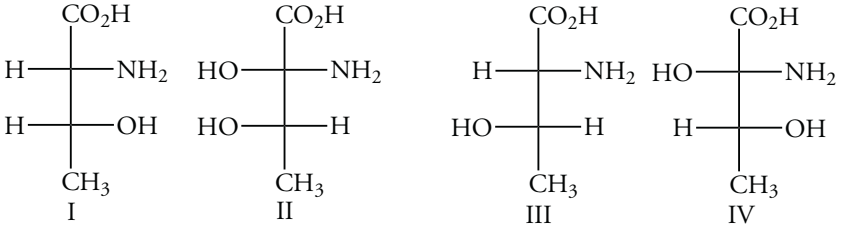
Problem 6.7

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?

$$\overset{4}{C}H_3\overset{3}{C}H(OH)\overset{2}{C}H(NH_2)\overset{1}{C}O_2H$$

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 2S,3R.

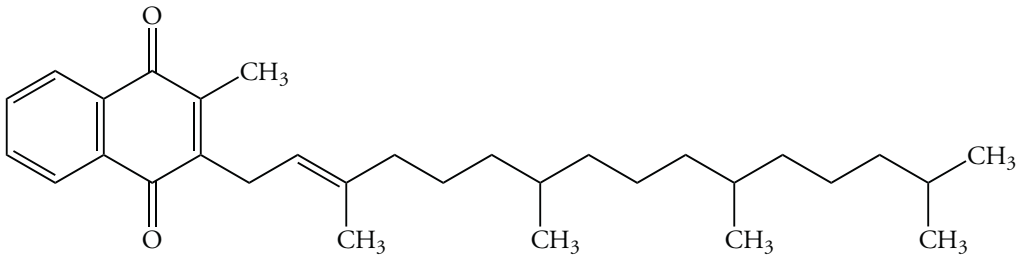


Problem 6.8

Write the Fischer projection formulas of the stereoisomeric 2,3-dibromobutanes. What relationships should exist between the optical activities of these isomers?

Problem 6.9

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



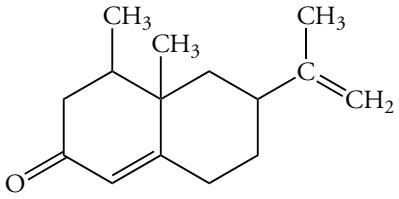
Solution

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.

Problem 6.10

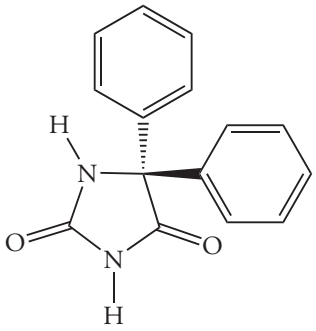
Determine the number of stereogenic centers in nootkatone, found in grapefruit oil. How many stereoisomers are possible?



Metabolic Variations Within and Among Species

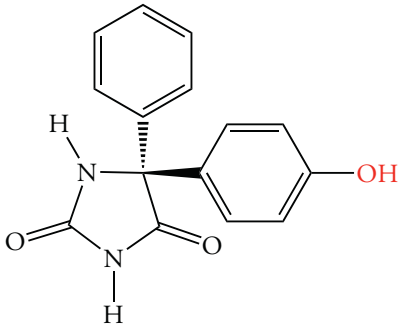
The metabolism of drugs is often species dependent—a fact that must be considered because drugs are usually tested on animals prior to human trials. Even within the same species there are often strain differences, which are common among inbred test animals such as mice and rabbits. Genetic differ-

ences in drug metabolism have been clearly established in humans. The differences between African Americans, Northern Europeans, Eskimos, and Asians must be considered in prescribing certain drugs. For example, the antituberculosis agent isoniazid is metabolized at different rates by individuals with different genetic backgrounds. Eskimos metabolize the drug far faster than Egyptians. Drug metabolism also varies by sex. Some oxidative processes are controlled by sex hormones, particularly the androgens. This factor is important and drugs are tested in men and women. Metabolism in men is more easily studied because of smaller hormonal changes day to day. Also of concern is the possible effect of drugs on a very early fetus before a woman knows she's pregnant.

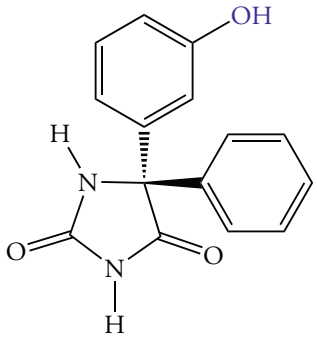


phenytoin

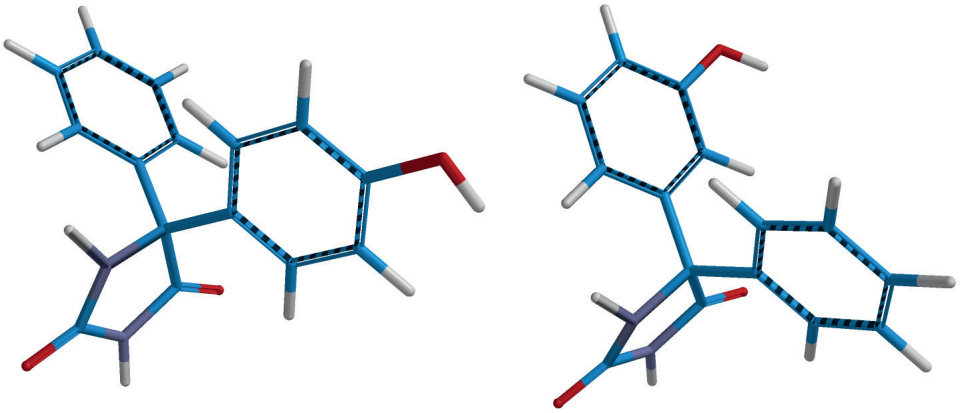
The anticonvulsant phenytoin shows a dramatic difference in metabolism depending on species. This achiral compound is oxidized to a chiral phenol. In humans, the hydroxylation occurs at the para position of one ring, and the compound has the S configuration. In dogs, the hydroxylation occurs at the *meta* position of the other ring, and the compound has the R configuration.



(S)-(-)-*p*-hydroxyphenytoin
(human)

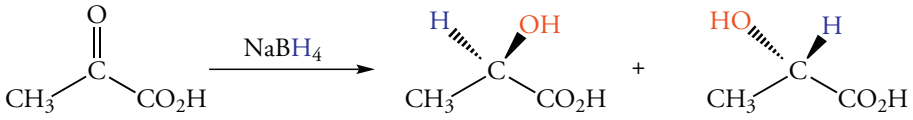


(R)-(+)-*m*-hydroxyphenytoin
(dog)



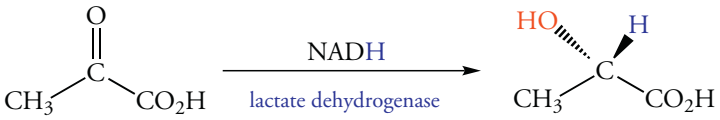
6.7 SYNTHESIS OF STEREOISOMERS

Reaction of an achiral reactant with an achiral reagent to produce a compound with a stereogenic center gives a 50:50 mixture of enantiomers called a **racemic mixture**. Consider the reduction of pyruvic acid with $NaBH_4$. C-2 atom is a carbonyl carbon atom. The atoms directly bonded to the carbonyl carbon atom are arranged in a trigonal plane. Addition of hydrogen to the carbon atom can occur from either face of the molecular plane. Thus the tetrahedral carbon atom of the lactic acid formed can have two possible configurations.



pyruvic acid | *(R)*-(+)-lactic acid | *(S)*-(–)-lactic acid

The individual lactic acid molecules produced are optically active. But a solution containing the products of the reaction is not optically active because the rotation of plane-polarized light by the *(R)*-lactic acid is canceled by the opposite optical rotation of *(S)*-lactic acid, which is formed in equal amounts. Note that there is a difference between a racemic mixture and a *meso* compound. A racemic mixture contains optically active components; the *meso* compound is a single achiral substance. If we wish to synthesize a chiral product from an achiral reactant, the reaction must occur in a chiral environment. Protein catalysts called enzymes are examples of chiral reagents. Reduction of pyruvic acid using the liver enzyme lactate dehydrogenase yields exclusively *(S)*-lactic acid. The reducing agent for the reaction is nicotinamide adenine dinucleotide, NADH.

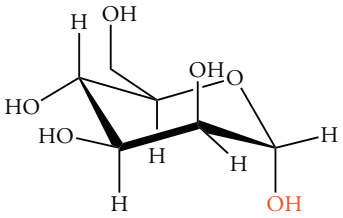


pyruvic acid | *(S)*-(–)-lactic acid

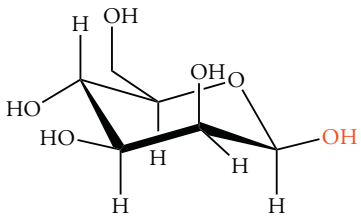
Chirality and Our Senses of Taste and Smell

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.

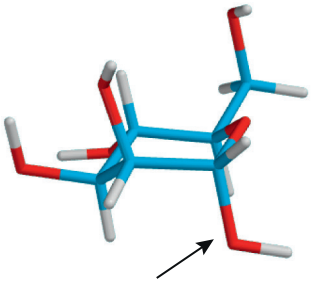
Diastereomers interact with highly specific sensory receptors. For example, D-mannose, a carbohydrate, exists in two diastereomeric forms that differ in the configuration of a hydroxyl group at one center. The two isomers are designated α and β. The α form tastes sweet, but the β form tastes bitter.



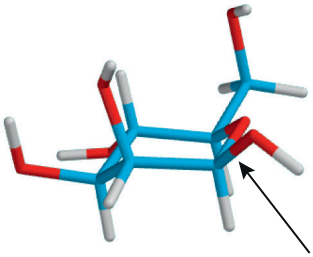
α-D-mannose
(The hydroxy group is axial in the α isomer)



β-D-mannose
(The hydroxy group is equatorial in the β isomer)

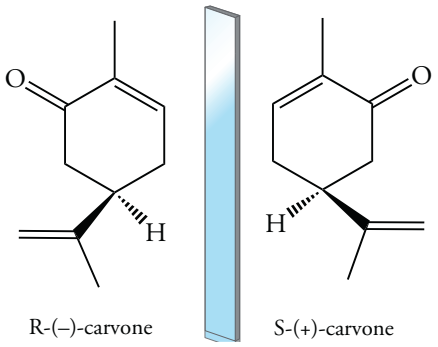


α-D-mannose (axial hydroxyl group)



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.



R-(–)-carvone S-(+)-carvone

Problem 6.11

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.

Solution

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

Problem 6.12

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?

6.8 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 6.12). 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.

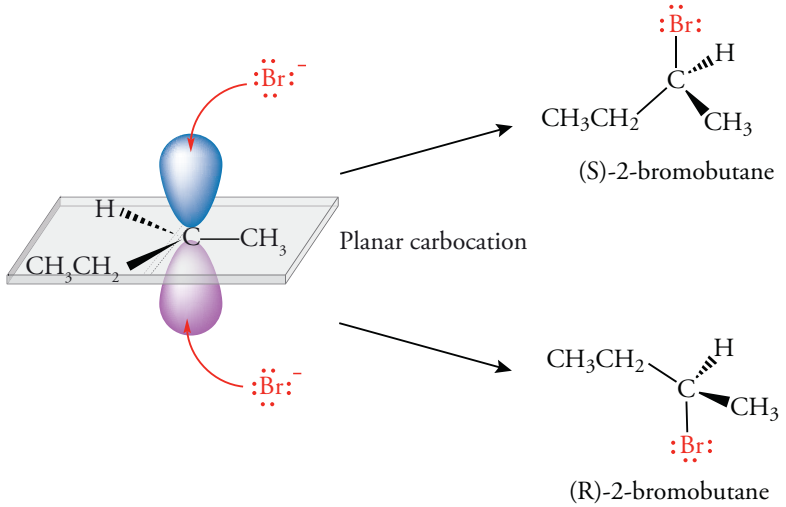
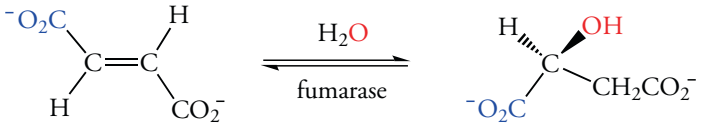


Figure 6.12 Stereochemistry of Markovnikov Addition of HBr to 1-Butene
A proton adds to the double bond of 1-butene to give an intermediate secondary carbocation. It is achiral because it has a plane of symmetry. Bromide ion can attack with equal probability from the top or the bottom to give a racemic 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. Thus, 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.



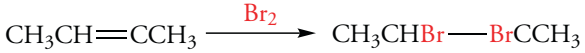
fumarate
(the conjugate base of fumaric acid)

(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 4.6? 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 (2R,3R)- and (2S,3S)-dibromobutanes (Figure 6.13a). Although the bromonium ion could form by attack equally well on the top or bottom, let's examine the intermediate obtained from attack on the top. (The intermediate obtained from attack on the bottom is the same because it is achiral.) Subsequent attack of bromide ion can occur at either the right or left carbon atom. Attack at the right carbon atom gives the 2R,3R isomer. Attack at the left carbon atom gives the 2S,3S 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 6.13b). The bromonium ion results from attack on the top. Bromide ion attacks equally well at the right and left carbon atoms, giving the 2S,3R and 2R,3S 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.

These results support 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.

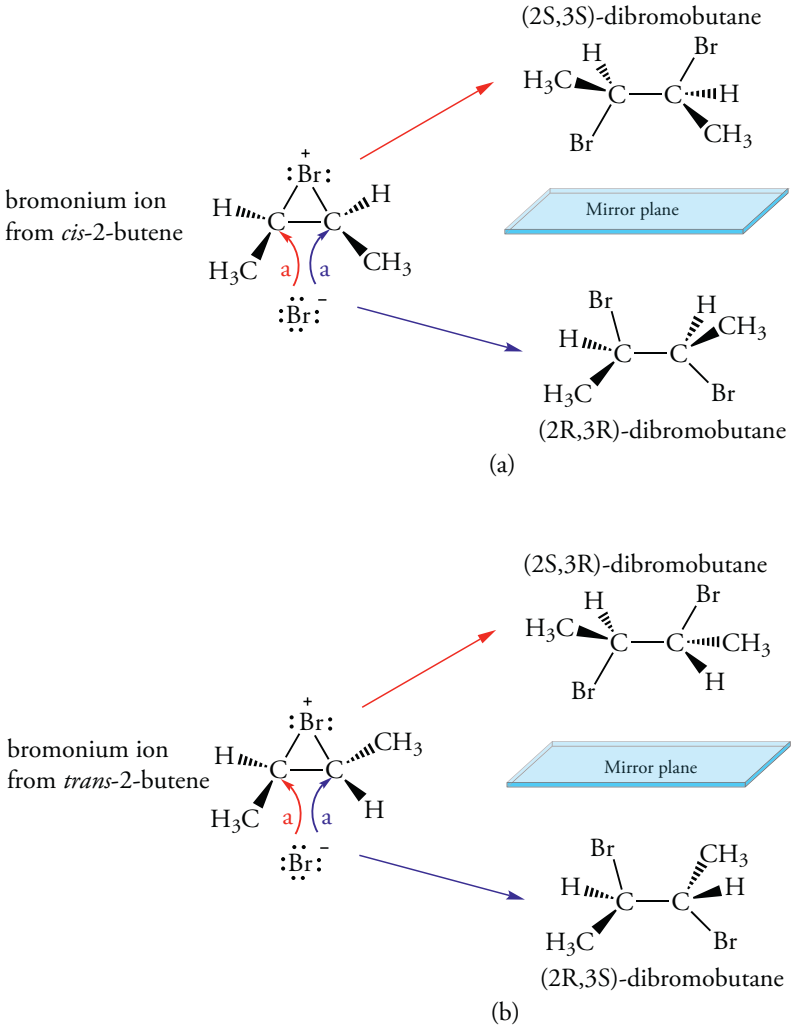
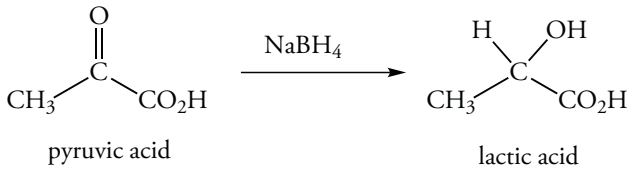


Figure 6.13
Stereochemistry of Bromine Addition to Alkenes
The reaction of bromine with an alkene produces a bromonium ion intermediate. This intermediate reacts with bromide ion in a process that results in net anti addition of bromine. The stereochemical consequences for adding bromine to *cis*-2-butene and *trans*-2-butene are different. *cis*-2-Butene yields a pair of enantiomers; *trans*-2-butene yields a *meso* compound.

Problem 6.13

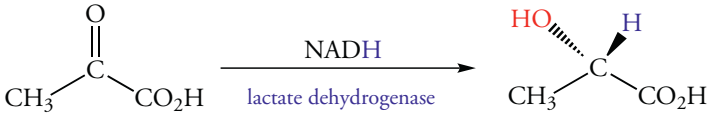
Sodium borohydride ($NaBH_4$) reacts with the C-2 carbonyl carbon atom of pyruvic acid to give lactic acid. What is the optical rotation of the product(s)?



pyruvic acid lactic acid

Problem 6.14

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

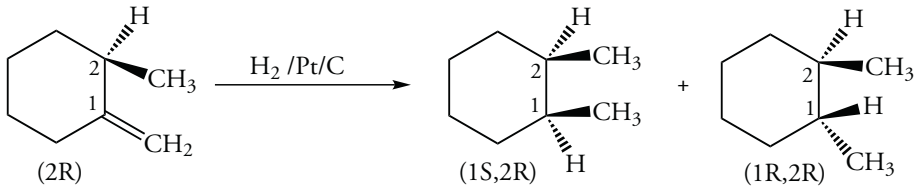


pyruvic acid *(S)*-(-)-lactic acid

6.9 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 as 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, 1S,2R and 1R,2R, form, but in unequal amounts. Approximately 70% of the product is the *cis* isomer (1S,2R).



(2R) (1S,2R) (1R,2R)

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 6.15

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

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.

Problem 6.16

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

Exercises

Chirality

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

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

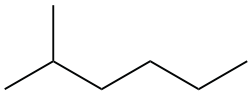
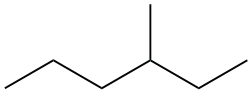
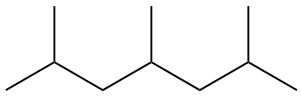
6.2 Which of the following isomeric bromohexanes has a chiral center?

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

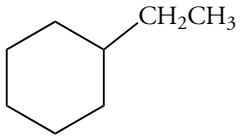
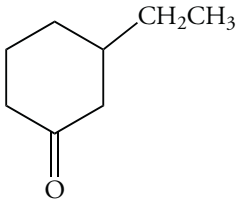
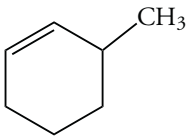
6.3 Which of the compounds with molecular formula $C_5H_{11}Cl$ has a chiral center?

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

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

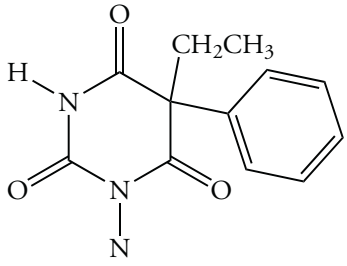
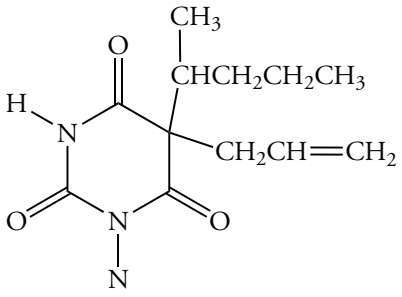
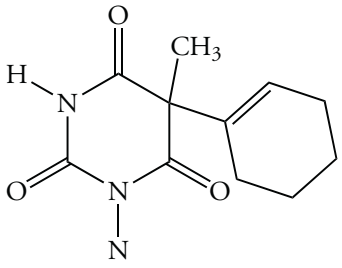
(a)  (b)  (c) 

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

(a)  (b)  (c) 

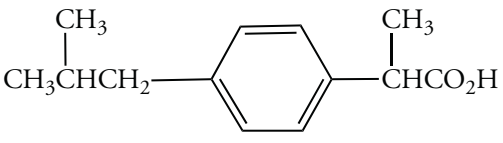
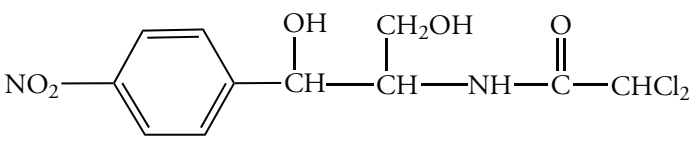
6.7 How many chiral centers does each of the following barbiturates have?

(a) phenobarbital (b) secobarbital (c) hexobarbital

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

(a) ibuprofen, an analgesic (b) chloramphenicol, an antibiotic

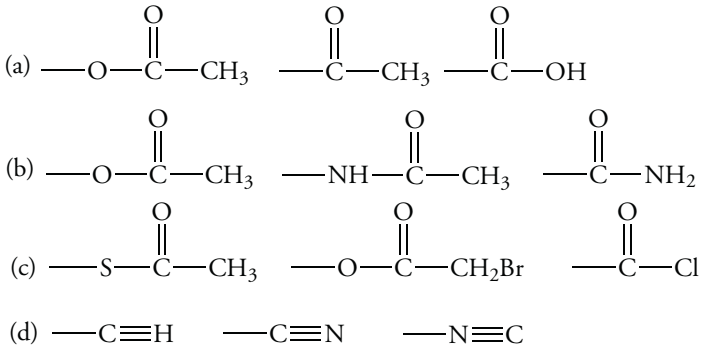
6.9 Arrange the groups in each of the following sets in order of increasing priority:

(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

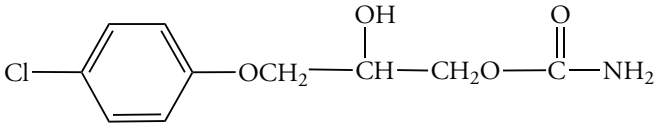
(d) —CH_2CH_3, —CH_2OH, —CH_2CH_2Cl, —OCH_3

6.10 Arrange the groups in each of the following sets in order of increasing priority:

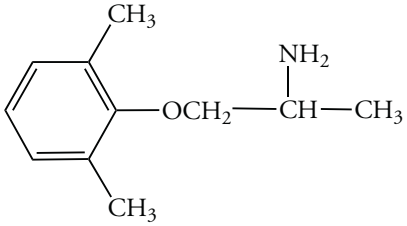


6.11 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority:

(a) chlorphenesin carbamate, a muscle relaxant

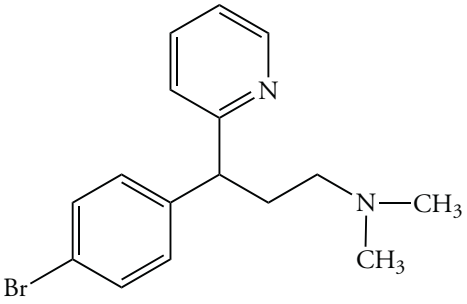


(b) mexiletine, an antiarrhythmic

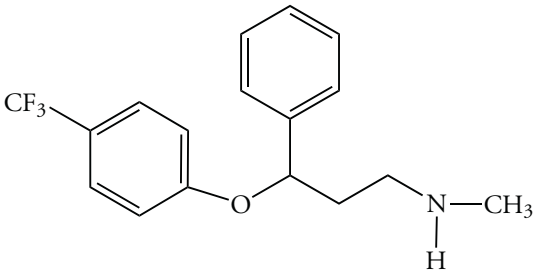


6.12 Examine the chiral carbon atom in each of the following drugs and arrange the groups from low to high priority:

(a) brompheniramine, an antihistamine



(b) fluoxetine, an antidepressant



R,S Configuration

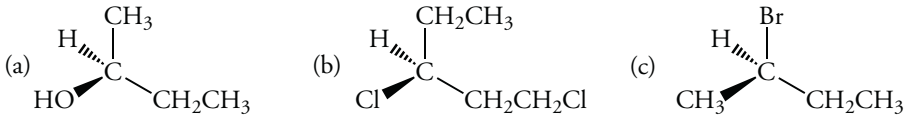
6.13 Draw the structure of each of the following compounds:

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

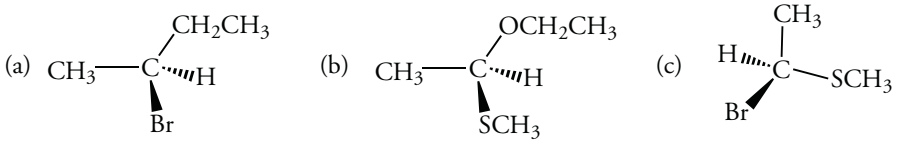
6.14 Draw the structure of each of the following compounds:

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

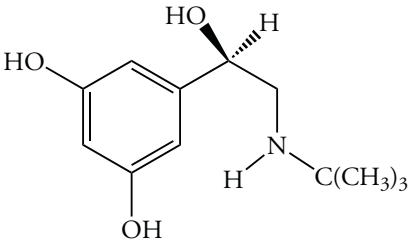
6.15 Assign the configuration of each of the following compounds:



6.16 Assign the configuration of each of the following compounds:

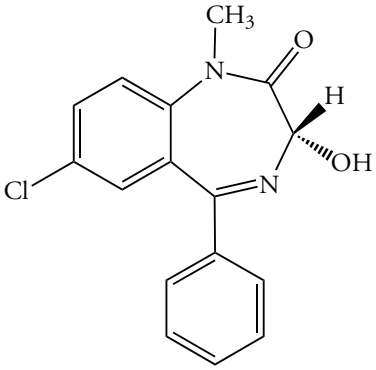


6.17 Assign the configuration of terbutaline, a drug used to treat bronchial asthma.



terbutaline

6.18 Assign the configuration of the following hydroxylated metabolite of diazepam, a sedative:



Optical Activity

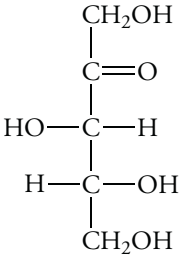
6.19 The naturally occurring form of glucose has a specific rotation of +53. What is the specific rotation of its enantiomer?

6.20 The naturally occurring form of the amino acid threonine has a specific rotation of +26.3. What is the specific rotation of its enantiomer?

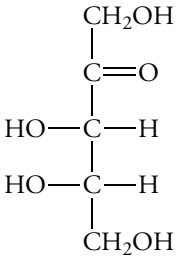
6.21 What do the various prefixes in *(R)*-(+)-glyceraldehyde and *(S)*-(−)-lactic acid mean?

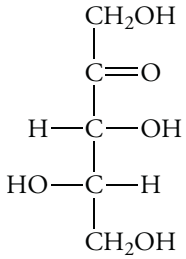
6.22 *(R)*-(−)-lactic acid is converted into a methyl ester when it reacts with methanol. What is the configuration of the ester? Can you predict its sign of rotation?

6.23 Consider the following four projection formulas. Determine the two missing rotations.

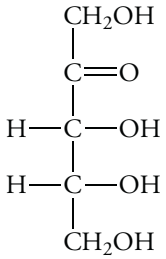


$[\alpha] = +19.6^{\circ}$

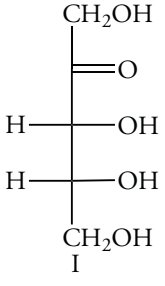




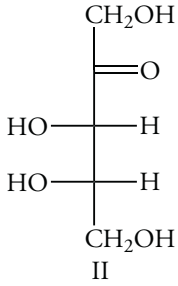
$[\alpha] = -14.8^{\circ}$



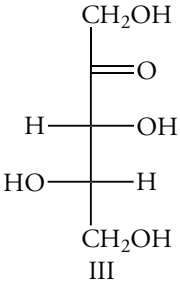
6.24 What stereochemical relationship exists between any and all pairs of the following structures of carbohydrates?



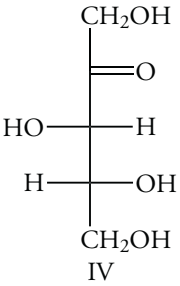
I



II



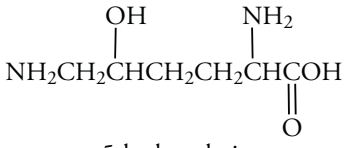
III



IV

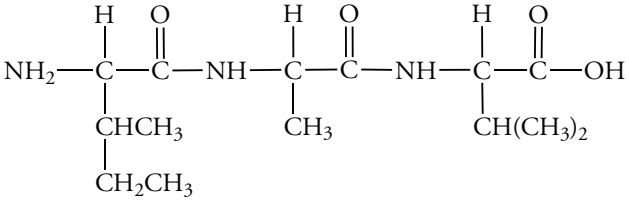
Diastereomers

6.25 5-Hydroxylysine is an amino acid isolated from collagen. Determine the number of possible stereoisomers.

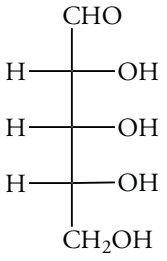


5-hydroxylysine

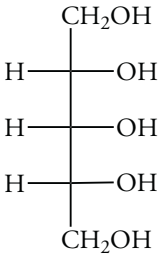
6.26 Consider the structure of the following tripeptide, and determine the number of stereoisomers possible.



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



ribose



ribitol

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

Chemical Reactions

6.29 Addition of HBr to 1-butene yields a racemic mixture of 2-bromobutanes. Explain why.

6.30 Reduction of acetophenone with $NaBH_4$ produces a racemic mixture of 1-phenyl-1-ethanols. Explain why.

6.31 How many products are possible when HBr adds to the double bond of *(R)*-3-bromo-1-butene? Which are optically active?

6.32 How many products are possible when HBr adds to the double bond of 4-methylcyclohexene? Which are optically active?

Stereoisomers in Biochemistry

6.33 D-Glucose is a sugar that the body can metabolize. Suggest what would happen if one were to eat its enantiomer.

6.34 The mold *Penicillium glaucum* can metabolize one enantiomer of optically active tartaric acid. Explain what would happen if a racemic mixture of tartaric acid were added to the mold.

6.35 Natural adrenaline is levorotatory. The enantiomer has about 5% of the biological activity of the natural compound. Explain why.

6.36 The following isomer of hydroxycitronellal has the odor of lily of the valley. Its mirror image has a minty odor. Explain why.