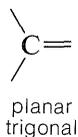
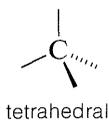


# STEREISOMERISM OF ORGANIC MOLECULES

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**B**y now you should be familiar with *position isomers* wherein compounds of the same molecular formula differ because substituents, chain branches, and so on, are not at the same positions in the molecules. 1-Chloropropane and 2-chloropropane are straightforward examples of position isomers. A much more subtle form of isomerism is present when two *different* compounds have the *same* molecular formulas, the *same* substituent and chain-branching positions, and, indeed, even have the *same* names by all of the nomenclature rules we have given you so far. *Such isomers are different because their molecules have different arrangements of the atoms in space.* These are **stereoisomers** and this type of isomerism, called **stereoisomerism**, is of enormous importance to all areas of organic chemistry and biochemistry.

To understand stereoisomerism of carbon compounds, we must understand the ways in which the bonds to carbon atoms are arranged in space. As shown in Section 2-2A, this depends on whether the carbon atoms form single, double, or triple bonds to another atom. Thus, four single bonds to a carbon form a tetrahedral arrangement; two single bonds and one double bond to a carbon give a planar array with bond angles near  $120^\circ$ , while one single bond and one triple bond (or two double bonds) to a carbon are arranged linearly:



Finally, if you have not studied the material already, you may wish to return to the last part of Chapter 3 and become acquainted with the nomenclature of cycloalkanes, alkenes, cycloalkenes, and alkynes (Sections 3-2 to 3-4).

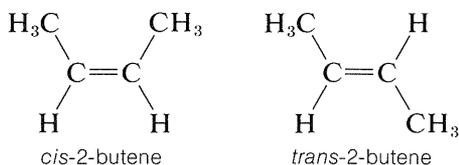
## 5-1 CONFIGURATIONAL ISOMERS

### 5-1A Geometric Isomerism

We have defined isomers in a very general way as nonidentical molecules that possess the same number and kind of atoms. However, there are several ways in which isomers can be nonidentical. Among the alkenes, 1- and 2-butene are position isomers, because in these compounds the double bond has a different position in the carbon chain:

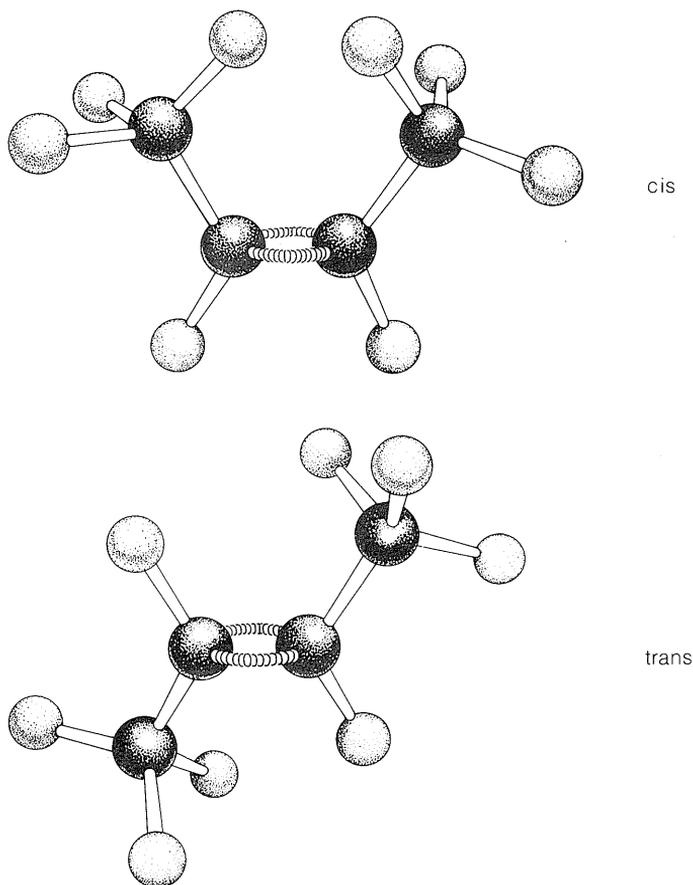


Most, but not all alkenes, also have stereoisomers that are not identical because of different *spatial* arrangements of the component atoms. Thus there are two stereoisomers of 2-butene that differ in the geometric arrangement of the groups attached to the double bond. In one isomer, both methyl groups are on the *same* side of the double bond (*cis*-2-butene) and in the other, the methyl groups are on *opposite* sides of the double bond (*trans*-2-butene):



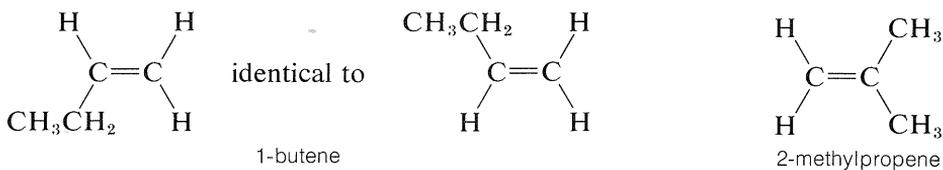
The two isomers clearly have the same structural framework but they differ in the arrangement of this framework in space—hence the designation *stereoisomers*. They owe their separate existence to the fact that the double bond is rigid and the parts of the molecule are not free to rotate with respect to each other about this bond. Therefore the isomers do not interconvert without breaking the double bond, and they exist as different compounds, each with its own chemical and physical properties. Ball-and-stick models of *cis*- and *trans*-2-butene are shown in Figure 5-1, and the rigidity of the double bond is simulated in the model by a pair of stiff springs or bent sticks connecting the two carbons of the double bond.

It should be clear to you that there will be no *cis-trans* isomers of alkenes in which one end of the double bond carries identical groups. Thus we do not expect there to be *cis-trans* isomers of 1-butene or 2-methylpropene, and



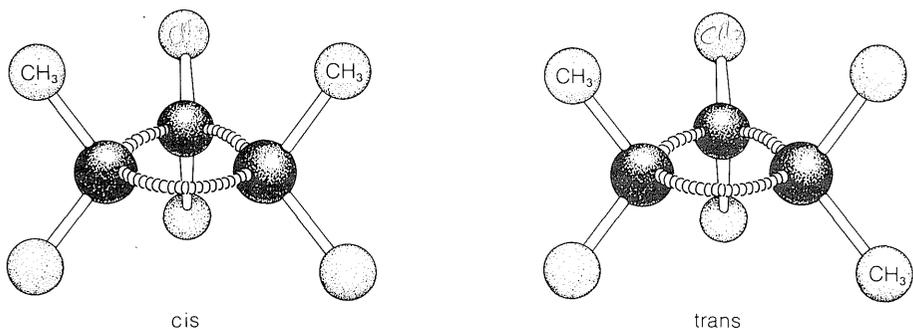
**Figure 5-1** Ball-and-stick models of *cis*- and *trans*-2-butene

indeed none are known:



You may wish to verify this by making ball-and-stick models of these substances.

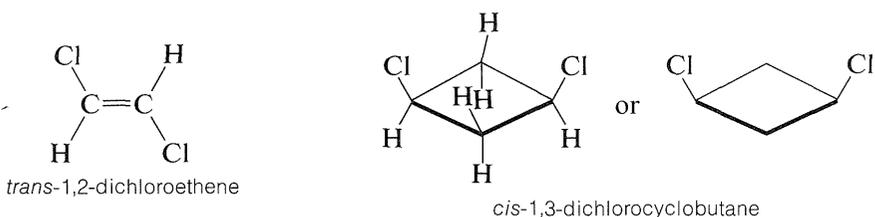
Ring formation also confers rigidity on molecular structure such that rotation about the ring bonds is prevented. As a result, stereoisomerism of the *cis-trans* type is possible. For example, 1,2-dimethylcyclopropane exists in two forms that differ in the arrangement of the two methyl groups with re-



**Figure 5-2** Ball-and-stick models of cis and trans isomers of 1,2-dimethylcyclopropane

spect to the ring. In the cis isomer, the methyl groups both are situated above (or below) the plane of the ring and in the trans isomer they are situated one above and one below, as shown in Figure 5-2. Interconversion of these isomers does not occur without breaking one or more chemical bonds.

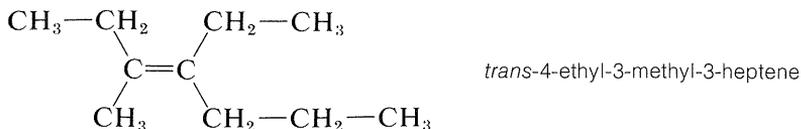
Stereoisomers that do not interconvert rapidly under normal conditions, and therefore are stable enough to be separated, specifically are called **configurational isomers**. Thus *cis*- and *trans*-2-butene are configurational isomers, as are *cis*- and *trans*-1,2-dimethylcyclopropane. The terms *cis-trans isomerism* or *geometric isomerism* commonly are used to describe **configurational isomerism** in compounds with double bonds and rings. When referring to the *configuration* of a particular isomer, we mean to specify its geometry. For instance, the isomer of 1,2-dichloroethene shown below has the *trans* configuration; the isomer of 1,3-dichlorocyclobutane has the *cis* configuration:



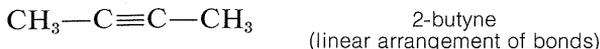
(These structures are drawn in perspective; the ring carbons are shown to be in a horizontal plane and the attached atoms are above or below this plane. If not all of the attached hydrogens are explicitly shown, as in the structure at right, their presence is understood.)

Cis-trans isomerism is encountered very frequently. By one convention, *the configuration of a complex alkene is taken to correspond to the configuration of the longest continuous chain as it passes through the double bond*. Thus the following compound is *trans*-4-ethyl-3-methyl-3-heptene, despite the fact that two identical groups are *cis* with respect to each other, because

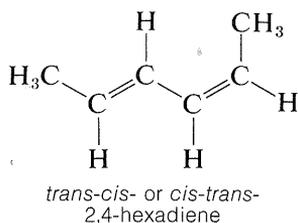
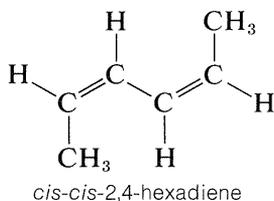
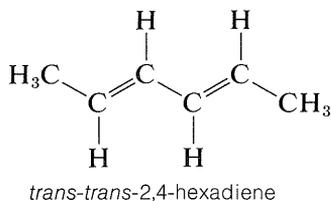
the longest continuous chain is *trans* as it passes through the double bond:



Notice that *cis-trans* isomerism is not possible at a carbon-carbon triple bond, as for 2-butyne, because the bonding arrangement at the triply bonded carbons is linear:



Many compounds have more than one double bond and each may have the potential for the *cis* or *trans* arrangement. For example, 2,4-hexadiene has *three* different configurations, which are designated as *trans-trans*, *cis-cis*, and *trans-cis*. Because the two ends of this molecule are identically substituted, the *trans-cis* becomes identical with *cis-trans*:

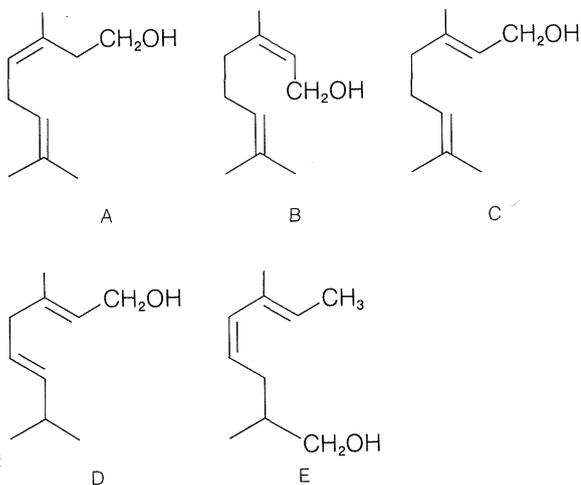


**Exercise 5-1** Draw structures showing the configuration of the following compounds. You may wish to review the nomenclature of alkenes, given in Section 3-3.

- |  |   |
|--|---|
| <p>a. <i>trans</i>-3-methyl-3-hexene</p> <p>b. 2-chloro-<i>cis</i>-2,<i>trans</i>-4-heptadiene</p> | <p>c. (<i>cis</i>-1-propenyl)cyclobutane</p> <p>d. <i>trans</i>-1,2-di-(<i>cis</i>-1-propenyl)cyclobutane</p> |
|--|---|

**Exercise 5-2** Geraniol is a naturally occurring compound found in certain grasses and is used in perfumes to simulate the odor of roses. The IUPAC name for this compound is 3,7-dimethyl-*trans*-2,6-octadien-1-ol (where “-1-ol” signifies that there is an OH group on the lowest-numbered carbon of the chain). Select the correct structure

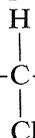
from among the following:



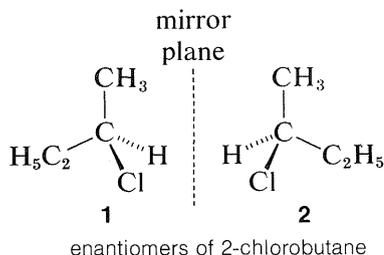
## 5-1B Chirality

The most important type of stereoisomerism is that which arises when molecules possess two structures that are not identical and also are mirror images of one another. This is not a difficult or unfamiliar concept. Many things around us, such as our hands, and pairs of shoes, are not identical and also are mirror images of one another. In the same way, nonidentical molecules exist in which the only distinction between them is that one is the mirror image of the other. A common statement is that such isomers are mirror images of one another, but these images are *not* "superimposable." A simple example of this type of

stereoisomerism is 2-chlorobutane,  $\text{CH}_3\text{—CH}_2\text{—C—CH}_3$ , which can exist



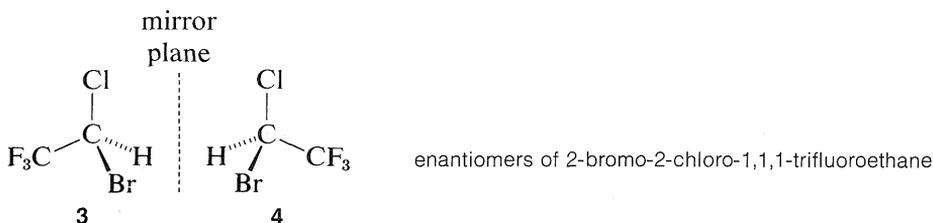
in two spatial configurations, **1** and **2**, that correspond to reflections of each other. These isomers are specifically called **enantiomers**.



To be convinced that there really are two nonidentical forms of this molecule, you should construct molecular models of both configurations and try to superimpose them, as in Figure 5-3. If you put  $\text{CH}_3$  and  $\text{CH}_3$  together, and  $\text{C}_2\text{H}_5$  and  $\text{C}_2\text{H}_5$  together, you find that Cl and Cl are on opposite sides, and H and H are on opposite sides. No matter how you turn the models around, they cannot be superimposed unless you break bonds at the number 2 carbon and interchange the positions of any two atoms or groups.

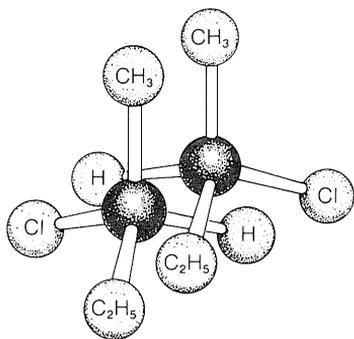
Compounds that lack **reflection symmetry**—meaning that they are *not* identical with their mirror images—are said to be **chiral** (pronounced “ki-rall”, rhymes with spiral). This term is derived from the Greek word  $\chi\epsilon\iota\rho$  = hand; and “handedness” or **chirality** is a property of **dissymmetric** molecules such that *two* configurational isomers are possible that are nonidentical mirror images. Compounds that possess reflection symmetry—meaning that they are identical with their mirror images—are said to be **achiral**. Enantiomers are not possible for achiral compounds. An **enantiomeric pair** is a pair of substances whose molecules are *nonidentical* mirror images.

The pressing question at this point is how can we tell whether a substance will be chiral or achiral. The most common origin of chirality in molecules, and the one originally recognized by van't Hoff and Le Bel, is the presence of one or more atoms, usually carbon atoms, each of which forms noncoplanar bonds to *four different atoms or groups*. This is the case for 2-chlorobutane, because the second tetrahedral carbon along the chain is bonded to four different groups: hydrogen, chlorine, methyl, and ethyl. Therefore there is a pair of enantiomers, **1** and **2**. Another example is 2-bromo-2-chloro-1,1,1-trifluoroethane, which is a widely used inhalation anaesthetic. The four different groups in this case are hydrogen, chlorine, bromine, and trifluoromethyl; the pair of enantiomers is shown in Structures **3** and **4**:



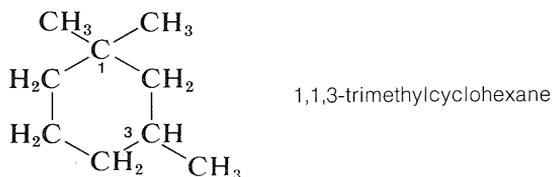
The atom that carries the four different substituents in **1** and **2**, or **3** and **4**, is called a **chiral atom** or **chiral center**. The latter is the more general term because, as we shall see later (Section 13-5A), dissymmetry in molecules need not be centered at an atom.<sup>1</sup>

<sup>1</sup>In the older literature, chiral centers often are called **asymmetric centers** and you may be confused by the difference between *asymmetric* and *dissymmetric*. Both asymmetric and dissymmetric molecules (or objects) are chiral. An asymmetric object has no symmetry at all and looks different from all angles of view. Formulas **3** and **4** represent asymmetric molecules. A dissymmetric molecule is chiral, but looks the same from more than one angle of view. A helical spring is dissymmetric—it looks the same from each end. We will encounter dissymmetric molecules later.

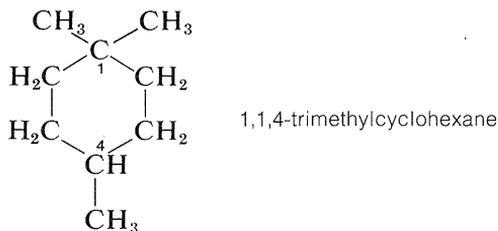


**Figure 5-3** Use of ball-and-stick models to show nonidentity of the enantiomers of 2-chlorobutane, **1** and **2**

In evaluating a chemical structure for chirality, you should look for carbons carrying four *different* attached groups. There may be more than one chiral carbon, and you should be alert to the fact that structural differences in the attached groups do not necessarily show up at the first, or even the second, position along a chain. As an example, consider the chirality of 1,1,3-trimethylcyclohexane,



Carbons C2, C4, C5, and C6 are clearly achiral because each is connected to two identical groups, which for these atoms are hydrogens. The same is true for C1 because it is connected to two  $\text{CH}_3$  groups. You might conclude that C3 also is an achiral position because it is connected to two  $\text{CH}_2$  groups. But this would be wrong. If you look farther, you will see that the groups attached to C3 actually are different and are  $\text{H}$ ,  $\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ , and  $-\text{CH}_2\text{C}(\text{CH}_3)_2$ . Therefore 1,1,3-trimethylcyclohexane has a chiral center at C3. In contrast, the 1,1,4-isomer has no chiral centers because the groups attached to the ring at C4 are identical:



Several other terms that we shall use frequently in addition to chirality are **racemic mixture**, **resolution**, and **racemization**. A mixture of *equal* amounts

of both enantiomers is a **racemic mixture**; separation of a racemic mixture into its component enantiomers is a **resolution**, and the conversion of either enantiomer into equal parts of both is called **racemization**.

### 5-1C Optical Activity

Until recently, the phenomenon of chirality has been better known as **optical isomerism**, and configurational isomers that are enantiomers were referred to as **optical antipodes**. The reasons for this are mainly historical. It was discovered early in the nineteenth century that many compounds, whether solid, liquid, or gas, have the property of rotating the plane of polarization of polarized light and can be said to be "**optically active**." A satisfactory explanation of the origin of optical activity came much later and developed in its modern form from the classic researches of Louis Pasteur, and from the concept of the three-dimensional carbon atom expressed independently by J. H. van't Hoff and J. A. Le Bel.<sup>2</sup>

Pasteur's contribution to stereochemistry came as a result of his studies of the shapes of crystals of tartaric acid,  $\text{HO}_2\text{C}-\text{CHOH}-\text{CHOH}-\text{CO}_2\text{H}$ , and its salts. Tartaric acid, a by-product of wine production, was known to be optically active, and Pasteur showed that it, and nineteen different salts of it, all formed crystals that were *not* identical with their mirror images. A different substance known as "racemic acid," for which we can write the same condensed formula,  $\text{HO}_2\text{C}-\text{CHOH}-\text{CHOH}-\text{CO}_2\text{H}$ , was known to be optically *inactive*, and Pasteur expected that when he crystallized this acid or its salts he would obtain crystals that would be identical with their mirror images. However, crystallization of the sodium ammonium salt of racemic acid from water at temperatures below  $28^\circ$  gave crystals of *two* different shapes and these shapes were mirror images of one another. Pasteur carefully picked apart the two kinds of crystals and showed that one of them was identical with the corresponding salt of tartaric acid. The other kind of crystal turned out to be the salt of a new form of tartaric acid that had the same physical properties as the already known tartaric acid, except that it rotated the plane of polarization of polarized light in the opposite direction. This separation of racemic acid into two optically active forms now is called a "resolution of racemic acid."

On the basis of his discoveries, Pasteur postulated that "optical isomerism" had to be related to the molecular dissymmetry of substances such that nonidentical mirror-image forms could exist. However, it remained for van't Hoff and Le Bel to provide, almost simultaneously, a satisfactory explanation at the molecular level. In his first published work on tetrahedral carbon van't Hoff said ". . . it appears more and more that the present con-

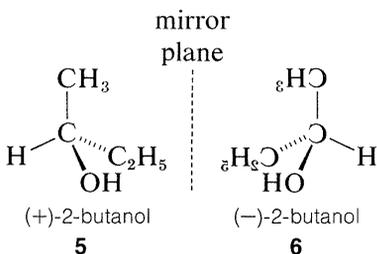
<sup>2</sup>The tetrahedral carbon was first proposed by E. Paterno in 1869 (see Section 1-1E), but he apparently did not recognize its implications for chirality. These implications were recognized first by van't Hoff and Le Bel, with van't Hoff proceeding on the basis of bonds to carbon being directed to the corners of a regular tetrahedron. Le Bel was opposed to such a rigid formulation of the bonds to carbon.

stitutional formulae are incapable of explaining certain cases of isomerism; the reason for this is perhaps the fact that we need a more definite statement about the actual positions of the atoms.”<sup>3</sup> He goes on to discuss the consequences of the tetrahedral arrangements of atoms about carbon, explicitly in connection with optical isomerism and geometric, or *cis-trans*, isomerism.

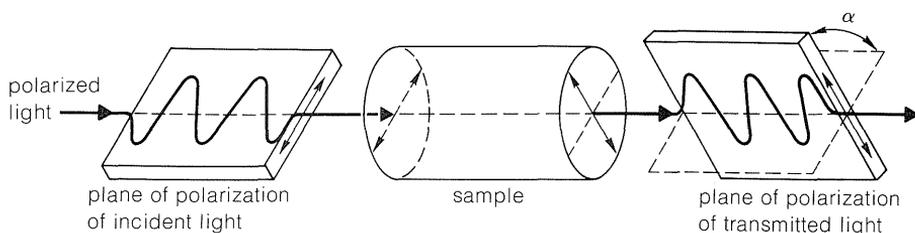
It is not easy for the chemist of today to appreciate fully the contributions of these early chemists because we have long accepted the tetrahedral carbon as an experimentally established fact. At the time the concept was enunciated, however, even the existence of atoms and molecules was questioned openly by many scientists, and to ascribe “shapes” to what in the first place seemed like metaphysical conceptions was too much for many to accept.

## 5-1D Properties of Enantiomers

Optical activity is an experimentally useful property and usually is measured as the angle of rotation ( $\alpha$ ) of the plane of polarization of polarized light passing through solutions of the substances under investigation (see Figure 5-4). Where measurable optical activity is present, it is found that one enantiomer rotates the plane of polarization in one direction, whereas the other causes the plane to rotate *equally* but in the opposite direction. With reference to the plane of incident light, the enantiomer that rotates the plane to the right is called *dextrorotatory* and is symbolized by either *d* or (+); the enantiomer that rotates the plane to the left is *levorotatory*, symbolized by *l* or (–). A racemic mixture then can be designated as *dl* or ( $\pm$ ), and will have no net optical rotation. It is very important to know that *d*, *l*, (+), or (–) do not designate configuration. Thus, although (+)-2-butanol actually has configuration **5** and (–)-2-butanol has configuration **6**, there is no simple way to predict that a particular sign of rotation will be associated with a particular configuration. Methods used in assigning the true configurations to enantiomers will be discussed later.



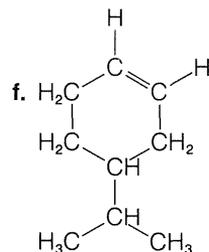
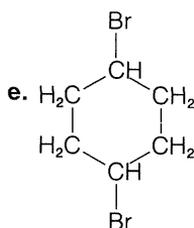
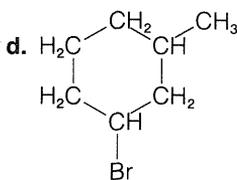
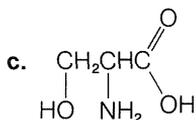
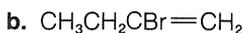
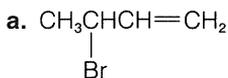
<sup>3</sup>An interesting account and references to van't Hoff's early work can be found in "The Reception of J. H. van't Hoff's Theory of the Asymmetric Carbon" by H. A. M. Snelders, *J. Chem. Educ.* **51**, 2 (1974). A century has passed since van't Hoff first published his theory, which he did before he obtained his doctoral degree from the University of Utrecht. van't Hoff was the first recipient of the Nobel Prize in chemistry (1901) for his later work in thermodynamics and chemical kinetics.



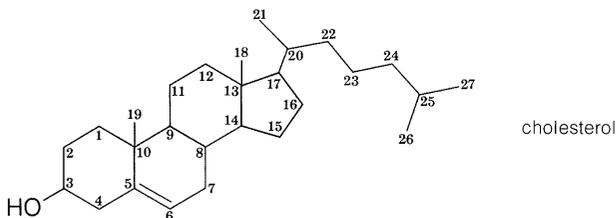
**Figure 5-4** Schematic representation of the rotation of the plane of polarization of polarized light by an optically active compound. Plane-polarized light is different from ordinary light in that its electrical component vibrates in a plane rather than in all directions. The angle  $\alpha$  is the angle between the plane of polarization of light entering the sample and the plane of polarization of the emerging light.

A very important point to keep in mind about any pair of enantiomers is that they will have identical chemical and physical properties, except for the signs of their optical rotations, with one important proviso: All of the properties to be compared must be determined using achiral reagents in a solvent made up of achiral molecules or, in short, in an *achiral environment*. Thus the melting and boiling points (but not the optical rotations) of **5** and **6** will be identical in an achiral environment. How a chiral environment or chiral reagents influence the properties of substances such as **5** and **6** will be considered in Chapter 19.

**Exercise 5-3** Identify the chiral carbon atoms by an asterisk (\*) in each of the following structures. If no chiral carbons are present, write *achiral*.



**Exercise 5-4** How many chiral centers are evident in the structure of cholesterol? Identify them by the number of the carbon atom.



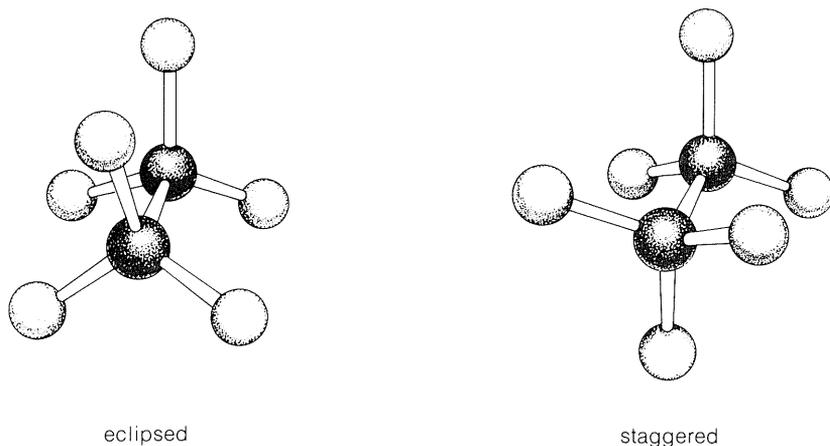
**Exercise 5-5** The work of the German chemist Wislicenus on hydroxypropanoic acids was influential in the development of van't Hoff's ideas on stereoisomerism. By 1869, Wislicenus had established that there are three isomeric hydroxypropanoic acids, let us call them A, B, and C, of partial structure  $C_2H_4(OH)(CO_2H)$ . Isomer A was isolated from sour milk and Isomer B from a meat extract. Both A and B had the same physical properties, except for optical rotation, wherein A was levorotatory and B was dextrorotatory. Isomer C was not optically active and had considerably different physical and chemical properties from A or B. Work out structures A, B, and C in as much detail as you can from the information given.

**Exercise 5-6** Examine the structures of  $\beta$ -carotene and vitamin A shown on p. 33 and p. 50 and determine the configuration at each of the double bonds in the chain attached to the ring(s). Are these substances chiral or achiral?

## 5-2 CONFORMATIONAL ISOMERS

When using ball-and-stick models, if one allows the sticks to rotate in the holes, it will be found that for ethane,  $CH_3-CH_3$ , an infinite number of different atomic orientations are possible, depending on the angular relationship (the so-called *torsional angle*) between the hydrogens on each carbon. Two extreme orientations or **conformations** are shown in Figure 5-5. In end-on views of the models, the *eclipsed* conformation is seen to have the hydrogens on the forward carbon directly in front of those on the back carbon. The *staggered* conformation has each of the hydrogens on the forward carbon set between each of the hydrogens on the back carbon. It has not been possible to obtain separate samples of ethane that correspond to these or intermediate orientations because actual ethane molecules appear to have essentially "free rotation" about the single bond joining the carbons. Free, or at least rapid, rotation is possible around all C-C *single* bonds, except when the carbons are part of a ring as in cyclopropane or cyclohexane.

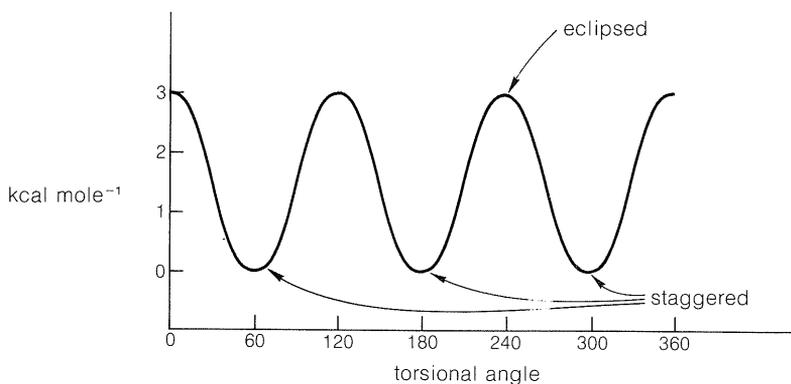
For ethane and its derivatives, the staggered conformations are more stable than the eclipsed conformations. The reason for this in ethane is not



**Figure 5-5** Two rotational conformations of ethane

wholly clear, but doubtless depends on the fact that, in the staggered conformation, the C–H bonding electrons are as far away from one another as possible and give the least interelectronic repulsion. With groups larger than hydrogen atoms substituted on ethane carbons, space-filling models usually show less interference (**steric hindrance**) for staggered conformations than for eclipsed conformations.

The energy difference between eclipsed and staggered ethane is approximately  $3 \text{ kcal mole}^{-1}$ .<sup>4</sup> This is shown in Figure 5-6 as the height of the peaks (eclipsed forms) separating the valleys (staggered forms) on a curve showing the potential energy of ethane as the methyl groups rotate with respect to each

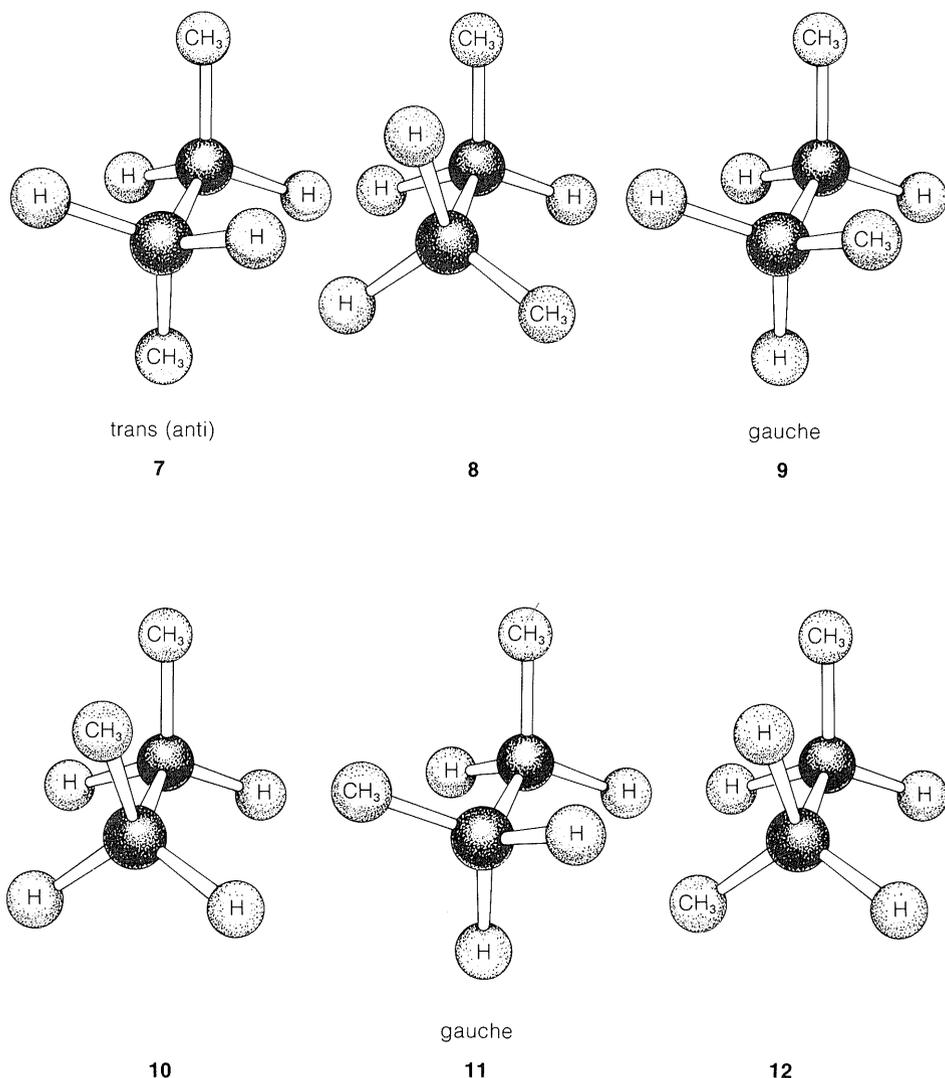


**Figure 5-6** Potential-energy curve for rotation about the C–C bond in ethane

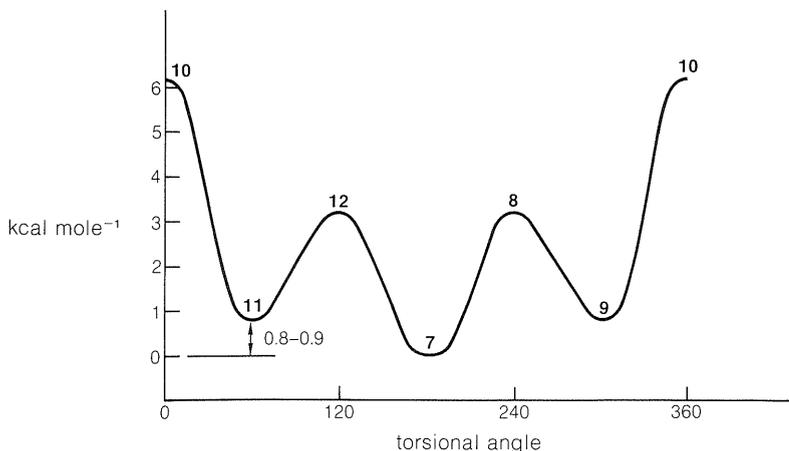
<sup>4</sup>This is by no means a trivial amount of energy – the difference in energy between the staggered and eclipsed forms of 1 mole (30 g) of ethane being enough to heat 30 g of water from  $0^\circ$  to  $100^\circ$ .

other through  $360^\circ$ . Rotation then is not strictly “free” because there is a  $3\text{-kcal mole}^{-1}$  energy barrier to overcome on eclipsing the hydrogens. Even so, the barrier is low enough that rotation is very rapid at room temperature, occurring on the order of  $10^{10}$  times per second.

In butane,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$ , a  $360^\circ$  rotation about the central C–C bond allows the molecule to pass through three different eclipsed arrangements (**8**, **10**, **12**), and three different staggered arrangements (**7**, **9**, **11**), as shown in Figure 5-7. Experiment shows that butane favors the staggered form



**Figure 5-7** Six rotational conformations about the 2,3 C–C bond of butane. The forward groups are shown here as rotating counterclockwise with respect to the rear groups.



**Figure 5-8** Conformational energies and rotational barriers in butane, the difference in energy between the anti and gauche forms is 0.8–0.9 kcal mole<sup>-1</sup>. The energies are relative to conformation **7** as zero.

**7** in which the methyl groups are farthest apart. This form is called the *anti* (or *trans*) conformation (sometimes **conformer**), and 63% of the molecules of butane exist in this form at room temperature. The other two staggered forms **9** and **11** are called *gauche* (*syn* or *skew*) conformations and have a torsional angle of 60° between the two methyl groups. Forms **9** and **11** actually are non-identical mirror images, but bond rotation is so rapid that the separate enantiomeric conformations cannot be isolated. The populations of the two gauche forms are equal at room temperature (18.5% of each) so any optical rotation caused by one form is exactly canceled by an opposite rotation caused by the other.

The populations of the eclipsed forms of butane, like the eclipsed forms of ethane, are small and represent energy maxima for the molecule as rotation occurs about the central C–C bond. The energy differences between the butane conformations are represented diagrammatically in Figure 5-8. The valleys correspond to staggered forms and the energy difference between the anti and gauche forms is 0.8–0.9 kcal mole<sup>-1</sup>.

Pioneering work in the field of conformational analysis was contributed by O. Hassel (Norway) and D. R. H. Barton (Britain), for which they shared the Nobel Prize in chemistry in 1969. Hassel's work involved the physical determination of preferred conformations of small molecules, whereas Barton was the first to show the general importance of conformation to chemical reactivity. Study of conformations and conformational equilibria has direct application to explaining the extraordinary specificity exhibited by com-

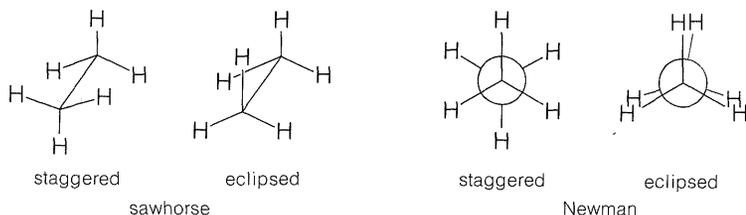
pounds of biological importance. The compounds of living systems are tailor-made to perform highly specific or even unique functions by virtue of their particular configurations and conformations.

## 5-3 REPRESENTATION OF ORGANIC STRUCTURE

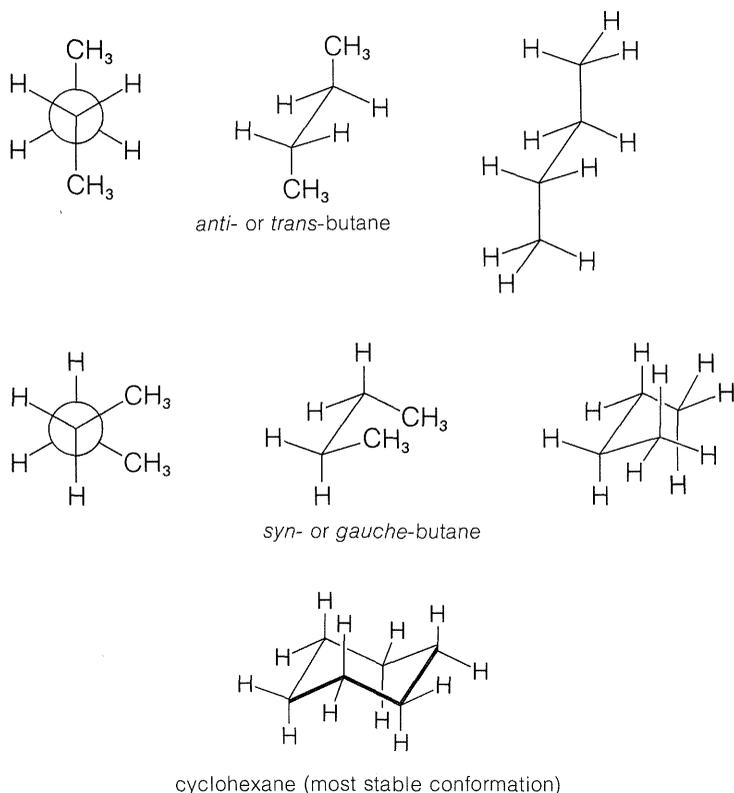
Many problems in organic chemistry require consideration of structures in three dimensions, and it is very helpful to use molecular models to visualize the relative positions of the atoms in space. Unfortunately, we are forced to communicate three-dimensional concepts by means of drawings in two dimensions, and not all of us are equally gifted in making or visualizing such drawings. Obviously, communication by means of drawings, such as those in Figures 5-5 and 5-7, would be impractically difficult and time consuming, thus some form of abbreviation is necessary.

### 5-3A Conformational Drawings

Two styles of abbreviating the eclipsed and staggered conformations of ethane are shown in Figure 5-9; in each, the junction of lines representing bonds is assumed to be a carbon atom. Using the "sawhorse" convention, we always consider that we are viewing the molecule slightly from above and from the right, and it is understood that the central C-C bond is perpendicular to the plane of the paper. With the "Newman" convention, we view the molecule directly down the C-C bond axis so the carbon in front hides the carbon behind. The circle is only a visual aid to help distinguish the bonds of the back carbon from those of the front carbon. The rear atoms in the eclipsed conformation are drawn slightly offset from a truly eclipsed view so the bonds to them can be seen.



**Figure 5-9** Conventions for showing the staggered and eclipsed conformations of ethane

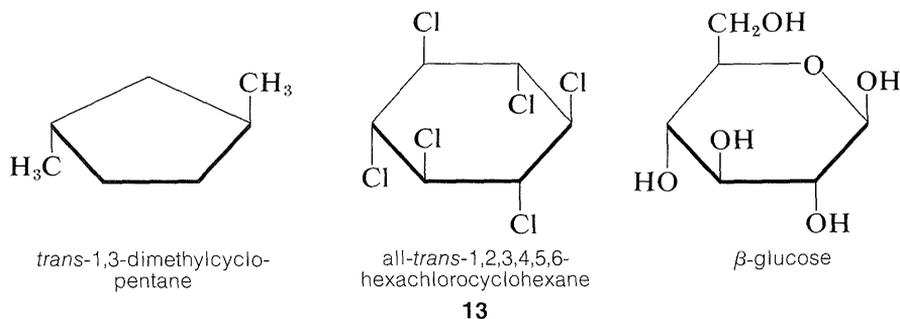


**Figure 5-10** Sawhorse and Newman conventions for showing the staggered conformations of butane. Only one gauche form is shown. Cyclohexane is shown to emphasize the resemblance of its stable conformation to the gauche conformation of butane.

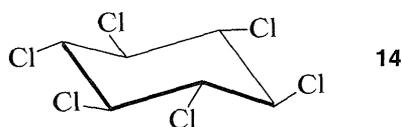
The staggered conformations of butane are shown in Figure 5-10 in both the sawhorse and Newman conventions. There is little to choose between the two conventions for simple ethane derivatives, but the sawhorse convention is strongly favored for representing more complex molecules. It is particularly useful in representing the conformations of ring compounds such as cyclohexane. The resemblance between the gauche forms of butane and the most stable conformation of cyclohexane is strikingly apparent in the sawhorse representations of both, as shown in Figure 5-10. Notice that the ring carbons of cyclohexane do not lie in one plane and that all the bond angles are tetrahedral. The conformations of this interesting and important molecule are discussed in detail in Chapter 12.

Despite the usefulness of the sawhorse-type drawing, cyclic molecules often are drawn with planar rings and distorted bond angles even though the

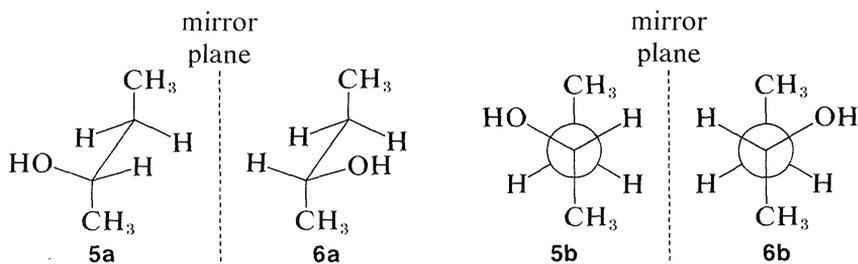
rings actually may not be planar. The reason for this is partly that planar rings are easier to draw and partly to emphasize the configuration of attached groups, irrespective of the conformation. Typical examples follow:



Generally we shall avoid such drawings and suggest that it is much better to learn to draw molecules in as nearly correct perspective as possible. Once the sawhorse representation of cyclohexane is mastered, it is almost as easy to draw **14** as **13**, and **14** is much more informative about the shape of the molecule:



We have indicated how the enantiomers of 2-butanol differ by drawing their structures **5** and **6** (Section 5-1D) in perspective to show the tetrahedral configuration of substituents at the chiral carbon. This configuration also can be represented by the sawhorse or Newman formulas using any one of the several possible staggered conformations such as **5a** and **6a** or **5b** and **6b**:



These drawings are clear but can be cumbersome, particularly for more complex molecules, and we shortly shall describe other means of representing the configurations of chiral molecules.

---

**Exercise 5-7** Draw the staggered conformations of each of the following compounds using the indicated convention:

- 2,3-dimethylbutane (sawhorse)
- 1,2-dibromo-1,1,2,2-tetrafluoroethane (Newman)
- the *d,l* isomers of 1-chloro-1-fluoroethane (Newman)

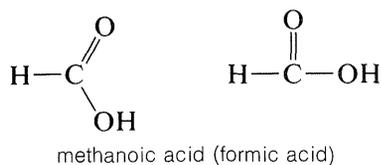
**Exercise 5-8** Draw the conformation of 2,2,5,5-tetramethylhexane that you expect to be of lowest energy.

---

### 5-3B Planar Structures

Planar molecules such as benzene, ethene, and methanal are best drawn in the plane of the paper with bond angles of about  $120^\circ$ . When it is desired to draw them as viewed on edge (out of plane) care must be taken to provide proper perspective. The forward bonds can be drawn with slightly heavier lines; a tapered bond indicates direction, the wide end pointing toward the viewer and the narrow end away from the viewer (Figure 5-11). Barred lines are used here to indicate a rear or receding bond (many writers use dashed lines, but these may be confused with other uses of dashed lines, as for partial bonds).

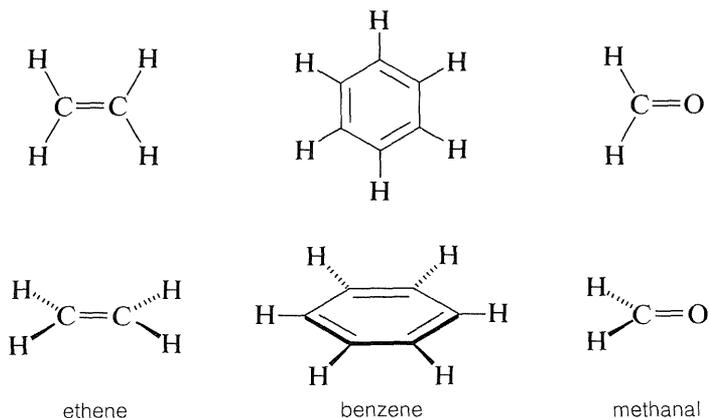
However, you will find other representations of planar carbons with rather grossly distorted bond angles. For example, methanoic acid is planar with nearly  $120^\circ$  bond angles, but often is drawn with  $\text{H}-\text{C}-\text{O}$  angles of  $90^\circ$  and  $180^\circ$ :



The distorted structures commonly are used to save space and, regrettably, we have to use them very frequently for this reason.

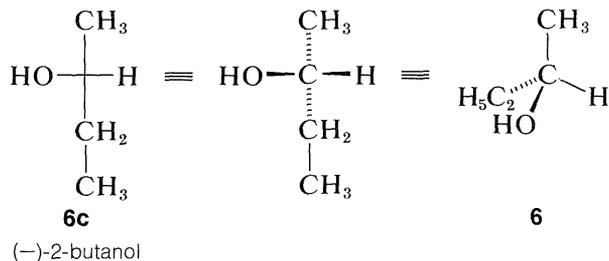
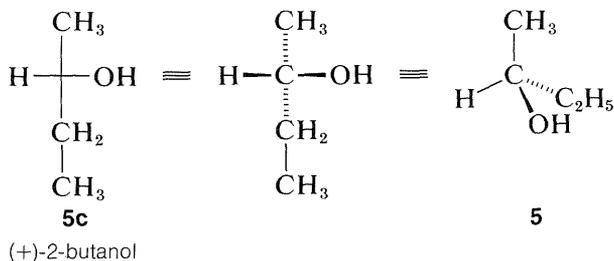
### 5-3C Projection Formulas

The sawhorse or Newman representations of 2-butanol, **5a** and **5b** and **6a** and **6b**, are excellent for showing the arrangements of the atoms in conformations, but are needlessly complex for representing the stereochemical *configuration*. **Fischer projection formulas** are widely used to show configurations and are quite straightforward, once one gets the idea of what they represent.



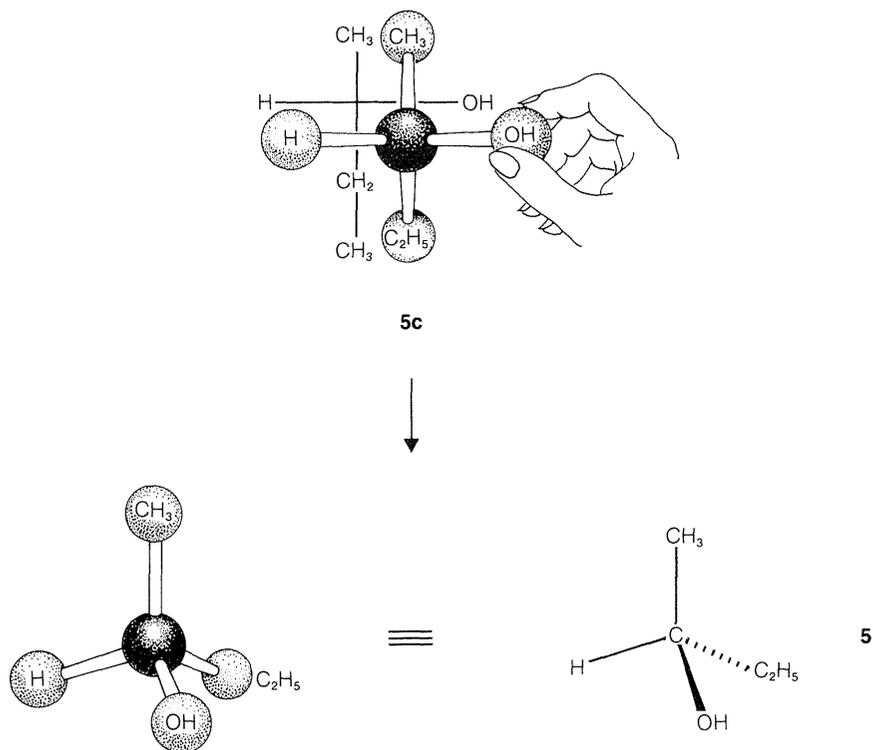
**Figure 5-11** Front and side views of planar molecules showing some conventions used to indicate perspective

The projection formulas of 2-butanol are **5c** and **6c**:



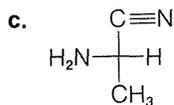
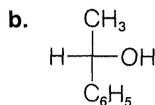
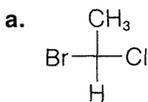
As shown by the formulas next to **5c** and **6c**, we are to understand that the horizontal bonds to the chiral center extend *out of the plane of the paper, toward you*, while the vertical bonds extend *behind the plane of the paper, away from you*. The overall translation of the projection formulas into the mirror-image, perspective drawings **5** and **6** may give you more trouble. The

easiest way to facilitate this translation is with a ball-and-stick model, as shown in Figure 5-12.

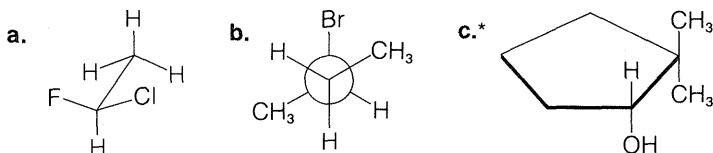


**Figure 5-12** Procedure for relating a projection formula to a configurational drawing with the aid of a ball-and-stick model. Assemble the ball-and-stick model over the projection formula (here **5c**) so that the groups are arranged by the convention of the formula (horizontal bonds out, vertical bonds back), then turn the model so the appropriate groups, here  $\text{CH}_3$  and  $\text{H}$ , are parallel to the plane of the paper and make the perspective drawing agree with the model. The reverse procedure translates the perspective drawing into the projection formula.

**Exercise 5-9** Draw a staggered conformation in both the sawhorse and Newman representations that corresponds to the configurations shown in the projection formulas a–c.

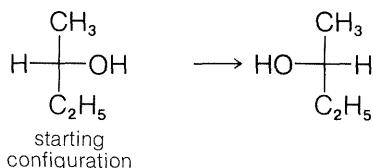


**Exercise 5-10** Draw projection formulas that correspond to the specific configurations shown in the following structures:

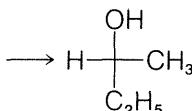


**Exercise 5-11** This exercise can clarify for you the constraints on manipulating projection formulas. You will be helped by checking the configuration with models, as in Figure 5-12. The idea is to determine what effect there is, if any, on the configuration represented by the formula by making various changes in the projection. Your answer for each part should be that the operation changes, or does not change, the configuration.

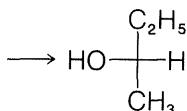
a. interchange of substituents across the horizontal bond:



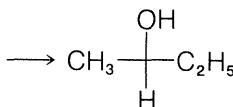
b. interchange of other substituents:



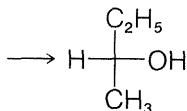
c. 180° rotation in plane of paper:



d. 90° rotation in plane of paper:



e. end-over-end flip *outside* of plane of paper:

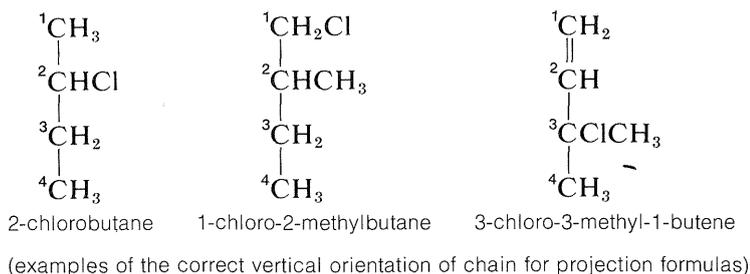


## 5-4 THE D,L CONVENTION FOR DESIGNATING STEREOCHEMICAL CONFIGURATIONS

We pointed out in Chapter 3 the importance of using systematic names for compounds such that the name uniquely describes the structure. It is equally important to be able to unambiguously describe the configuration of a compound.

The convention that is used to designate the configurations of chiral carbons of naturally occurring compounds is called the D,L system. To use it, we view the molecule of interest according to the following rules:

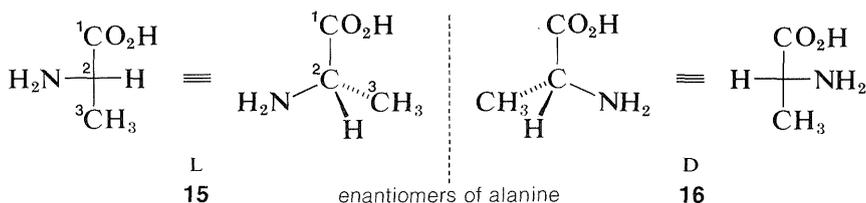
1. The main carbon chain is oriented vertically with the *lowest* numbered carbon at the *top*. The numbering used for this purpose must follow the IUPAC rules:



2. Next, the structure must be arranged at the particular chiral carbon whose configuration is to be assigned so the horizontal bonds to that carbon extend toward you and the vertical bonds extend away from you. This arrangement will be seen to be precisely the same as the convention of projection formulas such as **5c** and **6c** (Section 5-3C).

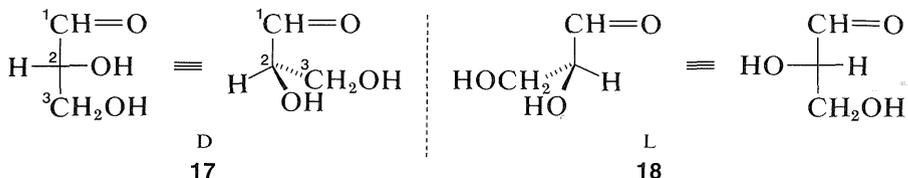
3. Now the relative positions of the substituents on the horizontal bonds at the chiral centers are examined. If the main substituent is on the *left* of the main chain, the L configuration is assigned; if this substituent is on the *right*, the D configuration is assigned.

For example, the two configurations of the amino acid, alanine, would be represented in perspective or projection as **15** and **16**. The carboxyl carbon is C1 and is placed at the top. The substituents at the chiral carbon connected to the horizontal bonds are amino ( $-\text{NH}_2$ ) and hydrogen. The amino substituent is taken to be the main substituent; when this is on the *left* the acid has the L configuration, and when it is on the *right*, the D configuration. All of the amino acids that occur in natural proteins have been shown to have the L configuration.



Glyceraldehyde,  $\text{CH}_2\text{OHCHOHCHO}$ , which has one chiral carbon bonded to an aldehyde function, hydrogen, hydroxyl, and hydroxymethyl ( $\text{CH}_2\text{OH}$ ), is of special interest as the simplest chiral prototype of sugars

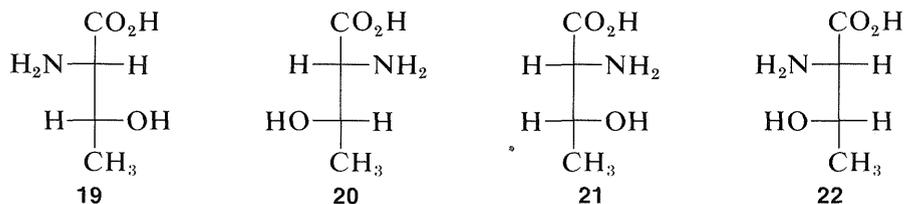
(carbohydrates). Perspective views and Fischer projections of the D and L forms correspond to **17** and **18**, respectively, where the carbon of the aldehyde function ( $\text{—CH=O}$ ) is C1:



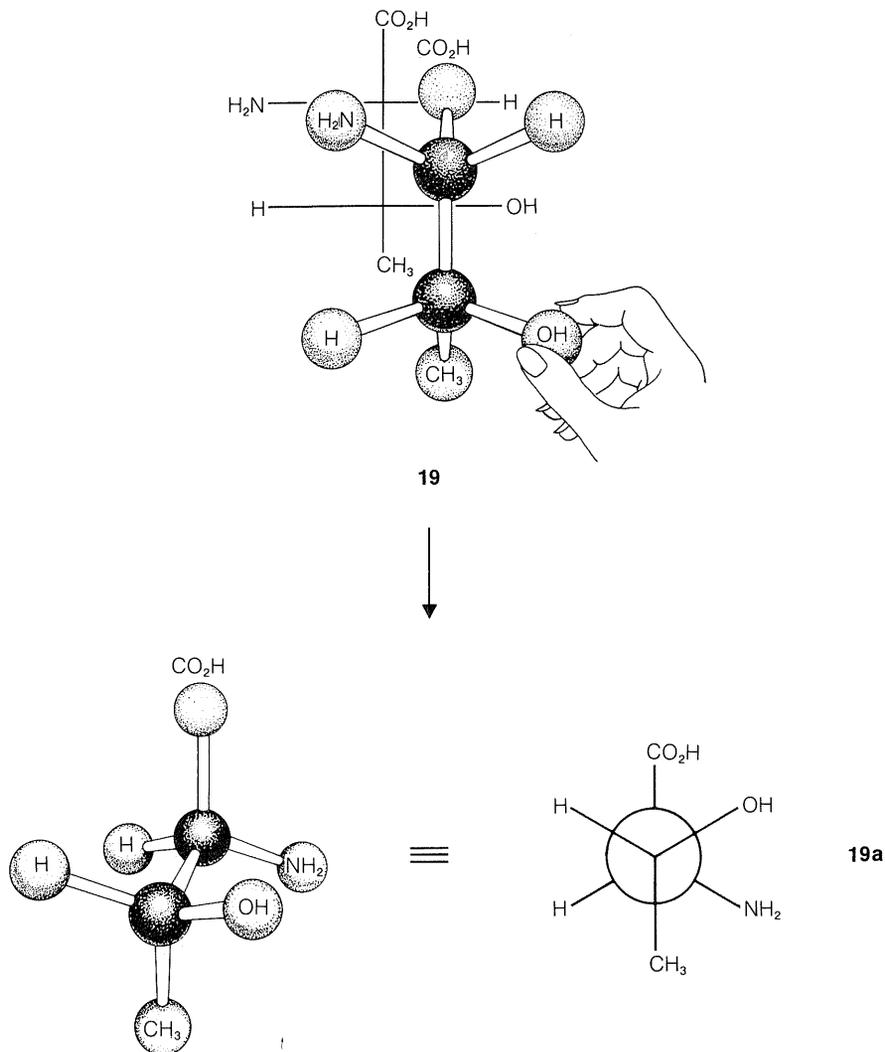
The D,L system of designating configuration only can be applied when there *is* a main chain, and when we can make an unambiguous choice of the main substituent groups. Try, for instance, to assign D and L configurations to enantiomers of bromochlorofluoromethane. An excellent set of rules has been worked out for such cases that leads to unambiguous configurational assignments by what is called the *R,S* convention. We discuss the *R,S* system in detail in Chapter 19 and, if you wish, you can turn to it now. However, for the next several chapters, assigning configurations is much less important to us than knowing what kinds of stereoisomers are possible.

## 5-5 MOLECULES WITH MORE THAN ONE CHIRAL CENTER. DIASTEREOMERS

We have seen examples of molecules with one chiral center that exist in two mirror-image configurations, which we call enantiomers. What happens when there is more than one chiral center? How many stereoisomers should we expect? Consider the stereoisomers of the important amino acid, threonine, (2-amino-3-hydroxybutanoic acid). For this substance, if we write all of the possible configurations of its *two* chiral carbons, we have *four* different projection formulas, **19–22**, corresponding to four different stereoisomers:



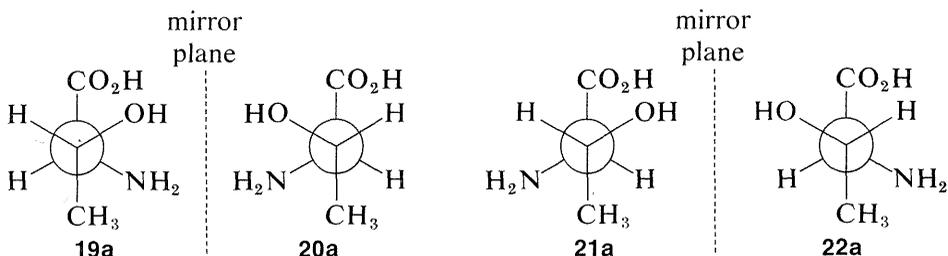
You should build a ball-and-stick model of **19** by the procedure shown in Figure 5-13 (also see Figure 5-12) and by putting the model over **20–22** verify that none of these projections have the configurations of *both* chiral carbons the same as your model of **19**.



**Figure 5-13** Translation of a projection formula to a ball-and-stick model and then to a Newman formula. The first step is to assemble the model over the projection formula in the same way as shown in Figure 5-12, except that configurations at each of two atoms are involved. Next, the model is turned and rotated around the center C-C bond to put the methyl and carboxyl groups *anti* to one another. The Newman formula then is drawn to correspond to the ball-and-stick model.

Because each chiral center added to a chain doubles the number of possible configurations, we expect eight different stereoisomers with three chiral carbons, sixteen with four, and so on. The simple rule then is  $2^n$  possible different stereoisomers for  $n$  chiral centers. As we shall see later, this rule has to be modified in some special cases.

What is the relationship between stereoisomers **19–22**? This will be clearer if we translate each of the projection formulas into a three-dimensional representation, as shown in Figure 5-13. You will be helped greatly if you work through the sequence yourself with a ball-and-stick model. Drawn as Newman projections, **19–22** come out as shown in **19a–22a**:



It should be clear (and, if it isn't, ball-and-stick models will be invaluable) that **19a** and **20a** are mirror images of one another and that **21a** and **22a** similarly are mirror images.<sup>5</sup> What about other combinations such as **19a** and **21a** or **20a** and **22a**? If you look at the pairs closely you will find that they are not mirror images and are not identical. Such substances, related to each other in this way and which can be converted one into the other only by changing the configurations at one or more chiral centers, are called **diastereomers**.

The difference between enantiomers and diastereomers is more than just geometry. Diastereomers have substantially different chemical and physical properties, whereas enantiomers have identical physical properties (apart from their optical rotations). This is illustrated in Table 5-1 for the threonine stereoisomers. The reason for the difference in physical properties between diastereomers can be seen very simply for a substance with two chiral centers by noting that a right shoe on a right foot (D,D) is a mirror image, or has the same physical properties, as a left shoe on a left foot (L,L), but is not a mirror image, nor does it have the same physical properties, as a left shoe on a right foot (L,D), or a right shoe on a left foot (D,L).

### 5-5A Meso Compounds (Achiral Diastereomers)

All of the threonine stereoisomers **19–22** are chiral substances; that is, they are not identical with their mirror images. However, it is important to recognize that not all diastereomers are chiral. To illustrate this point, we return to the tartaric acids mentioned previously in connection with Pasteur's discoveries (Section 5-1C).

<sup>5</sup>The same information can be obtained from projection formulas. You can see that projections **19** and **20** are mirror images and that **20**, **21**, or **22** can not be superimposed on **19**. However, in some situations confusion can result in making such comparisons and it is important to be able to translate the projection formulas into ball-and-stick models or perspective drawings.

**Table 5-1**

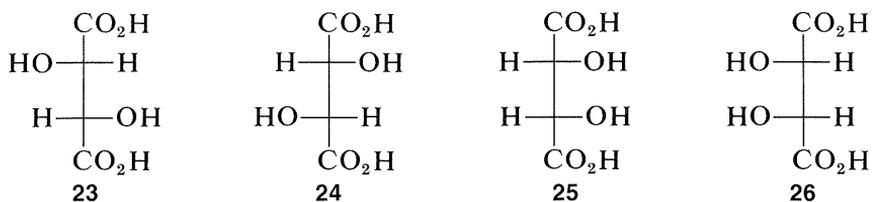
Reported Physical Properties of the Stereoisomers of Threonine,  
2-Amino-3-hydroxybutanoic Acid

Common name:	L-threonine <sup>a</sup>	D-threonine	L-allothreonine	D-allothreonine
Mp, °C:	251–253	251–252	268–272	269–272
Specific rotation, [α] <sub>D</sub> <sup>20</sup> in H <sub>2</sub> O <sup>b</sup> :	−28.5°	+28.5°	+9.6°	−9.1°

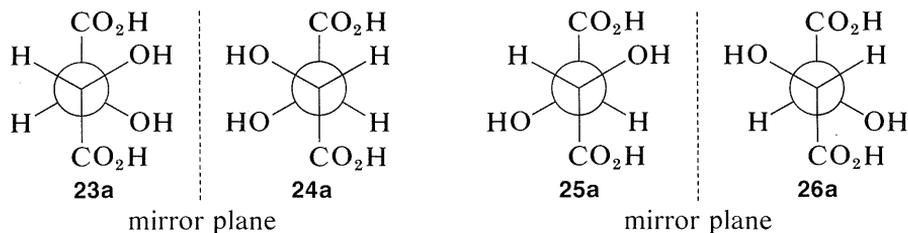
<sup>a</sup>This is the naturally occurring stereoisomer and is an important constituent of many proteins.

<sup>b</sup>The specific rotation  $[\alpha]_D^{20}$  is obtained from a measured rotation  $\alpha$  of the plane of polarization of polarized light (see Figure 5-4) by the equation  $[\alpha]_D^{20} = 100\alpha/lc$ , in which  $l$  is the length of the sample in decimeters,  $c$  is the concentration in g per 100 ml,  $t$  is the temperature, and  $\lambda$  the wavelength of the light (D stands for sodium D light); see Section 19-2.

Proceeding as we did for threonine, we can write four projection formulas for tartaric acid, 2,3-dihydroxybutanedioic acid, as shown by **23–26**:

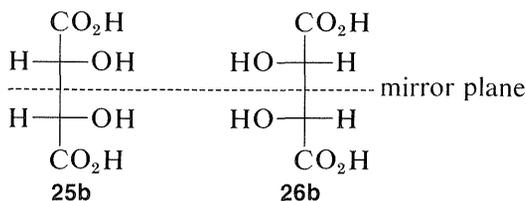


These projection formulas can be translated into the respective Newman representations, **23a–26a**. (We highly recommend that you verify this by the procedure of Figure 5-13.)

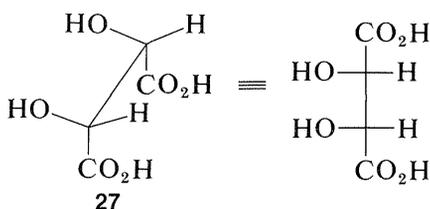


There are two pairs of mirror images **23a** and **24a**, as well as **25a** and **26a**. However, what will not be so immediately clear, but what you *must* verify for yourself is that **25a** and **26a** are, in fact, identical. This means that **25a** and **26a** are representations of a *single* achiral substance, identical with its mirror image. *Substances that have chiral centers but are themselves achiral are called meso compounds.*

The condition that makes possible the existence of meso compounds is an appropriate degree of molecular symmetry. There are several kinds of such molecular symmetry. In the case of projection formulas **25** (or **26**) there is a **plane of symmetry**, which means that a plane can be placed through the molecule such that *one half of the molecule is a mirror image of the other half*. The mirror plane for *meso*-tartaric acid can be seen easily from its projection formulas **25b** and **26b**. These two formulas are superimposable if one is rotated 180° in the plane of the paper.



The Newman representation **25a** or **26a** of *meso*-tartaric acid does *not* have a mirror plane. Why is it different from the Fischer projections in this respect? The reason is that the projection formulas represent a particular *eclipsed* conformation **27** of *meso*-tartaric acid that does have a mirror plane:



Therefore, if you are confronted with a particular sawhorse or Newman formula and you have to decide whether it represents a *meso* compound, the best procedure is to make a ball-and-stick model of the conformation and then rotate around the bonds to see if it can be brought into a conformation (staggered or eclipsed) that has a plane of symmetry (such as **27**) or is identical with its mirror image.

As expected from our previous discussions diastereomers of tartaric acid have different physical properties (Table 5-2).

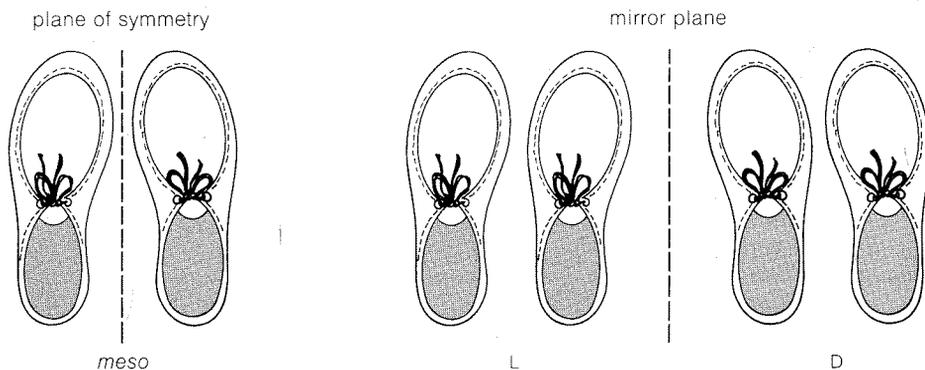
If you find yourself confused about the D,L, and *meso* forms of tartaric acid, a simple analogy may help keep matters straight. Consider three sets of shoes. A right shoe beside a left shoe is a *meso* combination with a plane of symmetry. A left shoe next to a left shoe is not identical with, but is

**Table 5-2**  
Physical Properties of Tartaric Acids

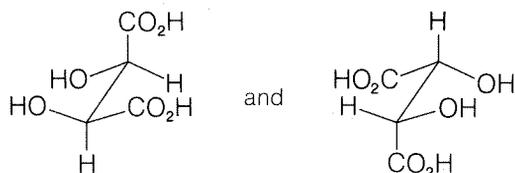
Tartaric acid	$[\alpha]_D^{20}$ in H <sub>2</sub> O	Melting point, °C	Density, g ml <sup>-1</sup>	Solubility in H <sub>2</sub> O, g/100 ml at 25°
<i>meso</i>	—	140	1.666	120 <sup>(15)</sup>
(-)	-11.98°	170	1.760	147
(+)	+11.98°	170	1.760	147
(±) <sup>a</sup>	—	205	1.788	25

<sup>a</sup>Racemic acid (Section 5-1C) has a higher melting point and lower solubility than either of its constituents, (+)- or (-)-tartaric acid. This is a result of how the molecules fit together in the crystals. Apparently a stronger crystal is made by mixing the D and L molecules than can be made from either alone.

the mirror image of, a right shoe next to a right shoe. None of the three combinations are identical. Each right or left shoe corresponds to a right or left configuration of a tartaric acid carbon so the three sets correspond to *meso*-, L-, and D-tartaric acid, respectively.



**Exercise 5-12** Analysis of the crystals of a particular tartaric acid show them to be made up of equal amounts of the following conformations:

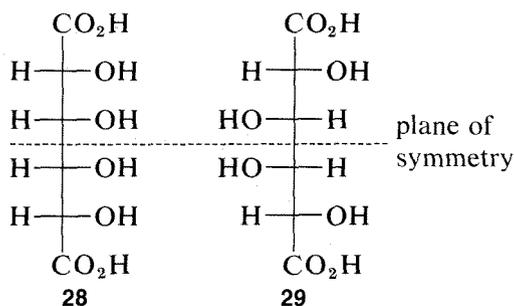


Use ball-and-stick models to determine the relationship between these two conformations.

mations and also whether this tartaric acid is *meso*-tartaric acid, an optically active tartaric acid, or racemic acid. Give your reasoning.

There is another symmetry test for meso configurations that is applicable to staggered conformations and can be illustrated with the tartaric acids. If you make models of **25a** and **26a** you will find that they are mirror images and identical but, as we have said, they have no plane of symmetry. In this conformation, the molecules do have a **center of symmetry**. Thus a line drawn at any angle through the midpoint of the central C–C bond of **25a** (or **26a**) has an identical environment on each side of the midpoint. Another way of putting it is that each half of the molecule is the *photographic image* (i.e., reverse) of the other half. For a molecule with chiral centers, if its projection formula has a plane of symmetry or if we can find a rotational conformation with either a plane or center of symmetry, then it will be meso and achiral.

The idea that for every  $n$  chiral centers there can be  $2^n$  different configurations will be true only if none of the configurations has sufficient symmetry to be identical with its mirror image. For every meso form there will be one less pair of enantiomers and one less total number of possible configurations than is theoretically possible according to the number of chiral centers. At most, one meso compound is possible for structures with two chiral centers, whereas two are possible for structures with four chiral centers. An example is offered by the meso forms of tetrahydroxyhexanedioic acid which, with four chiral atoms, have configurations **28** and **29**:



**Exercise 5-13** Write structures for all the configurations possible for 2,4-dibromopentane. Which stereoisomers are enantiomers? Which are diastereomers? What combination of isomers would give a racemic mixture? Which isomer is achiral?

**Exercise 5-14** From the compounds listed select all those that may have achiral meso configurations and draw the configurations for each of them.

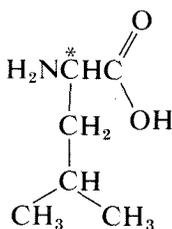
- |                                    |                                     |
|------------------------------------|-------------------------------------|
| <b>a.</b> 1,2-dichlorocyclopropane | <b>d.</b> 2,3-dichloropentane       |
| <b>b.</b> 1,4-dichlorocyclohexane  | <b>e.</b> 2,3,4-trichloropentane    |
| <b>c.</b> 1,3-dichlorocyclohexane  | <b>f.</b> 2,3,4,5-tetrachlorohexane |

## 5-6 SOME EXAMPLES OF THE IMPORTANCE OF STEREOISOMERISM TO BIOLOGY.

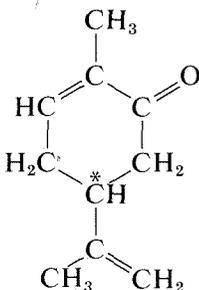
### BIOLOGICAL STEREOSPECIFICITY

Symmetrical reagents do not differentiate between the members of a pair of enantiomers for the same reason that an ordinary sock fits equally well on a right foot as on a left foot. However, asymmetric or chiral reagents can differentiate between enantiomers, especially by having at least some difference in reactivity toward them. A good analogy is the comparison between the ease of putting a left shoe on a left foot and a left shoe on a right foot. The difference may not be very pronounced for simple compounds with only one or two chiral centers, but generally the larger and more complex the chiral reagent becomes, the greater is its selectivity or power to discriminate between enantiomers and diastereomers as well. The property of being able to discriminate between stereoisomers is called *stereospecificity*, and this is an especially important characteristic of biological systems.

For example, our ability to taste and smell is regulated by chiral molecules in our mouths and noses that act as receptors to “sense” foreign substances. We can anticipate, then, that enantiomers may interact differently with the receptor molecules and induce different sensations. This appears to be the case. The two enantiomers of the amino acid, leucine, for example, have different tastes—one is bitter, whereas the other is sweet. Enantiomers also can smell different, as is known from the odors of the two carvones. One has the odor of caraway and the other of spearmint.



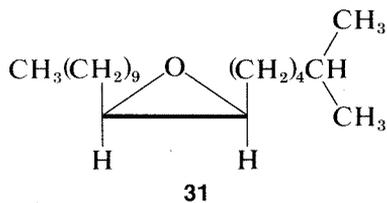
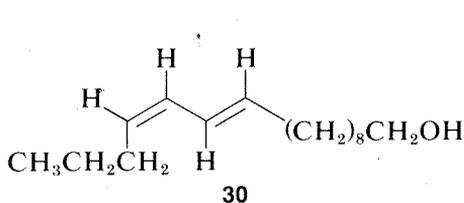
leucine  
(\*denotes the chiral carbon)



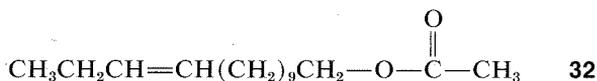
carvone  
(\*denotes the chiral carbon)

Some animals, and especially insects, rely on what amounts to a “sense-of-smell” for communication with others of their species. Substances synthesized by a particular species, and used to send messages in this way, are called **pheromones**. Many of these substances have rather simple molecular structures because they must be reasonably volatile and yet they are remarkably specific

in the response they induce. When stereoisomerism is possible, usually only one isomer is effective. The sex attractant of the silkworm moth *Bombyx mori* has been identified as *trans*-10-*cis*-12-hexadecadien-1-ol, **30**, familiarly known as "bombykol," and that of the gypsy moth is 2-methyl-*cis*-7-epoxy-octadecane, **31**, or "disparlure":



There is hope that insect sex lures can be used to disrupt the mating pattern of insects and thereby control insect population. This approach to pest control has important advantages over conventional insecticides in that the chemical lures are specific for a particular species; also they are effective in remarkably low concentrations and are relatively nontoxic. There are problems, however, not the least of which is the isolation and identification of the sex attractant that is produced by the insects only in minute quantities. Also, synergistic effects are known to operate in several insect species such that not one but several pheromones act in concert to attract the opposite sex. Two notable pests, the European corn borer and the red-banded leaf roller, both use *cis*-11-tetradecenyl ethanoate, **32**, as the primary sex attractant, but the pure *cis* isomer is ineffective unless a small amount of *trans* isomer also is present. The optimum amount appears to be between 4% and 7% of the *trans* isomer.



We shall discuss many other examples of biological stereospecificity in later chapters.

### Additional Reading

- G. Natta and M. Farina, *Stereochemistry*, Harper and Row, New York, 1972.
- K. Mislow, *Introduction to Stereochemistry*, W. A. Benjamin, Inc., Menlo Park, Calif., 1965.
- E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Company, New York, 1962.
- G. W. Wheland, *Advanced Organic Chemistry*, 3rd ed., John Wiley and Sons, New York, 1960, Chapters 6 and 7. Chapter 6 contains a translation of an amusing diatribe by H. Kolbe, in 1877, against van't Hoff's formulations of chiral molecules.
- E. L. Eliel, "Recent Advances in Stereochemical Nomenclature," *J. Chem. Educ.* **48**, 163 (1971).

"IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry," *J. Org. Chem.* **35**, 2849 (1970).

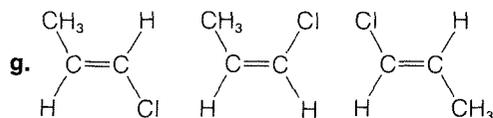
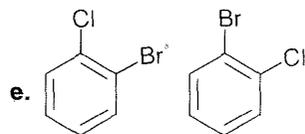
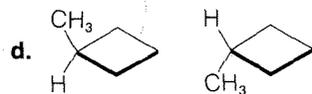
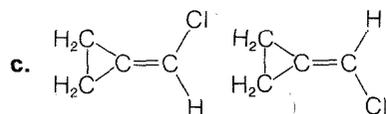
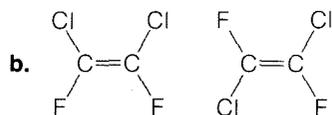
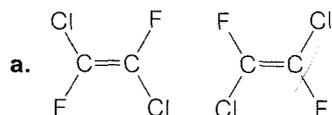
J. F. Amore, J. W. Johnston, and M. Rubin, "Stereochemical Theory of Odor," *Scientific American*, Feb. 1964.

D. E. Koshland, Jr., "Protein Shape and Biological Control," *Scientific American*, Oct. 1973.

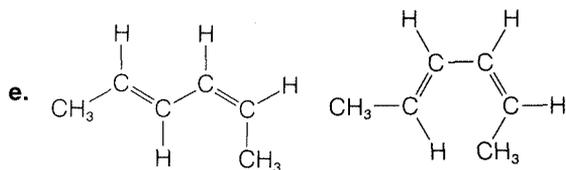
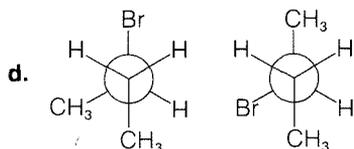
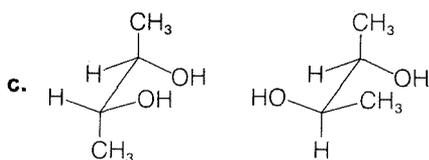
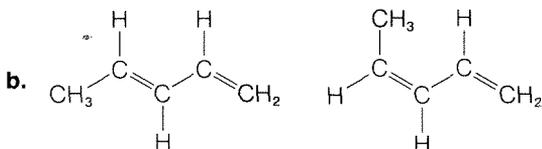
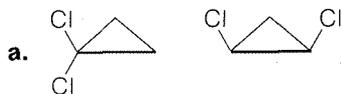
E. O. Wilson, "Pheromones," *Scientific American*, May 1963.

### Supplementary Exercises

**5-15** Look carefully at each pair of structures shown below and decide whether they are identical. If you are uncertain, use molecular models.



**5-16** The two structures shown in each of the following pairs are isomers. Determine whether they are position, configurational, or conformational isomers. Use of models will be very helpful.



**5-17** Which of the following compounds could exist as cis-trans configurational isomers?

- a. 1,2-dibromoethene      c. dibromoethyne  
b. 2,3-dibromopropene      d. 1,3-dibromopropene

**5-18** Which of the following compounds can exist as (1) a pair of enantiomers, (2) a pair of cis-trans isomers, and (3) as a cis pair of enantiomers and a trans pair of enantiomers?

- a. 3-chloro-1-butyne      d. 2-chloro-1,3-butadiene  
b. 4-chloro-1-butyne      e. 4-chloro-2-pentene  
c. 1-chloro-1,3-butadiene      f. 5-chloro-2-pentene

**5-19** Write structures showing the specified configurations for each of the following compounds. Make your drawings as clear as possible so there is no ambiguity as to

structure or configuration:

- |                                       |  |
|---------------------------------------|--|
| a. <i>cis</i> -1,2-diphenylethene     | e. <i>cis-cis</i> -2,4-heptadiene                        |
| b. <i>trans</i> -2-chloro-2-butene    | f. <i>trans-cis</i> -2,4-heptadiene                      |
| c. <i>trans</i> -1-propenylbenzene    | g. <i>cis-trans</i> -2,4-heptadiene                      |
| d. <i>trans-trans</i> -2,4-heptadiene | h. <i>cis</i> -1- <i>tert</i> -butyl-4-methylcyclohexane |

**5-20** Write structural formulas showing configuration for all of the possible *cis-trans* isomers of the following compounds:

- |                                |   |
|--------------------------------|---|
| a. 1,2,3-trimethylcyclopropane | c. 3-methyl-2,4-hexadiene                     |
| b. 1,3-dichlorocyclopentane    | d. 1-(3-methylcyclobutyl)-3-methylcyclobutane |

**5-21** Would you expect *cis*- or *trans*-1,2-dimethylcyclopropane to be the more stable? Explain.

**5-22** Draw suitable formulas for all of the position and configurational isomers possible (include optical isomers but not conformational isomers) for the following compounds of molecular formula:

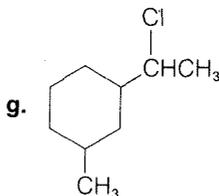
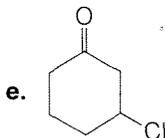
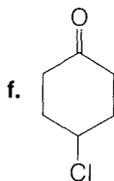
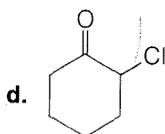
- |                      |                           |                          |
|----------------------|---------------------------|--------------------------|
| a. $C_3H_5Cl$ (five) | b. $C_5H_{10}$ (thirteen) | c. $C_4H_7Cl$ (nineteen) |
|----------------------|---------------------------|--------------------------|

**5-23** Show how the sawhorse and Newman conventions can be used to represent the *different* possible *staggered* conformations of the following substances:

- |                                |                       |
|--------------------------------|-----------------------|
| a. chloroethane                | c. 1,2-dichloroethane |
| b. 1,2-dichloro-1-fluoroethane | d. 2,3-dimethylbutane |

**5-24** Determine which of the following compounds are chiral and which are achiral. Indicate each chiral atom with an asterisk (\*), noting that more than one may be present in some examples.

- |                           |
|---------------------------|
| a. 2,3-dimethylpentane    |
| b. 2,3-dimethyl-2-pentene |
| c. 2-bromo-3-chlorobutane |

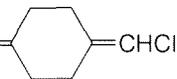
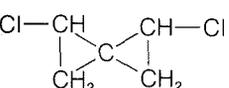


**5-25** Write structures that fit the following descriptions:

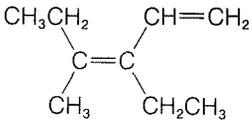
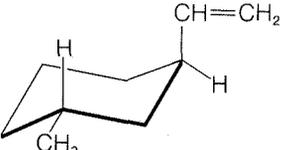
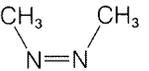
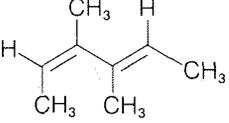
- |  |
|--|
| a. An achiral isomer of dimethylcyclohexane that has the methyl groups on different carbons. |
| b. All the chiral isomers of formula $C_5H_{12}O$ .  |

- c. A compound of formula  $C_4H_5Cl$  that has just one double bond and is chiral.  
 d.\* The conformation of 2,5-dimethylhexane you would anticipate to be the most stable.

**5-26** If you have a set of molecular models with which you can make or use bent bonds for double bonds, construct each of the following molecules and determine if stereoisomerism is possible and, if so, identify the type of stereoisomers.

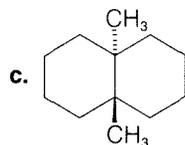
- a.  $ClCH=C=CHCl$   
 b.  $ClCH=C=C=CHCl$   
 c.   
 d.\* 

**5-27** Designate the configuration of the compounds whose structures are drawn below using the cis-trans terminology.

- a.   
 b.   
 c.   
 d.   
 e. 

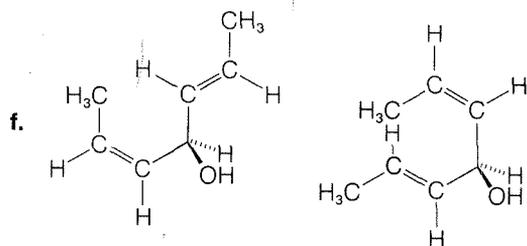
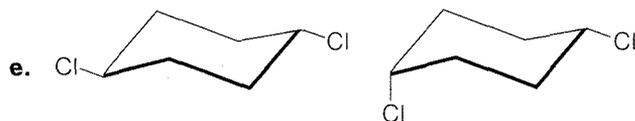
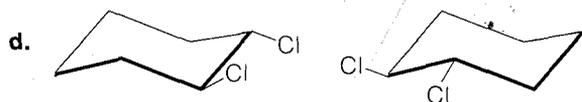
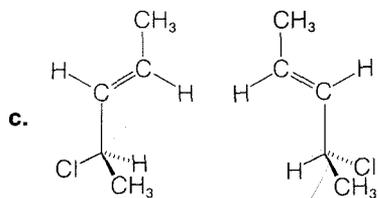
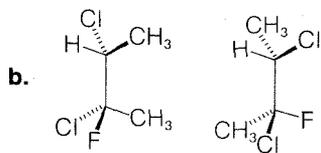
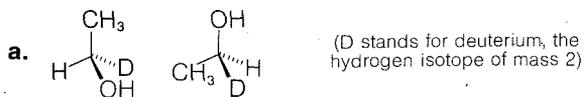
**5-28** Draw sawhorse formulas as in Figure 5-10 for the following cyclohexane derivatives:

- a. 1,1,3,3-tetramethylcyclohexane  
 b. *cis*-1,2-dimethylcyclohexane (two different ways)

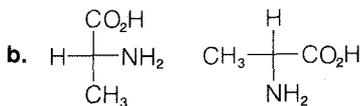
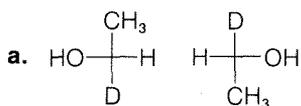


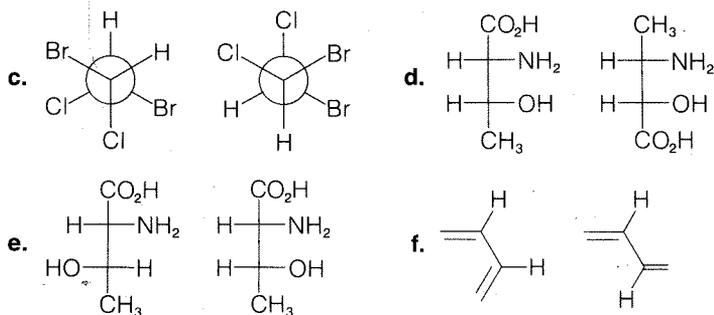
**5-29** Determine the relationship between the pairs of compounds written as perspective formulas as being enantiomers, diastereomers, conformational isomers, cis-trans

isomers, or some combination of these. Models will be very helpful.



**5-30** This is a problem similar to 5-29, except that the structures are written mostly as projection formulas of the Fischer or Newman type. Determine the relationship between the pairs of compounds as one of the following: identical, position isomers, enantiomers, diastereomers, conformational isomers, or cis-trans isomers. (D stands for deuterium, the hydrogen isotope of mass 2.)

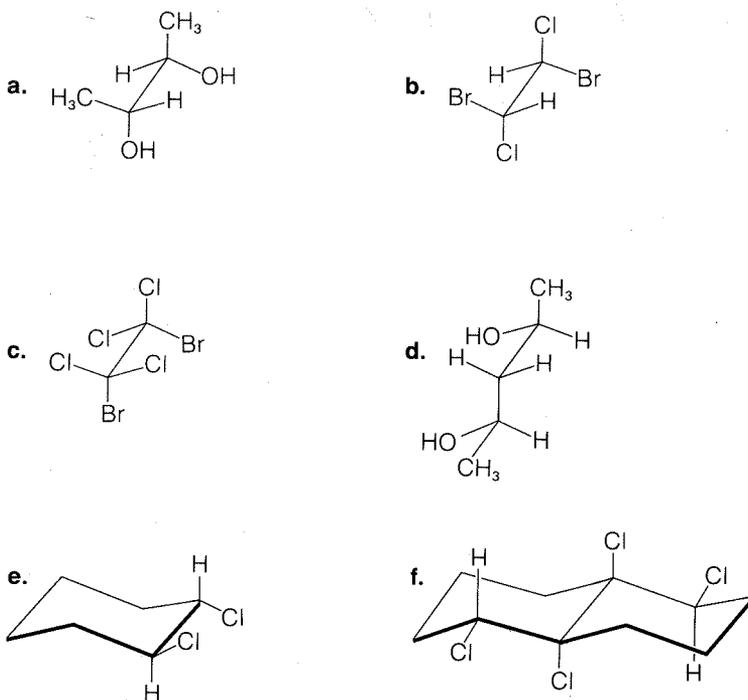




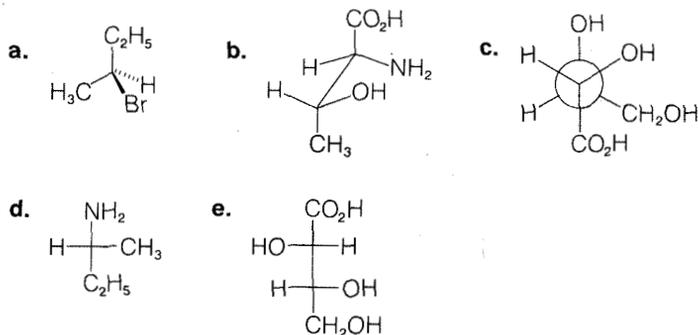
**5-31** Draw structures for all the possible configurational isomers of the following compounds. In Part **a**, D stands for deuterium, the hydrogen isotope of mass 2.

- |  |  |
|--|--|
| <b>a.</b> ethene-1,2-D <sub>2</sub> (1,2-dideuterioethene) | <b>g.</b> 3-chlorocyclooctene (use models)   |
| <b>b.</b> 3-phenoxy-1-butene                               | <b>h.</b> 4-chloromethylcyclohexane          |
| <b>c.</b> 4-iodo-2-pentene                                 | <b>i.</b> 3-chloromethylcyclohexane          |
| <b>d.</b> 2-chloro-3-phenylbutane                          | <b>j.</b> 1-methyl-4-(1-propenyl)cyclohexane |
| <b>e.</b> 2,3-diphenylbutane                               | <b>k.</b> 1-methyl-3-(1-propenyl)cyclohexane |
| <b>f.</b> 3-chlorocyclohexene                              |  |

**5-32** Determine which of the following conformations is identical with its mirror image (models will be very helpful). For the purpose of this part of the problem, assume that the compounds are locked in the conformations shown. For Parts **a-d**, determine which of these substances becomes achiral on free rotation.



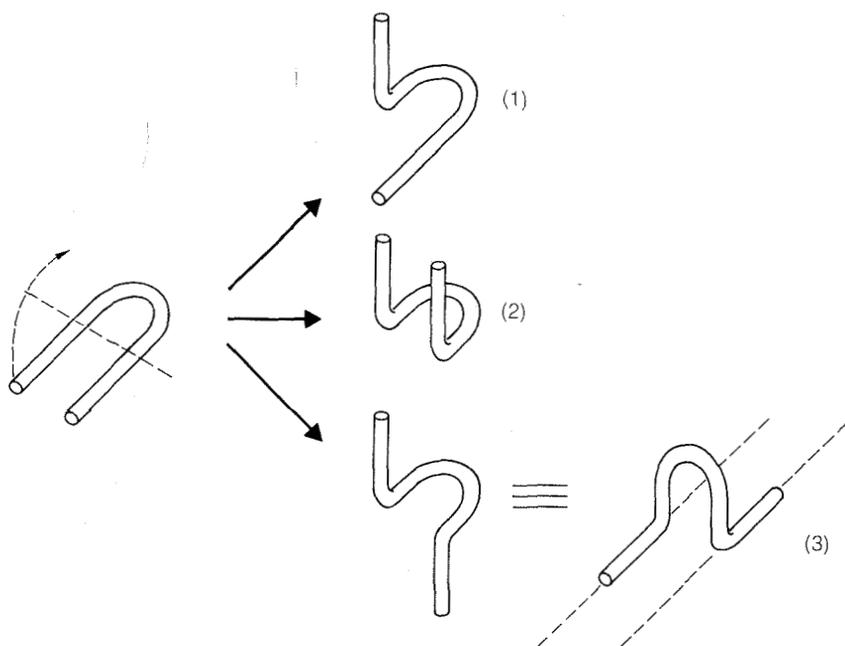
**5-33** Redraw the perspective drawings **a**, **b**, and **c** as Fischer projection formulas, leaving the configuration at the chiral centers unchanged. Similarly, redraw **d** and **e** in perspective, using a staggered sawhorse representation for **e**.



**5-34** Use the D,L system to designate the configuration at each chiral center in Structures **a–e** in Exercise 5-33.

**5-35** This problem is designed to illustrate chirality, asymmetry, and dissymmetry with simple models or common objects.

**a.** Bend three pieces of wire into a hair-pin shape with *equal* legs. Now take one piece and make a  $90^\circ$  bend in one of the legs in the middle to give (1). Bend up both legs equally of another piece to give (2), and one up and the other down to give (3). Determine whether (1), (2), and (3) are chiral or achiral, and asymmetric, dissymmetric, or symmetric. (See footnote 1, p. 116.)



b. Classify each of the following as chiral, achiral, asymmetric, dissymmetric or symmetric: a cup, a shirt, a bicycle, a tennis racket, an automobile, a penny, a pair of scissors, a flat spiral (4), and a conical spring (5). Indicate any ambiguities that may be involved.

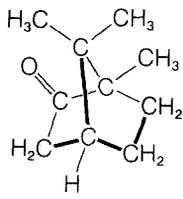


(4)

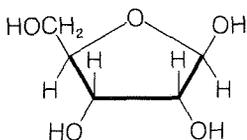


(5)

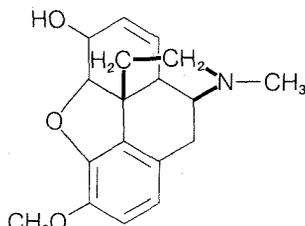
5-36 The structures of some biochemically interesting compounds are shown below. Mark the chiral carbons in each and calculate by the  $2^n$  rule how many stereoisomers might be expected. Explain why only *one* pair of enantiomers is known for camphor (ball-and-stick models will be very helpful here). How many different stereoisomers would you expect actually could be prepared of the quinine and codeine structures?



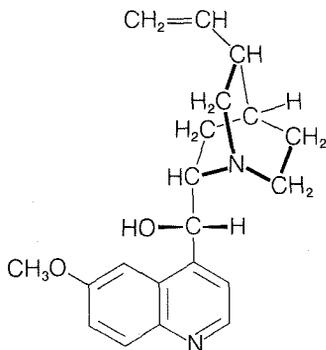
camphor  
(counterirritant)



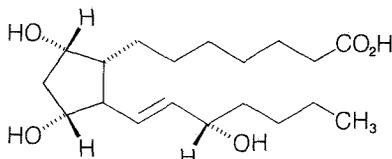
ribose  
(sugar component  
of RNA)



codeine  
(narcotic analgesic)



quinine  
(antimalarial drug)



prostaglandin F  
(hormone)