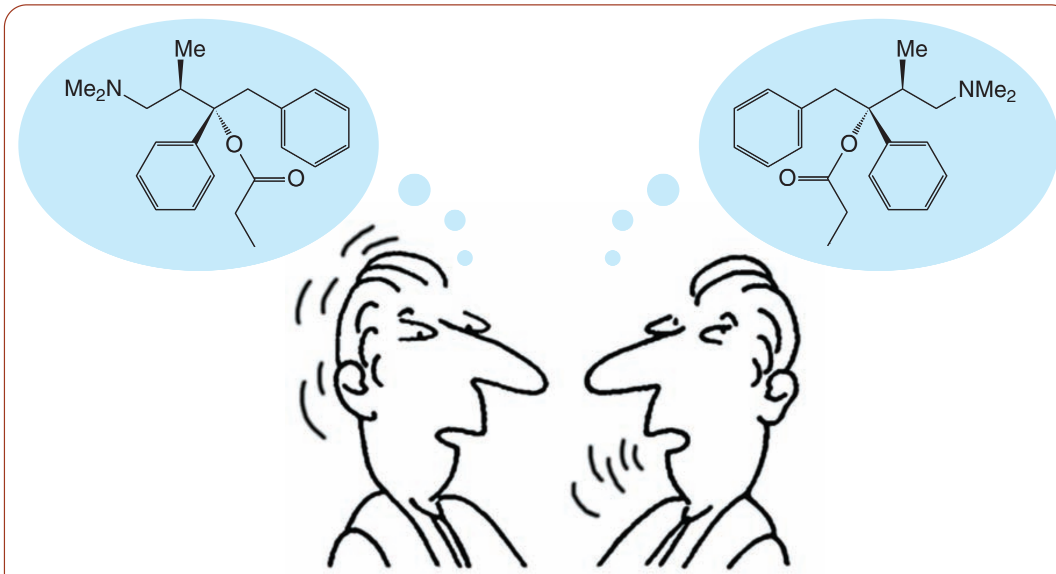
5 Stereochemistry

Chiral Molecules



DARVON
(painkiller)

NOVRAD
(anticough agent)

We are all aware of the fact that certain everyday objects such as gloves and shoes possess the quality of "handedness." A right-handed glove only fits a right hand; a left-handed shoe only fits a left foot. Objects that can exist in right-handed and left-handed forms are said to be **chiral**. In this chapter we shall find that molecules can also be chiral and can exist in right- and left-handed forms. For example, one chiral form of the molecule shown above is a painkiller (Darvon), and the other, a cough suppressant (Novrad)! It is easy to see why it is important to understand chirality in molecules.

5.1 *Chirality and Stereochemistry*

The glass and its mirror image are superposable.

Chirality is a phenomenon that pervades the universe. How can we know whether a particular object is **chiral** or **achiral** (not chiral)?

- We can tell if an object has **chirality** by examining the object and its mirror image.

Every object has a mirror image. Many objects are achiral. By this we mean that *the object and its mirror image are identical*, that is, the object and its mirror image are **superposable** one on the other.* Superposable means that one can, in one's mind's eye, place one object on the other so that all parts of each coincide. Simple geometrical objects such as a sphere or a cube are achiral. So is an object like a water glass.

- **A chiral object is one that cannot be superposed on its mirror image**.

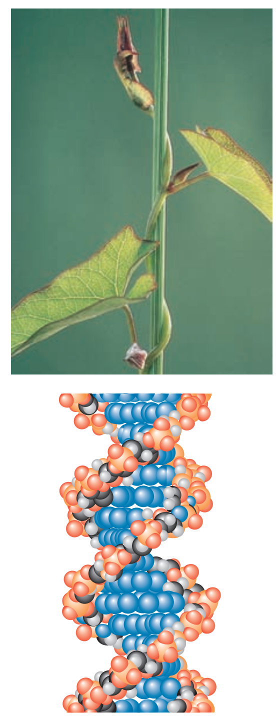
*To be superposable is different than to be super*im*posable. Any two objects can be superimposed simply by putting one object on top of the other, whether or not the objects are the same. To *superpose* two objects (as in the property of superposition) means, on the other hand, that **all parts of each object must coincide**. The condition of superposability must be met for two things to be **identical**.

Figure 5.1 The mirror image of a right hand is a left hand.

Figure 5.2 Left and right hands are not superposable.

Each of our hands is chiral. When you view your right hand in a mirror, the image that you see in the mirror *is a left hand* (Fig. 5.1). However, as we see in Fig. 5.2, your left hand and your right hand are not identical because *they are not superposable*. Your hands are chiral. In fact, the word chiral comes from the Greek word *cheir* meaning hand. An object such as a mug may or may not be chiral. If it has no markings on it, it is achiral. If the mug has a logo or image on one side, it is chiral.

This mug is chiral.



Bindweed (top photo) *(Convolvulus sepium)* winds in a right-handed fashion, like the right-handed helix of DNA.

5.1A The Biological Significance of Chirality

The human body is structurally chiral, with the heart lying to the left of center and the liver to the right. Helical seashells are chiral and most are spiral, such as a right-handed screw. Many plants show chirality in the way they wind around supporting structures. Honeysuckle winds as a left-handed helix; bindweed winds in a right-handed way. DNA is a chiral molecule. The double helical form of DNA turns in a right-handed way.

Chirality in molecules, however, involves more than the fact that some molecules adopt left- or right-handed conformations. As we shall see in this chapter, it is the nature of groups bonded at specific atoms that can bestow chirality on a molecule. Indeed, all but one of the 20 amino acids that make up naturally occurring proteins are chiral, and all of these are classified as being left-handed. The molecules of natural sugars are almost all classified as being right-handed. In fact, most of the molecules of life are chiral, and most are found in only one mirror image form.*

* For interesting reading, see Hegstrum, R. A.; Kondepudi, D. K. The Handedness of the Universe. *Sci. Am.* **1990**, *262*(1), 98–105, and Horgan, J. The Sinister Cosmos. *Sci. Am.* **1997**, *276*(5), 18–19.

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Chirality has tremendous importance in our daily lives. Most pharmaceuticals are chiral. Usually only one mirror-image form of a drug provides the desired effect. The other mirror-image form is often inactive or, at best, less active. In some cases the other mirror-image form of a drug actually has severe side effects or toxicity (see Section 5.5 regarding thalidomide). Our senses of taste and smell also depend on chirality. As we shall see, one mirror-image form of a chiral molecule may have a certain odor or taste while its mirror image smells and tastes completely different. The food we eat is largely made of molecules of one mirror-image form. If we were to eat food that was somehow made of molecules with the unnatural mirror-image form, we would likely starve because the enzymes in our bodies are chiral and preferentially react with the natural mirror-image form of their substrates.

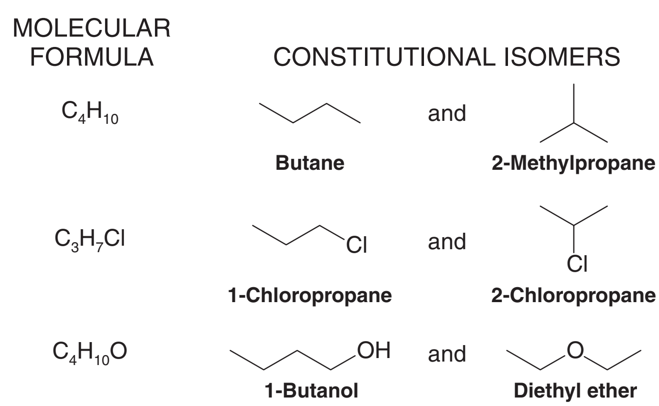
Let us now consider what causes some molecules to be chiral. To begin, we will return to aspects of isomerism.

5.2 *Isomerism: Constitutional Isomers and Stereoisomers*

5.2A Constitutional Isomers

Isomers are different compounds that have the same molecular formula. In our study thus far, much of our attention has been directed toward isomers we have called constitutional isomers.

- **Constitutional isomers** have the same molecular formula but different connectivity, meaning that their atoms are connected in a different order. Examples of constitutional isomers are the following:



5.2B Stereoisomers

Stereoisomers are not constitutional isomers.

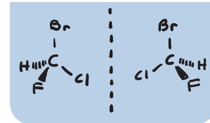
- **Stereoisomers** have their atoms connected in the same sequence (the same constitution), but they differ in the arrangement of their atoms in space. The consideration of such spatial aspects of molecular structure is called **stereochemistry**.

We have already seen examples of some types of stereoisomers. The cis and trans forms of alkenes are stereoisomers (Section 1.13B), as are the cis and trans forms of substituted cyclic molecules (Section 4.13).

5.2C Enantiomers and Diastereomers

Stereoisomers can be subdivided into two general categories: those that are **enantiomers** of each other, and those that are **diasteromers** of each other.

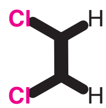
- **Enantiomers are stereoisomers whose molecules are nonsuperposable mirror images of each other**.



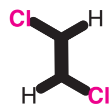
All other stereoisomers are diastereomers.

- **Diastereomers are stereoisomers whose molecules are not mirror images of each other**.

The alkene isomers *cis*- and *trans*-1,2-dichloroethene shown here are stereoisomers that are **diastereomers**.



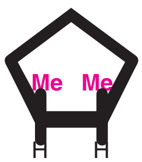
***cis*-1,2-Dichloroethene**
($C_2H_2Cl_2$)



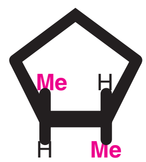
***trans*-1,2-Dichloroethene**
($C_2H_2Cl_2$)

By examining the structural formulas for *cis*- and *trans*-1,2-dichloroethene, we see that they have the same molecular formula ($C_2H_2Cl_2$) and the same connectivity (both compounds have two central carbon atoms joined by a double bond, and both compounds have one chlorine and one hydrogen atom attached to each carbon atom). But, their atoms have a different arrangement in space that is not interconvertible from one to another (due to the large barrier to rotation of the carbon–carbon double bond), making them stereoisomers. Furthermore, they are stereoisomers that are not mirror images of each other; therefore they are diastereomers and not enantiomers.

Cis and trans isomers of cycloalkanes furnish us with another example of stereoisomers that are diastereomers. Consider the following two compounds:



***cis*-1,2-Dimethylcyclopentane**
(C_7H_{14})

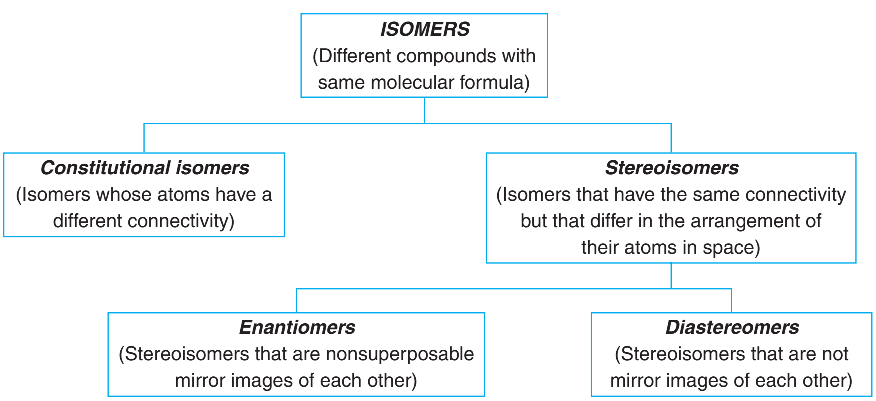


***trans*-1,2-Dimethylcyclopentane**
(C_7H_{14})

These two compounds have the same molecular formula (C_7H_{14}), the same sequence of connections for their atoms, but different arrangements of their atoms in space. In one compound both methyl groups are bonded to the same face of the ring, while in the other compound the two methyl groups are bonded to opposite faces of the ring. Furthermore, the positions of the methyl groups cannot be interconverted by conformational changes. Therefore, these compounds are stereoisomers, and because they are stereoisomers that are not mirror images of each other, they can be further classified as diastereomers.

In Section 5.12 we shall study other molecules that can exist as diastereomers but are not cis and trans isomers of each other. First, however, we need to consider enantiomers further.

SUBDIVISION OF ISOMERS



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5.3 Enantiomers and Chiral Molecules

Enantiomers always have the possibility of existing in pairs. We may not always find that nature (or a reaction) has produced a pair of enantiomers, however. In fact, in nature we often find only one enantiomer of the two that are possible. We shall find out later why this is often the case. Typically, when we carry out a chemical reaction, we find that the reaction produces a pair of enantiomers. Again, we will explain later why this occurs.

What structural feature must be present for two molecules to exist as enantiomers?

- **Enantiomers occur only with compounds whose molecules are chiral**.

How do we recognize a chiral molecule?

- **A chiral molecule is one that is not superposable on its mirror image**.

What is the relationship between a chiral molecule and its mirror image?

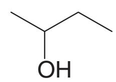
- **The relationship is one that is enantiomeric**. A chiral molecule and its mirror image are said to be enantiomers of each other.

Review Problem 5.1

Classify each of the following objects as to whether it is chiral or achiral:

(a) A screwdriver **(d)** A tennis shoe **(g)** A car
(b) A baseball bat **(e)** An ear **(h)** A hammer
(c) A golf club **(f)** A woodscrew

The chirality of molecules can be demonstrated with relatively simple compounds. Consider, for example, 2-butanol:



2-Butanol

Until now, we have presented the formula for 2-butanol as though it represented only one compound and we have not mentioned that molecules of 2-butanol are chiral. Because they are, there are actually two different 2-butanols and these two 2-butanols are enantiomers. We can understand this if we examine the drawings and models in Fig. 5.3.

Helpful Hint

Working with models is a helpful study technique whenever three-dimensional aspects of chemistry are involved.

If model **I** is held before a mirror, model **II** is seen in the mirror and vice versa. Models **I** and **II** are not superposable on each other; therefore, they represent different, but isomeric, molecules. ***Because models I and II are nonsuperposable mirror images of each other, the molecules that they represent are enantiomers***.

Review Problem 5.2

Construct handheld models of the 2-butanols represented in Fig. 5.3 and demonstrate for yourself that they are not mutually superposable. **(a)** Make similar models of 2-bromopropane. Are they superposable? **(b)** Is a molecule of 2-bromopropane chiral? **(c)** Would you expect to find enantiomeric forms of 2-bromopropane?

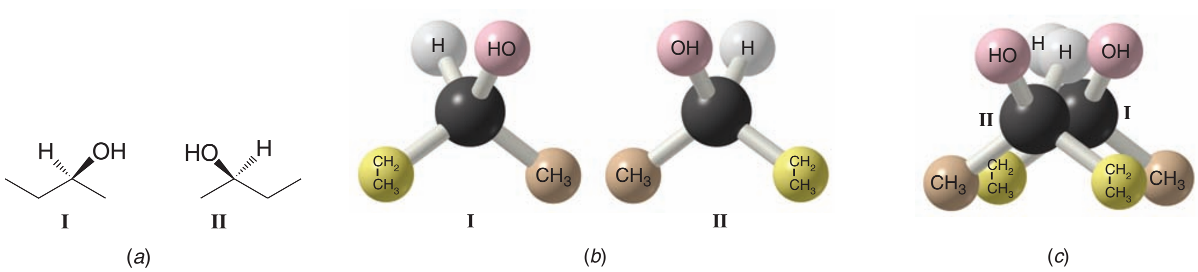
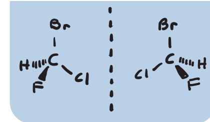


Figure 5.3 *(a)* Three-dimensional drawings of the 2-butanol enantiomers **I** and **II**. *(b)* Models of the 2-butanol enantiomers. *(c)* An unsuccessful attempt to superpose models of **I** and **II**.



5.4 *A Single Chirality Center Causes a Molecule to Be Chiral*

What structural feature can we use to know when to expect the possible existence of a pair of enantiomers?

- One way (but not the only way) is to recognize that *a pair of enantiomers is always possible for molecules that contain* **a single tetrahedral atom with four different groups attached to it**.

Traditionally such atoms have been called *asymmetric atoms*, or *stereogenic atoms*, or *stereocenters*. In 1996, however, the IUPAC recommended that such atoms be called **chirality centers**, and this is the usage that we shall follow in this text.* It is also important to state that chirality is a property of the molecule as a whole, and that a chirality center is a structural feature that can cause a molecule to be chiral.

Chirality centers are often designated with an asterisk (*). In 2-butanol the chirality center is C2 (Fig. 5.4). The four different groups that are attached to C2 are a hydroxyl group, a hydrogen atom, a methyl group, and an ethyl group.

An ability to find chirality centers in structural formulas will help us in recognizing molecules that are chiral, and that can exist as enantiomers. **The presence of a single chirality center in a molecule guarantees that the molecule is chiral and that enantiomeric forms are possible**. *However, as we shall see in Section 5.12, there are molecules with more than one chirality center that are not chiral, and there are molecules that do not contain a chirality center that are chiral.*

Figure 5.5 demonstrates that enantiomeric compounds can exist whenever a molecule contains a single chirality center.

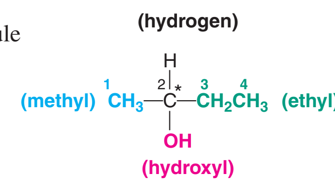


Figure 5.4 The tetrahedral carbon atom of 2-butanol that bears four different groups. [By convention, chirality centers are often designated with an asterisk (*).]

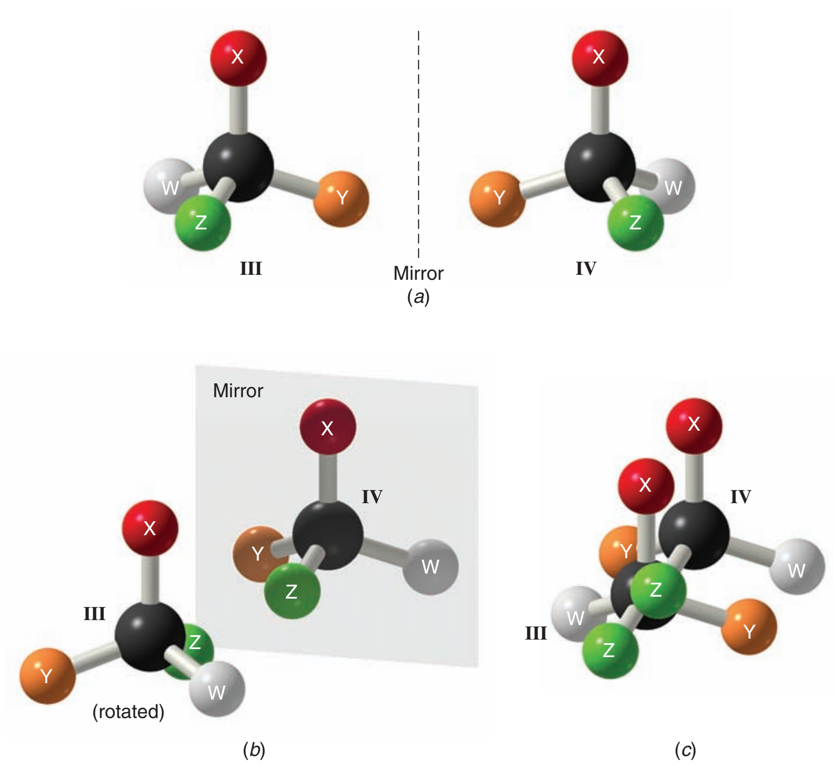


Figure 5.5 A demonstration of chirality of a generalized molecule containing one chirality center. *(a)* The four different groups around the carbon atom in **III** and **IV** are arbitrary. *(b)* **III** is rotated and placed in front of a mirror. **III** and **IV** are found to be related as an object and its mirror image. *(c)* **III** and **IV** are not superposable; therefore, the molecules that they represent are chiral and are enantiomers.

*The 1996 IUPAC recommended usage can be found at http://www.chem.qmw.ac.uk/iupac/stereo.

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Helpful Hint

Interchanging two groups of a model or three-dimensional formula is a useful test for determining whether structures of two chiral molecules are the same or different.

An important property of enantiomers with a single chirality center, such as 2-butanol, is that *interchanging any two groups at the chirality center converts one enantiomer into the other*. In Fig. 5.3*b* it is easy to see that interchanging the methyl and ethyl groups converts one enantiomer into the other. You should now convince yourself that interchanging any other two groups has the same result.

- Any atom at which an interchange of groups produces a stereoisomer is called a **stereogenic center**. (If the atom is a carbon atom it is usually called a **stereogenic carbon**.)

When we discuss interchanging groups like this, we must take care to notice that what we are describing is *something we do to a molecular model* or *something we do on paper*. An interchange of groups in a real molecule, if it can be done, requires breaking covalent bonds, and this is something that requires a large input of energy. This means that enantiomers such as the 2-butanol enantiomers ***do not interconvert*** spontaneously.

The *chirality center* of 2-butanol is one example of a *stereogenic center*, but there are stereogenic centers that are *not* chirality centers. The carbon atoms of *cis*-1,2-dichloroethene and of *trans*-1,2-dichloroethene (Section 5.2c) are stereogenic centers because an interchange of groups at either carbon atom produces the other stereoisomer. The carbon atoms of *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene are not chirality centers, however, because they do not have four different groups attached to them.

Review Problem 5.3

Demonstrate the validity of what we have represented in Fig. 5.5 by constructing models. Demonstrate for yourself that **III** and **IV** are related as an object and its mirror image *and that they are not superposable* (i.e., that **III** and **IV** are chiral molecules and are enantiomers). **(a)** Take **IV** and exchange the positions of any two groups. What is the new relationship between the molecules? **(b)** Now take either model and exchange the positions of any two groups. What is the relationship between the molecules now?

If all of the tetrahedral atoms in a molecule have two or more groups attached that *are the same*, the molecule does not have a chirality center. The molecule is superposable on its mirror image and is **achiral**. An example of a molecule of this type is 2-propanol; carbon atoms 1 and 3 bear three identical hydrogen atoms and the central atom bears two identical methyl groups. If we write three-dimensional formulas for 2-propanol, we find (Fig. 5.6) that one structure can be superposed on its mirror image.

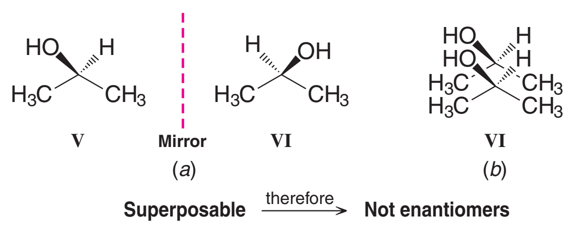


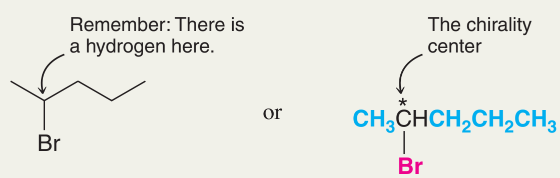
Figure 5.6 *(a)* 2-Propanol (**V**) and its mirror image (**VI**). *(b)* When either one is rotated, the two structures are superposable and so do not represent enantiomers. They represent two molecules of the same compound. 2-Propanol does not have a chirality center.

Thus, we would not predict the existence of enantiomeric forms of 2-propanol, and experimentally only one form of 2-propanol has ever been found.

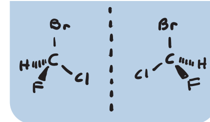
Solved Problem 5.1

Does 2-bromopentane have a chirality center? If so, write three-dimensional structures for each enantiomer.

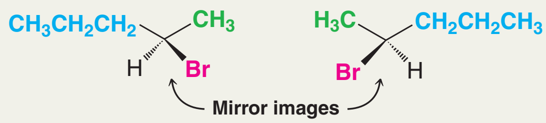
STRATEGY AND ANSWER First we write a structural formula for the molecule and look for a carbon atom that has four different groups attached to it. In this case, carbon 2 has four different groups: a hydrogen, a methyl group, a bromine, and a propyl group. Thus, carbon 2 is a **chirality center**.



2-Bromopentane



The enantiomers are



Some of the molecules listed here have a chirality center; some do not. Write three-dimensional formulas for both enantiomers of those molecules that do have a chirality center.

Review Problem 5.4

(a) 2-Fluoropropane
(b) 2-Methylbutane
(c) 2-Chlorobutane
(d) 2-Methyl-1-butanol
(e) *trans*-2-Butene
(f) 2-Bromopentane
(g) 3-Methylpentane
(h) 3-Methylhexane
(i) 2-Methyl-2-pentene
(j) 1-Chloro-2-methylbutane

5.4A Tetrahedral versus Trigonal Stereogenic Centers

It is important to clarify the difference between stereogenic centers, in general, and a chirality center, which is one type of stereogenic center. The chirality center in 2-butanol is a tetrahedral stereogenic center. The carbon atoms of *cis*- and *trans*-1,2-dichloroethene are also stereogenic centers, but they are trigonal stereogenic centers. They are *not* chirality centers. An interchange of groups at the alkene carbons of either 1,2-dichloroethene isomer produces a stereoisomer (a molecule with the same connectivity but a different arrangement of atoms in space), but it does not produce a nonsuperposable mirror image. A chirality center, on the other hand, is one that must have the possibility of nonsuperposable mirror images.

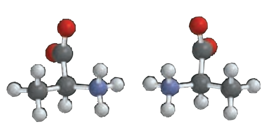
- Chirality centers are tetrahedral stereogenic centers.
- Cis and trans alkene isomers contain trigonal stereogenic centers.

THE CHEMISTRY OF . . .

Life's Molecular Handedness

The amino acids that make up our proteins possess "handedness." They are chiral. Although both mirror image forms are possible, such as those shown below for the amino acid alanine, life on Earth involves amino acids whose chirality is "left-handed" (designated L). The reason that most amino acids are of the left-handed form is not known, however.

In the absence of an influence that possesses handedness such as a living system, chemical reactions produce an equal mixture of both mirror-image forms. Since almost all theories about the origin of life presume that amino acids and other molecules central to life were present before self-replicating organisms came into being, it was assumed that they were present in equal mirror-image forms in the primordial soup.



Alanine enantiomers

But could the mirror-image forms of these molecules actually have been present in unequal amounts before life began, leading to some sort of preference as life evolved? A meteorite discovered in 1970, known as the Murchison meteorite, fueled speculation about this topic. Analysis of the meteorite showed that amino acids and other complex molecules associated with life were present, proving that molecules required for life could arise outside the confines of Earth. Even more interesting, recent experiments have shown that a 7–9% excess of four L-amino acids is present in the Murchison meteorite. The origin of this unequal distribution is uncertain, but some scientists speculate that electromagnetic radiation emitted in a corkscrew fashion from the poles of spinning neutron stars could lead to a bias of one mirror-image isomer over another when molecules form in interstellar space.

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5.5 *More about the Biological Importance of Chirality*

The origin of biological properties relating to chirality is often likened to the specificity of our hands for their respective gloves; the binding specificity for a chiral molecule (like a hand) at a chiral receptor site (a glove) is only favorable in one way. If either the molecule or the biological receptor site had the wrong handedness, the natural physiological response (e.g., neural impulse, reaction catalysis) would not occur. A diagram showing how only one amino acid in a pair of enantiomers can interact in an optimal way with a hypothetical binding site (e.g., in an enzyme) is shown in Fig. 5.7. Because of the chirality center of the amino acid, three-point binding can occur with proper alignment for only one of the two enantiomers.

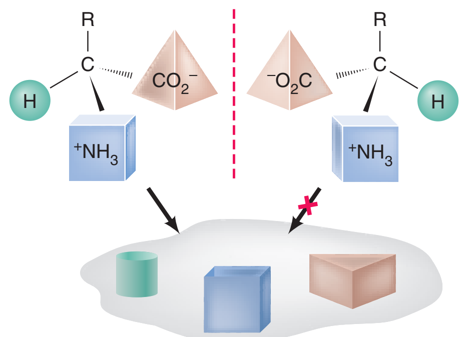
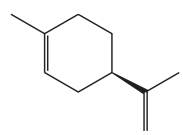
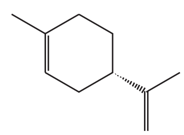


Figure 5.7 Only one of the two amino acid enantiomers shown (the left-hand one) can achieve three-point binding with the hypothetical binding site (e.g., in an enzyme).

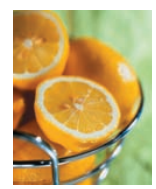
Chiral molecules can show their handedness in many ways, including the way they affect human beings. One enantiomeric form of a compound called limonene (Section 23.3) is primarily responsible for the odor of oranges and the other enantiomer for the odor of lemons.



(+)-Limonene (the enantiomer of limonene found in oranges)

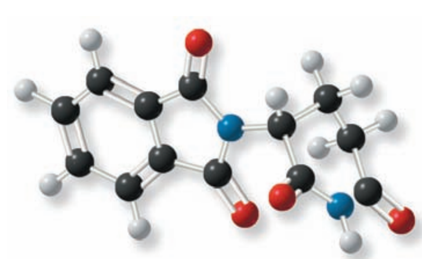


(–)-Limonene (the enantiomer of limonene found in lemons)

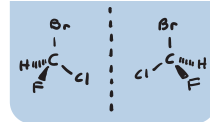


One enantiomer of a compound called carvone (Review Problem 5.14) is the essence of caraway, and the other is the essence of spearmint.

The activity of drugs containing chirality centers can similarly vary between enantiomers, sometimes with serious or even tragic consequences. For several years before 1963 the drug thalidomide was used to alleviate the symptoms of morning sickness in pregnant women. In 1963 it was discovered that thalidomide was the cause of horrible birth defects in many children born subsequent to the use of the drug.



Thalidomide (Thalomid®)



Even later, evidence began to appear indicating that whereas one of the thalidomide enantiomers (the right-handed molecule) has the intended effect of curing morning sickness, the other enantiomer, which was also present in the drug (in an equal amount), may be the cause of the birth defects. The evidence regarding the effects of the two enantiomers is complicated by the fact that, under physiological conditions, the two enantiomers are interconverted. Now, however, thalidomide is approved under highly strict regulations for treatment of some forms of cancer and a serious complication associated with leprosy. Its potential for use against other conditions including AIDS and rheumatoid arthritis is also under investigation. We shall consider other aspects of chiral drugs in Section 5.11.

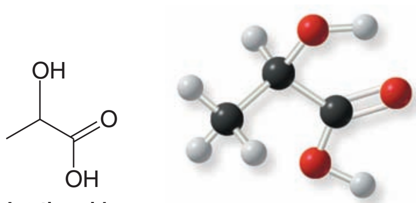
Review Problem 5.5

Which atom is the chirality center of **(a)** limonene and **(b)** of thalidomide?

Review Problem 5.6

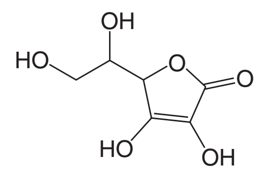
Which atoms in each of the following molecules are chirality centers?

(a)



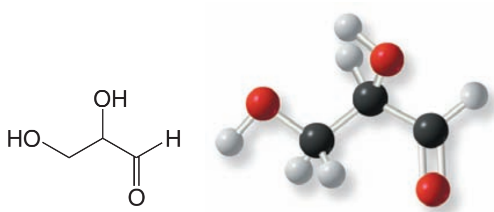
Lactic acid

(c)



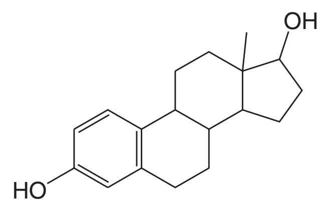
Ascorbic acid (vitamin C)

(b)



Glyceraldehyde

(d)



Estradiol (an estrogen)

5.6 How to Test for Chirality: Planes of Symmetry

The ultimate way to test for molecular chirality is to construct models of the molecule and its mirror image and then determine whether they are superposable. If the two models are superposable, the molecule that they represent is achiral. If the models are not superposable, then the molecules that they represent are chiral. We can apply this test with actual models, as we have just described, or we can apply it by drawing three-dimensional structures and attempting to superpose them in our minds.

There are other aids, however, that will assist us in recognizing chiral molecules. We have mentioned one already: **the presence of a *single* chirality center**. Other aids are based on the absence of certain symmetry elements in the molecule.

- A molecule will not be chiral if it possesses a plane of symmetry.
- A plane of symmetry (also called a mirror plane) is defined as an imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other.

The plane may pass through atoms, between atoms, or both. For example, 2-chloropropane has a plane of symmetry (Fig. 5.8*a*), whereas 2-chlorobutane does not (Fig. 5.8*b*).

- All molecules with a plane of symmetry in their most symmetric conformation are achiral.

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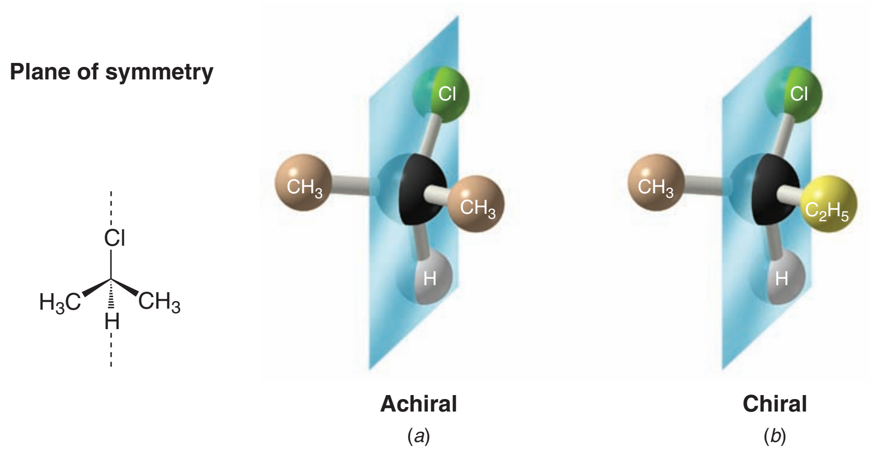
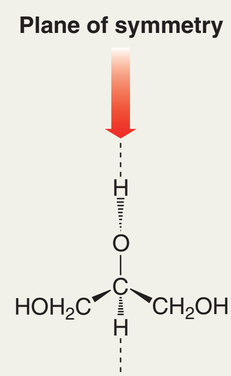


Figure 5.8 *(a)* 2-Chloropropane has a plane of symmetry and is achiral. *(b)* 2-Chlorobutane does not possess a plane of symmetry and is chiral.

Solved Problem 5.2

Glycerol, $CH_2OHCHOHCH_2OH$, is an important constituent in the biological synthesis of fats, as we shall see in Chapter 23. (**a**) Does glycerol have a plane of symmetry? If so, write a three-dimensional structure for glycerol and indicate where it is. (**b**) Is glycerol chiral?

STRATEGY AND ANSWER (**a**) Yes, glycerol has a plane symmetry. Notice we have to choose the proper conformation and orientation of the molecule to see the plane of symmetry. (**b**) No, it is achiral because it has a conformation containing a plane of symmetry.

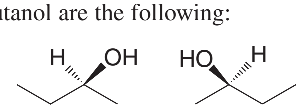


Review Problem 5.7 Which of the objects listed in Review Problem 5.1 possess a plane of symmetry and are, therefore, achiral?

Review Problem 5.8 Write three-dimensional formulas and designate a plane of symmetry for all of the achiral molecules in Review Problem 5.4. (In order to be able to designate a plane of symmetry you may need to write the molecule in an appropriate conformation.)

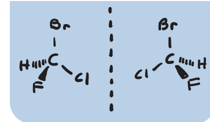
5.7 *Naming Enantiomers: The R,S-System*

The two enantiomers of 2-butanol are the following:



I **II**

If we name these two enantiomers using only the IUPAC system of nomenclature that we have learned so far, both enantiomers will have the same name: 2-butanol (or *sec*-butyl alcohol) (Section 4.3F). This is undesirable because *each compound must have its own distinct name*. Moreover, the name that is given a compound should allow a chemist



who is familiar with the rules of nomenclature to write the structure of the compound from its name alone. Given the name 2-butanol, a chemist could write either structure **I** or structure **II**.

Three chemists, R. S. Cahn (England), C. K. Ingold (England), and V. Prelog (Switzerland), devised a system of nomenclature that, when added to the IUPAC system, solves both of these problems. This system, called the ***R,S*-system** or the Cahn–Ingold–Prelog system, is part of the IUPAC rules.

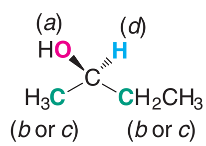
According to this system, one enantiomer of 2-butanol should be designated (*R*)-2-butanol and the other enantiomer should be designated (*S*)-2-butanol. [(*R*) and (*S*) are from the Latin words *rectus* and *sinister*, meaning right and left, respectively.] These molecules are said to have opposite **configurations** at C2.

5.7A How to Assign (*R*) and (*S*) Configurations

We assign (*R*) and (*S*) configurations on the basis of the following procedure.

1. Each of the four groups attached to the chirality center is assigned a **priority** or **preference** *a*, *b*, *c*, or *d*. Priority is first assigned on the basis of the **atomic number** of the atom that is directly attached to the chirality center. The group with the lowest atomic number is given the lowest priority, *d*; the group with next higher atomic number is given the next higher priority, *c*; and so on. (In the case of isotopes, the isotope of greatest atomic mass has highest priority.)

We can illustrate the application of the rule with the 2-butanol enantiomer, **II**:

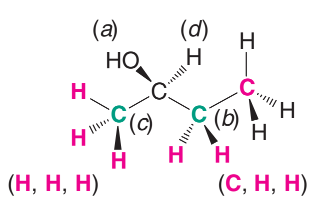


II

Oxygen has the highest atomic number of the four atoms attached to the chirality center and is assigned the highest priority, *a*. Hydrogen has the lowest atomic number and is assigned the lowest priority, *d*. A priority cannot be assigned for the methyl group and the ethyl group by this approach because the atom that is directly attached to the chirality center is a carbon atom in both groups.

2. When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made. *We assign a priority at the first point of difference*.*

When we examine the methyl group of enantiomer **II**, we find that the next set of atoms consists of three hydrogen atoms (**H, H, H**). In the ethyl group of **II** the next set of atoms consists of one carbon atom and two hydrogen atoms (**C, H, H**). Carbon has a higher atomic number than hydrogen, so we assign the ethyl group the higher priority, *b*, and the methyl group the lower priority, *c*, since (**C, H, H**) > (**H, H, H**):



*The rules for a branched chain require that we follow the chain with the highest priority atoms.

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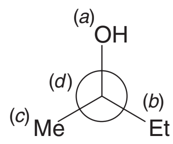
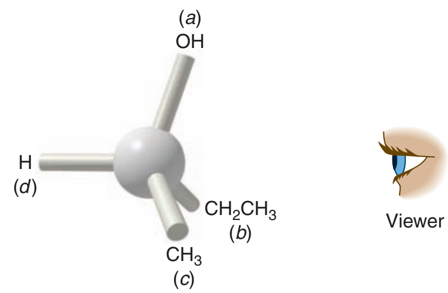
3. We now rotate the formula (or model) so that the group with lowest priority (*d*) is directed away from us:



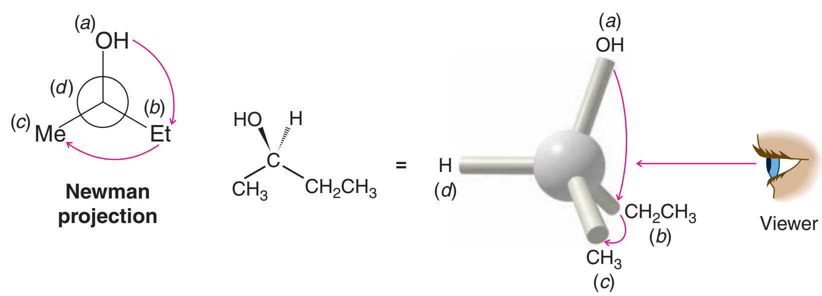
Newman projection



II

Then we trace a path from *a* to *b* to *c*. If, as we do this, the direction of our finger (or pencil) is *clockwise*, the enantiomer is designated (*R*). If the direction is *counterclockwise*, the enantiomer is designated (*S*).

On this basis the 2-butanol enantiomer **II** is (*R*)-2-butanol:

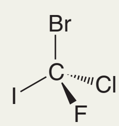


Arrows are clockwise.

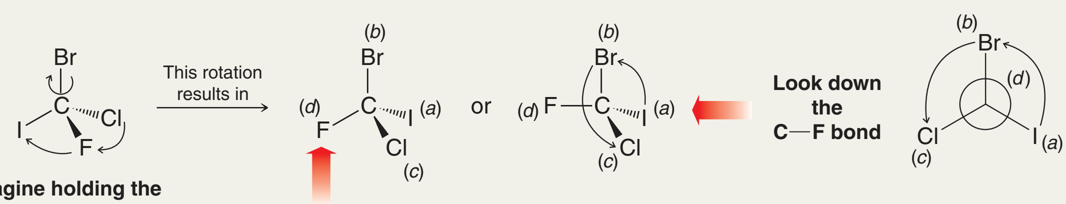
(*R*)-2-Butanol

Solved Problem 5.3

Shown here is an enantiomer of bromochlorofluoroiodomethane. Is it (*R*) or (*S*)?



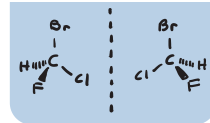
STRATEGY AND ANSWER



Imagine holding the molecule by the Br and rotating it as shown so that the lowest priority group (F, in this case) lies in the plane of the paper.

Lowest priority

The path we trace from highest to lowest is counterclockwise, so the enantiomer is (*S*).



Review Problem 5.9

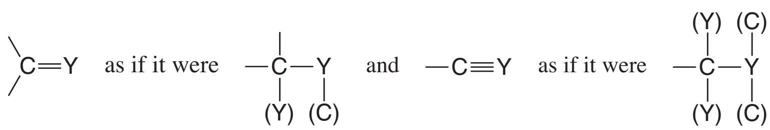
Write the enantiomeric forms of bromochlorofluoromethane and assign each enantiomer its correct (*R*) or (*S*) designation.

Review Problem 5.10

Give (*R*) and (*S*) designations for each pair of enantiomers given as answers to Review Problem 5.4.

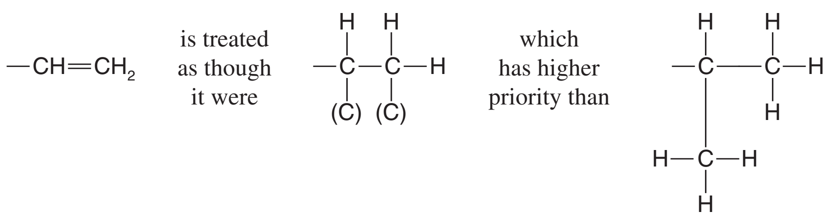
The first three rules of the Cahn–Ingold–Prelog system allow us to make an (*R*) or (*S*) designation for most compounds containing single bonds. For compounds containing multiple bonds one other rule is necessary:

4. Groups containing double or triple bonds are assigned priorities as if both atoms were duplicated or triplicated, that is,

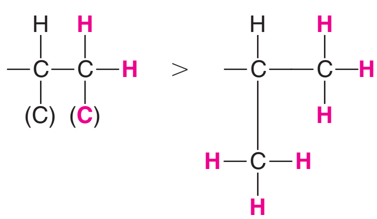


where the symbols in parentheses are duplicate or triplicate representations of the atoms at the other end of the multiple bond.

Thus, the vinyl group, —CH═CH_2, is of higher priority than the isopropyl group, —$CH(CH_3)_2$. That is,



because at the second set of atoms out, the vinyl group (see the following structure) is **C**, **H**, **H**, whereas the isopropyl group along either branch is **H**, **H**, **H**. (At the first set of atoms both groups are the same: **C**, **C**, **H**.)



C, H, H > **H, H, H**
Vinyl group **Isopropyl group**

Other rules exist for more complicated structures, but we shall not study them here.*

Review Problem 5.11

List the substituents in each of the following sets in order of priority, from highest to lowest:

(a) —Cl, —OH, —SH, —H

(b) —CH_3, —CH_2Br, —CH_2Cl, —CH_2OH

(c) —H, —OH, —CHO, —CH_3

(d) —$CH(CH_3)_2$, —$C(CH_3)_3$, —H, —CH═CH_2

(e) —H, —$N(CH_3)_2$, —OCH_3, —CH_3

(f) —OH, —OPO_3H_2, —H, —CHO

*Further information can be found in the Chemical Abstracts Service *Index Guide*.

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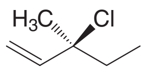
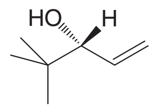
Review Problem 5.12

Assign (*R*) or (*S*) designations to each of the following compounds:

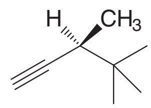
(a)



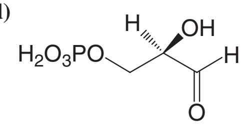
(b)



(c)



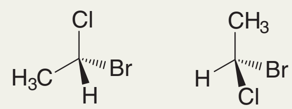
(d)



D-Glyceraldehyde-3-phosphate (a glycolysis intermediate)

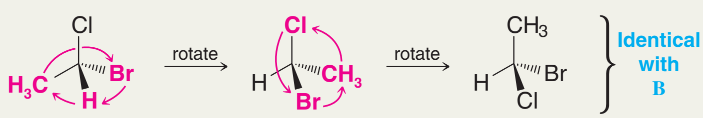
Solved Problem 5.4

Consider the following pair of structures and tell whether they represent enantiomers or two molecules of the same compound in different orientations:



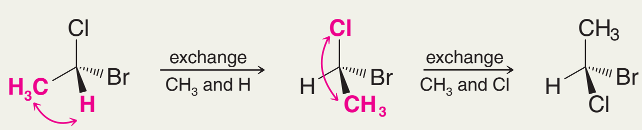
A **B**

STRATEGY One way to approach this kind of problem is to take one structure and, in your mind, hold it by one group. Then rotate the other groups until at least one group is in the same place as it is in the other structure. (Until you can do this easily in your mind, practice with models.) By a series of rotations like this you will be able to convert the structure you are manipulating into one that is either identical with or the mirror image of the other. For example, take **A**, hold it by the Cl atom and then rotate the other groups about the C*—Cl bond until the hydrogen occupies the same position as in **B**. Then hold it by the H and rotate the other groups about the C*—H bond. This will make **B** identical with **A**:



A **A** **A**

Another approach is to recognize that exchanging two groups at the chirality center *inverts the configuration of* that carbon atom and converts a structure *with only one chirality center* into its enantiomer; a second exchange recreates the original molecule. So we proceed this way, keeping track of how many exchanges are required to convert **A** into **B**. In this instance we find that two exchanges are required, and, again, we conclude that **A** and **B** are the same:

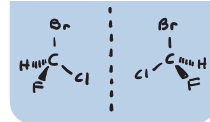


A **B**

A useful check is to name each compound including its (*R,S*) designation. If the names are the same, then the structures are the same. In this instance both structures are (*R*)-1-bromo-1-chloroethane.

Another method for assigning (*R*) and (*S*) configurations using one's hands as chiral templates has been described (Huheey, J. E. *J. Chem. Educ.* **1986**, *63*, 598–600). Groups at a chirality center are correlated from lowest to highest priority with one's wrist, thumb, index finger, and second finger, respectively. With the ring and little finger closed against the palm and viewing one's hand with the wrist away, if the correlation between the chirality center is with the left hand, the configuration is (*S*), and if with the right hand, (*R*).

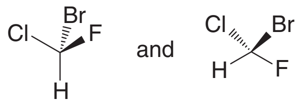
ANSWER **A** and **B** are two molecules of the same compound oriented differently.



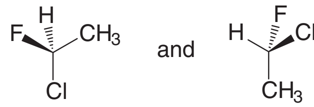
Review Problem 5.13

Tell whether the two structures in each pair represent enantiomers or two molecules of the same compound in different orientations.

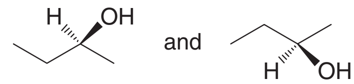
(a)



(b)



(c)



5.8 *Properties of Enantiomers: Optical Activity*

The molecules of enantiomers are not superposable and, on this basis alone, we have concluded that enantiomers are different compounds. How are they different? Do enantiomers resemble constitutional isomers and diastereomers in having different melting and boiling points? The answer is *no*. Pure enantiomers have *identical* melting and boiling points. Do pure enantiomers have different indexes of refraction, different solubilities in common solvents, different infrared spectra, and different rates of reaction with achiral reagents? The answer to each of these questions is also *no*.

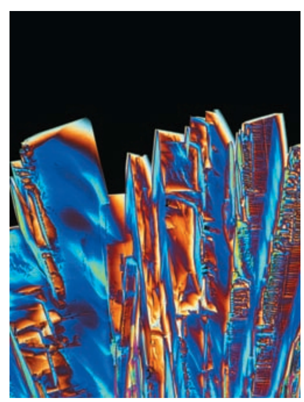
Many of these properties (e.g., boiling points, melting points, and solubilities) are dependent on the magnitude of the intermolecular forces operating between the molecules (Section 2.13), and for molecules that are mirror images of each other these forces will be identical. We can see an example of this if we examine Table 5.1, where boiling points of the 2-butanol enantiomers are listed.

TABLE 5.1 Physical Properties of 2-Butanol and Tartaric Acid Enantiomers

Compound	Boiling Point (bp) or Melting Point (mp)
(*R*)-2-Butanol	99.5°C (bp)
(*S*)-2-Butanol	99.5°C (bp)
(+)-(*R*,*R*)-Tartaric acid	168–170°C (mp)
(−)-(*S*,*S*)-Tartaric acid	168–170°C (mp)
(+/−)-Tartaric acid	210–212°C (mp)

Mixtures of the enantiomers of a compound have different properties than pure samples of each, however. The data in Table 5.1 illustrate this for tartaric acid. The natural isomer, (+)-tartaric acid, has a melting point of 168–170°C, as does its unnatural enantiomer, (−)-tartaric acid. An equal mixture tartaric acid enantiomers, (+/−)-tartaric acid, has a melting point of 210–212°C, however.

Enantiomers show different behavior only when they interact with other chiral substances, including their own enantiomer, as shown by the melting point data above. Enantiomers show different rates of reaction toward other chiral molecules, that is, toward reagents that consist of a single enantiomer or an excess of a single enantiomer. Enantiomers also show different solubilities in solvents that consist of a single enantiomer or an excess of a single enantiomer.



Tartaric acid is found naturally in grapes and many other plants. Crystals of tartaric acid can be sometimes be found with wine.

One easily observable way in which enantiomers differ is in *their behavior toward plane-polarized light*. When a beam of plane-polarized light passes through an enantiomer, the plane of polarization **rotates.** Moreover, separate enantiomers rotate the plane of plane-polarized light equal amounts *but in opposite directions*. Because of their effect on plane-polarized light, separate enantiomers are said to be **optically active compounds**.

In order to understand this behavior of enantiomers, we need to understand the nature of plane-polarized light. We also need to understand how an instrument called a polarimeter operates.

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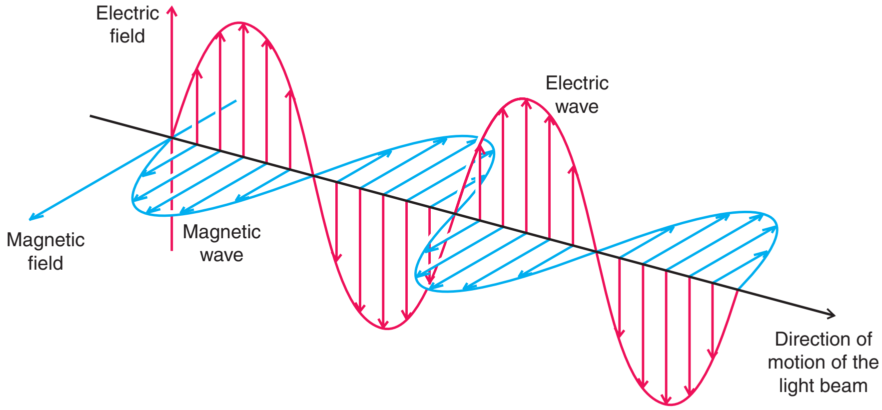


Figure 5.9 The oscillating electric and magnetic fields of a beam of ordinary light in one plane. The waves depicted here occur in all possible planes in ordinary light.

5.8A Plane-Polarized Light

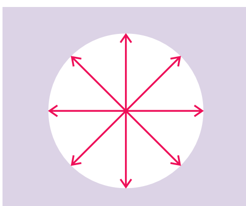
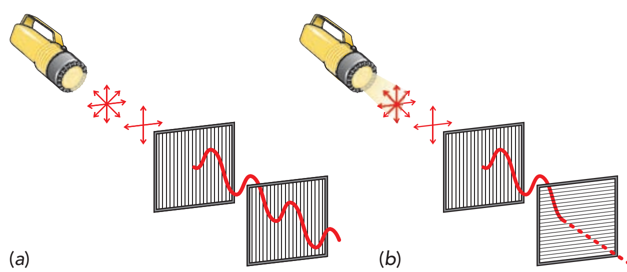


Figure 5.10 Oscillation of the electric field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.

Light is an electromagnetic phenomenon. A beam of light consists of two mutually perpendicular oscillating fields: an oscillating electric field and an oscillating magnetic field (Fig. 5.9).

If we were to view a beam of ordinary light from one end, and if we could actually see the planes in which the electrical oscillations were occurring, we would find that oscillations of the electric field were occurring in all possible planes perpendicular to the direction of propagation (Fig. 5.10). (The same would be true of the magnetic field.)

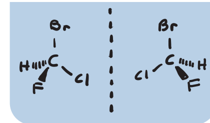
When ordinary light is passed through a polarizer, the polarizer interacts with the electric field so that the electric field of the light that emerges from the polarizer (and the magnetic field perpendicular to it) is oscillating only in one plane. Such light is called **plane-polarized light** (Fig. 5.11*a*). If the plane-polarized beam encounters a filter with perpendicular polarization, the light is blocked (Fig. 5.11*b*). This phenomenon can readily be demonstrated with lenses from a pair of polarizing sunglasses or a sheet of polarizing film (Fig. 5.11*c*).



(*a*) (*b*)

(*c*)

Figure 5.11 *(a)* Ordinary light passing through the first polarizing filter emerges with an electric wave oscillating in only one plane (and a perpendicular magnetic wave plane not shown). When the second filter is aligned with its polarizing direction the same as the first filter, as shown, the plane-polarized light can pass through. *(b)* If the second filter is turned 90°, the plane-polarized light is blocked. *(c)* Two polarizing sunglass lenses oriented perpendicular to each other block the light beam.



5.8B The Polarimeter

The device that is used for measuring the effect of optically active compounds on plane-polarized light is a **polarimeter**. A sketch of a polarimeter is shown in Fig. 5.12. The principal working parts of a polarimeter are (1) a light source (usually a sodium lamp), (2) a polarizer, (3) a cell for holding the optically active substance (or solution) in the light beam, (4) an analyzer, and (5) a scale for measuring the angle (in degrees) that the plane of polarized light has been rotated.

The analyzer of a polarimeter (Fig. 5.12) is nothing more than another polarizer. If the cell of the polarimeter is empty or if an optically *inactive* substance is present, the axes of the plane-polarized light and the analyzer will be exactly parallel when the instrument reads 0°, and the observer will detect the maximum amount of light passing through. If, by contrast, the cell contains an optically active substance, a solution of one enantiomer, for example, the plane of polarization of the light will be rotated as it passes through the cell. In order to detect the maximum brightness of light, the observer will have to rotate the axis of the analyzer in either a clockwise or counterclockwise direction. If the analyzer is rotated in a clockwise direction, the rotation, α (measured in degrees), is said to be positive (+). If the rotation is counterclockwise, the rotation is said to be negative (−). A substance that rotates plane-polarized light in the clockwise direction is also said to be **dextrorotatory**, and one that rotates plane-polarized light in a counterclockwise direction is said to be **levorotatory** (Latin: *dexter*, right, and *laevus*, left).

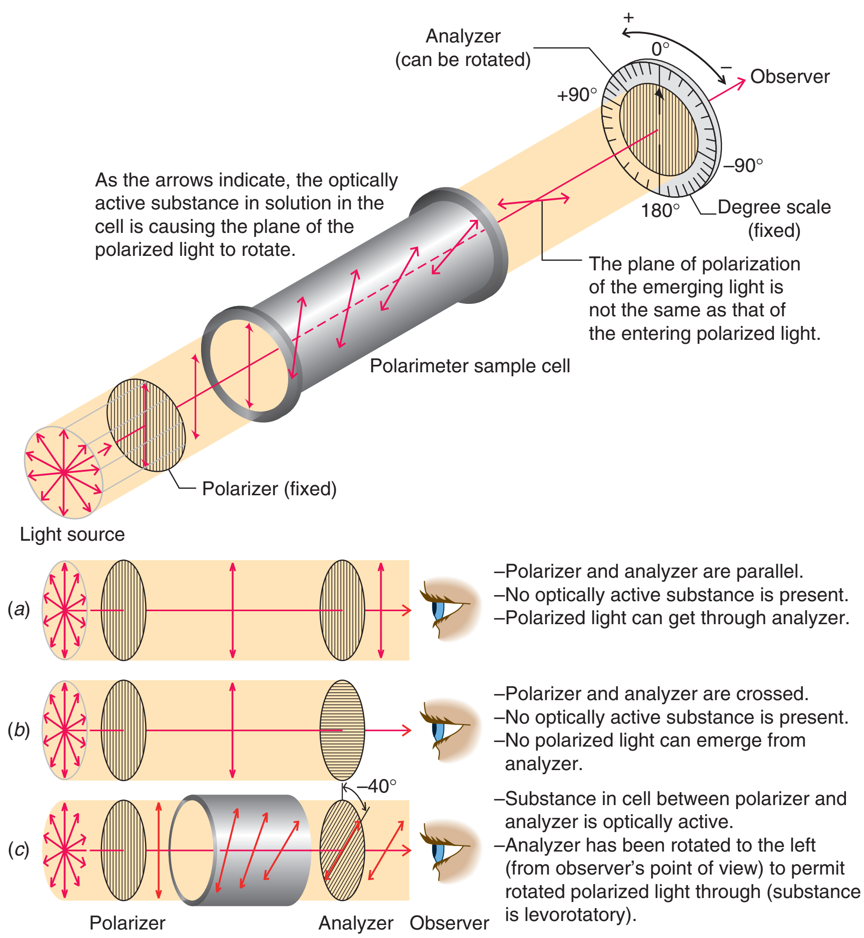


Figure 5.12 The principal working parts of a polarimeter and the measurement of optical rotation. (Reprinted with permission of John Wiley & Sons, Inc. from Holum, J. R., *Organic Chemistry: A Brief Course*, p. 316. Copyright 1975.)

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5.8C Specific Rotation

The number of degrees that the plane of polarization is rotated as the light passes through a solution of an enantiomer depends on the number of chiral molecules that it encounters. This, of course, depends on the length of the tube and the concentration of the enantiomer. In order to place measured rotations on a standard basis, chemists calculate a quantity called the **specific rotation**, $[\alpha]$, by the following equation:

$$[\alpha] = \frac{\alpha}{c \cdot l}$$

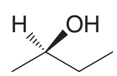
where $[\alpha]$ = the specific rotation
α = the observed rotation
c = the concentration of the solution in grams per milliliter of solution (or density in g mL^{-1} for neat liquids)
l = the length of the cell in decimeters (1 dm = 10 cm)

The specific rotation also depends on the temperature and the wavelength of light that is employed. Specific rotations are reported so as to incorporate these quantities as well. A specific rotation might be given as follows:

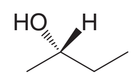
$$[\alpha]_D^{25} = +3.12$$

This means that the D line of a sodium lamp (λ = 589.6 nm) was used for the light, that a temperature of 25°C was maintained, and that a sample containing 1.00 g mL^{-1} of the optically active substance, in a 1-dm tube, produced a rotation of 3.12° in a clockwise direction.*

The specific rotations of (*R*)-2-butanol and (*S*)-2-butanol are given here:

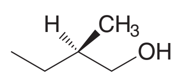


(*R*)-2-Butanol
$[\alpha]_D^{25} = -13.52$

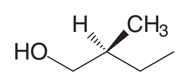


(*S*)-2-Butanol
$[\alpha]_D^{25} = +13.52$

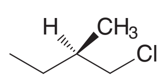
The direction of rotation of plane-polarized light is often incorporated into the names of optically active compounds. The following two sets of enantiomers show how this is done:



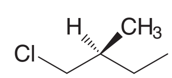
(*R*)-(+)-2-Methyl-1-butanol
$[\alpha]_D^{25} = +5.756$



(*S*)-(−)-2-Methyl-1-butanol
$[\alpha]_D^{25} = -5.756$



(*R*)-(−)-1-Chloro-2-methylbutane
$[\alpha]_D^{25} = -1.64$

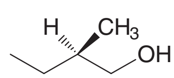


(*S*)-(+)-1-Chloro-2-methylbutane
$[\alpha]_D^{25} = +1.64$

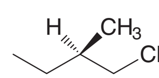
The previous compounds also illustrate an important principle:

- No obvious correlation exists between the (*R*) and (*S*) configurations of enantiomers and the direction [(+) or (−)] in which they rotate plane-polarized light.

(*R*)-(+)-2-Methyl-1-butanol and (*R*)-(−)-1-chloro-2-methylbutane have the same *configuration*; that is, they have the same general arrangement of their atoms in space. They have, however, an opposite effect on the direction of rotation of the plane of plane-polarized light:



Same configuration



(*R*)-(+)-2-Methyl-1-butanol **(*R*)-(−)-1-Chloro-2-methylbutane**

*The magnitude of rotation is dependent on the solvent used when solutions are measured. This is the reason the solvent is specified when a rotation is reported in the chemical literature.

These same compounds also illustrate a second important principle:

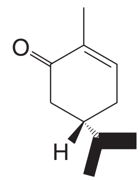
- No necessary correlation exists between the (*R*) and (*S*) designation and the direction of rotation of plane-polarized light.

(*R*)-2-Methyl-1-butanol is dextrorotatory (+), and (*R*)-1-chloro-2-methylbutane is levorotatory (−).

A method based on the measurement of optical rotation at many different wavelengths, called optical rotatory dispersion, has been used to correlate configurations of chiral molecules. A discussion of the technique of optical rotatory dispersion, however, is beyond the scope of this text.

Review Problem 5.14

Shown below is the configuration of (+)-carvone. (+)-Carvone is the principal component of caraway seed oil and is responsible for its characteristic odor. (−)-Carvone, its enantiomer, is the main component of spearmint oil and gives it its characteristic odor. The fact that the carvone enantiomers do not smell the same suggests that the receptor sites in the nose for these compounds are chiral, and that only the correct enantiomer binds well to its particular site (just as a hand requires a glove of the correct chirality for a proper fit). Give the correct (*R*) and (*S*) designations for (+)- and (−)-carvone.



(+)-Carvone

5.9 *The Origin of Optical Activity*

Optical activity is measured by the degree of rotation of plane-polarized light passing through a chiral medium. The theoretical explanation for the origin of optical activity requires consideration of *circularly*-polarized light, however, and its interaction with chiral molecules. While it is not possible to provide a full theoretical explanation for the origin of optical activity here, the following explanation will suffice. A beam of plane-polarized light (Fig. 5.13*a*)

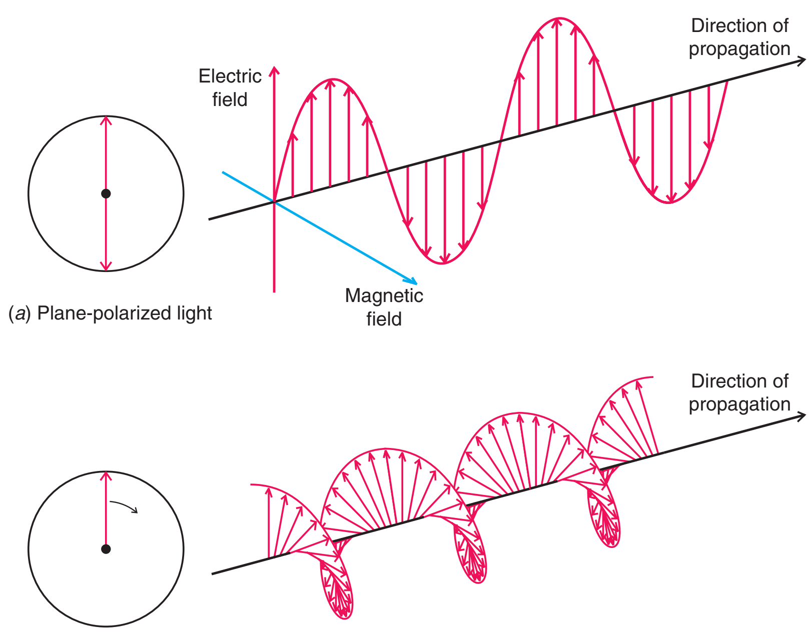


Figure 5.13 *(a)* Plane-polarized light. *(b)* Circularly-polarized light. *(c, next page)* Two circularly-polarized beams counterrotating at the same velocity (in phase) and their vector sum. The net result is like *(a)*. *(d, next page)* Two circularly-polarized beams counterrotating at different velocities, such as after interaction with a chiral molecule, and their vector sum. The net result is like *(b)*. Parts *c* and *d:* From ADAMSON. A TEXTBOOK OF PHYSICAL CHEMISTRY, 3E. © 1986 Brooks/Cole, a part of Cengage Learning, Inc. Reproduced by permission. *www.cengage.com/permissions*

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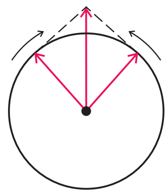
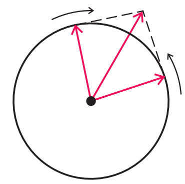


(*c*) Two circularly-polarized beams counter-rotating at the same velocity (in phase), and their vector sum. The net result is like (*a*) on the previous page.



(*d*) Two circularly-polarized beams counter-rotating at different velocities, such as after interaction with a chiral molecule, and their vector sum. The net result is like (*b*) on the previous page.

Figure 5.13 *(continued)*

can be described in terms of circularly-polarized light. A beam of circularly-polarized light rotating in one direction is shown in Fig. 5.13*b*. The vector sum of *two* counterrotating in-phase circularly-polarized beams is a beam of plane-polarized light (Fig. 5.13*c*). The optical activity of chiral molecules results from the fact that the two *counterrotating circularly-polarized beams travel with different velocities through the chiral medium*. As the difference between the two circularly-polarized beams propagates through the sample, their vector sum describes a plane that is progressively rotated (Fig. 5.13*d*). What we measure when light emerges from the sample is the net rotation of the plane-polarized light caused by differences in velocity of the circularly-polarized beam components. The origin of the differing velocities has ultimately to do with interactions between electrons in the chiral molecule and light.

Molecules that are not chiral cause no difference in velocity of the two circularly-polarized beams; hence there is no rotation of the plane of polarized light described by their vector sum. Achiral molecules, therefore, are not optically active.

5.9A Racemic Forms

A sample that consists exclusively or predominantly of one enantiomer causes a net rotation of plane-polarized light. Figure 5.14*a* depicts a plane of polarized light as it encounters a molecule of (*R*)-2-butanol, causing the plane of polarization to rotate slightly in one direction. (For the remaining purposes of our discussion we shall limit our description of polarized light to the resultant plane, neglecting consideration of the circularly-polarized components from which plane-polarized light arises.) Each additional molecule of (*R*)-2-butanol that the beam encounters would cause further rotation in the same direction. If, on the other hand, the mixture contained molecules of (*S*)-2-butanol, each molecule of that enantiomer would cause the plane of polarization to rotate in the opposite direction (Fig. 5.14*b*). If the (*R*) and (*S*) enantiomers were present in equal amounts, there would be no net rotation of the plane of polarized light.

- An equimolar mixture of two enantiomers is called a **racemic mixture** (or **racemate** or **racemic form**). **A racemic mixture causes no net rotation of plane-polarized light**.

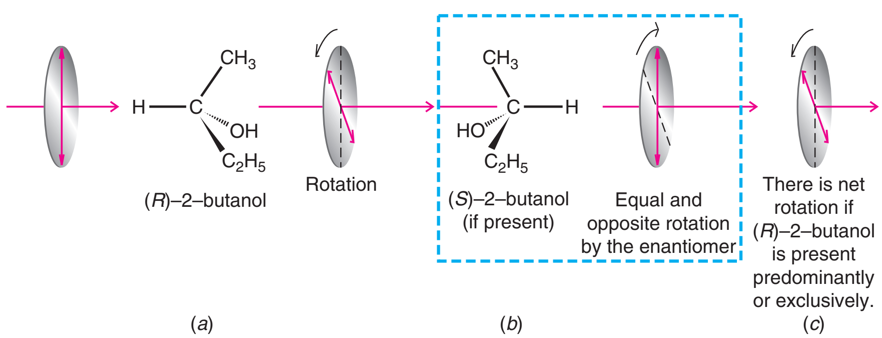


Figure 5.14 *(a)* A beam of plane-polarized light encounters a molecule of (*R*)-2-butanol, a chiral molecule. This encounter produces a slight rotation of the plane of polarization. *(b)* Exact cancellation of this rotation occurs if a molecule of *(S)*-2-butanol is encountered. *(c)* Net rotation of the plane of polarization occurs if *(R)*-2-butanol is present predominantly or exclusively.

In a racemic mixture the effect of each molecule of one enantiomer on the circularly-polarized beam cancels the effect of molecules of the other enantiomer, resulting in no net optical activity.

The racemic form of a sample is often designated as being (±). A racemic mixture of (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol might be indicated as

$$(\pm)\text{-2-butanol} \quad \text{or} \quad (\pm)\text{-}CH_3CH_2CHOHCH_3$$

5.9B Racemic Forms and Enantiomeric Excess

A sample of an optically active substance that consists of a single enantiomer is said to be **enantiomerically pure** or to have an **enantiomeric excess** of 100%. An enantiomerically pure sample of (*S*)-(+)-2-butanol shows a specific rotation of +13.52 ($[\alpha]_D^{25} = +13.52$). On the other hand, a sample of (*S*)-(+)-2-butanol that contains less than an equimolar amount of (*R*)-(−)-2-butanol will show a specific rotation that is less than +13.52 but greater than zero. Such a sample is said to have an *enantiomeric excess* less than 100%. The **enantiomeric excess (ee)**, also known as the **optical purity**, is defined as follows:

$$\%\ \text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

The enantiomeric excess can be calculated from optical rotations:

$$\%\ \text{Enantiomeric excess}^* = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

Let us suppose, for example, that a mixture of the 2-butanol enantiomers showed a specific rotation of +6.76. We would then say that the enantiomeric excess of the (*S*)-(+)-2-butanol is 50%:

$$\text{Enantiomeric excess} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

When we say that the enantiomeric excess of this mixture is 50%, we mean that 50% of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form. Since for the 50% that is racemic the optical rotations cancel one another out, only the 50% of the mixture that consists of the (+) enantiomer contributes to the observed optical rotation. The observed rotation is, therefore, 50% (or one-half) of what it would have been if the mixture had consisted only of the (+) enantiomer.

Solved Problem 5.5

What is the actual stereoisomeric composition of the mixture referred to above?

ANSWER Of the total mixture, 50% consists of the racemic form, which contains equal numbers of the two enantiomers. Therefore, half of this 50%, or 25%, is the (−) enantiomer and 25% is the (+) enantiomer. The other 50% of the mixture (the excess) is also the (+) enantiomer. Consequently, the mixture is 75% (+) enantiomer and 25% (−) enantiomer.

Review Problem 5.15

A sample of 2-methyl-1-butanol (see Section 5.8C) has a specific rotation, $[\alpha]_D^{25}$, equal to +1.151. **(a)** What is the percent enantiomeric excess of the sample? **(b)** Which enantiomer is in excess, the (*R*) or the (*S*)?

5.10 *The Synthesis of Chiral Molecules*

5.10A Racemic Forms

Reactions carried out with achiral reactants can often lead to *chiral* products. In the absence of any chiral influence from a catalyst, reagent, or solvent, the outcome of such a reaction is a racemic mixture. In other words, the chiral product is obtained as a 50:50 mixture of enantiomers.

*This calculation should be applied to a single enantiomer or to mixtures of enantiomers only. It should not be applied to mixtures in which some other compound is present.

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An example is the synthesis of 2-butanol by the nickel-catalyzed hydrogenation of butanone. In this reaction the hydrogen molecule adds across the carbon–oxygen double bond in much the same way that it adds to a carbon–carbon double bond.

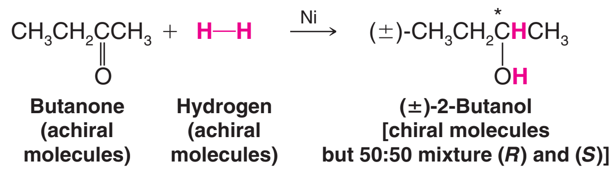


Figure 5.15 illustrates the stereochemical aspects of this reaction. Because butanone is achiral, there is no difference in presentation of either face of the molecule to the surface of the metal catalyst. The two faces of the trigonal planar carbonyl group interact with the metal surface with equal probability. Transfer of the hydrogen atoms from the metal to the carbonyl group produces a chirality center at carbon 2. Since there has been no chiral influence in the reaction pathway, the product is obtained as a racemic mixture of the two enantiomers, (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol.

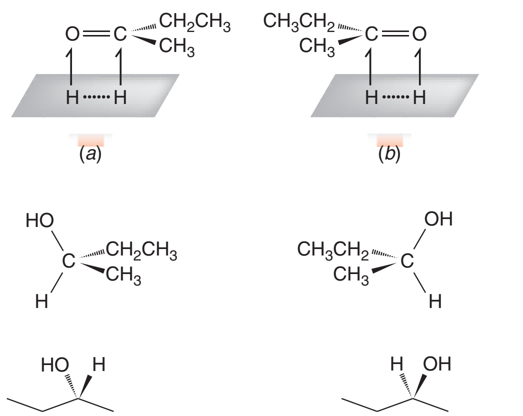


Figure 5.15 The reaction of butanone with hydrogen in the presence of a nickel catalyst. The reaction rate by path *(a)* is equal to that by path *(b)*. *(R-15)*-(−)-2-Butanol and *(S)*-(+)-2-butanol are produced in equal amounts, as a racemate.

We shall see that when reactions like this are carried out in the presence of a chiral influence, such as an enzyme or chiral catalyst, the result is usually not a racemic mixture.

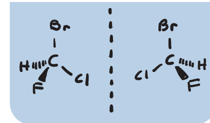
5.10B Stereoselective Syntheses

Stereoselective reactions are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed.

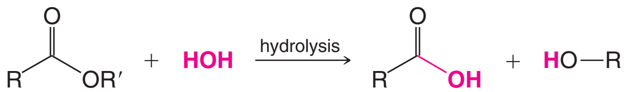
- If a reaction produces preferentially one enantiomer over its mirror image, the reaction is said to be **enantioselective**.
- If a reaction leads preferentially to one diastereomer over others that are possible, the reaction is said to be **diastereoselective**.

For a reaction to be either enantioselective or diastereoselective, a chiral reagent, catalyst, or solvent must assert an influence on the course of the reaction.

In nature, where most reactions are stereoselective, the chiral influences come from protein molecules called **enzymes**. Enzymes are biological catalysts of extraordinary efficiency. Not only do they have the ability to cause reactions to take place much more rapidly than they would otherwise, they also have the ability to assert a *dramatic chiral influence* on a reaction. Enzymes do this because they, too, are chiral, and they possess an active site where the reactant molecules are momentarily bound while the reaction takes place. The active site is chiral (See Fig. 5.7), and only one enantiomer of a chiral reactant fits it properly and is able to undergo the reaction.

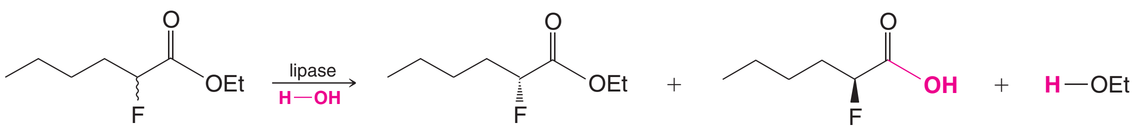


Many enzymes have found use in the organic chemistry laboratory, where organic chemists take advantage of their properties to bring about stereoselective reactions. One of these is an enzyme called **lipase**. Lipase catalyzes a reaction called **hydrolysis**, whereby an ester (Section 2.10B) reacts with a molecule of water to produce a carboxylic acid and an alcohol.



Ester **Water** **Carboxylic acid** **Alcohol**

If the starting ester is chiral and present as a mixture of its enantiomers, the lipase enzyme reacts selectively with one enantiomer to release the corresponding chiral carboxylic acid and an alcohol, while the other ester enantiomer remains unchanged or reacts much more slowly. The result is a mixture that consists predominantly of one stereoisomer of the reactant and one stereoisomer of the product, which can usually be separated easily on the basis of their different physical properties. Such a process is called a **kinetic resolution**, where the rate of a reaction with one enantiomer is different than with the other, leading to a preponderance of one product stereoisomer. We shall say more about the resolution of enantiomers in Section 5.16. The following hydrolysis is an example of a kinetic resolution using lipase:



Ethyl (±)-2-fluorohexanoate [an ester that is a racemate of (*R*) and (*S*) forms]

Ethyl (*R*)-(+)-2-fluorohexanoate (>99% enantiomeric excess)

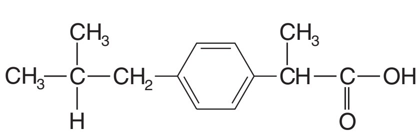
(*S*)-(−)-2-Fluorohexanoic acid (>69% enantiomeric excess)

Other enzymes called hydrogenases have been used to effect enantioselective versions of carbonyl reductions like that in Section 5.10A. We shall have more to say about the stereoselectivity of enzymes in Chapter 12.

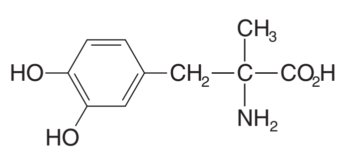
5.11 *Chiral Drugs*

The U.S. Food and Drug Administration and the pharmaceutical industry are very interested in the production of chiral drugs, that is, drugs that contain a single enantiomer rather than a racemate. The antihypertensive drug **methyldopa** (Aldomet), for example, owes its effect exclusively to the (*S*) isomer. In the case of **penicillamine**, the (*S*) isomer is a highly potent therapeutic agent for primary chronic arthritis, while the (*R*) isomer has no therapeutic action and is highly toxic. The anti-inflammatory agent **ibuprofen** (Advil, Motrin, Nuprin) is marketed as a racemate even though only the (*S*) enantiomer is the active agent. The (*R*) isomer of ibuprofen has no anti-inflammatory action and is slowly converted to the (*S*) isomer in the body. A formulation of ibuprofen based on solely the (*S*) isomer, however, would be more effective than the racemate.

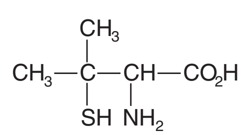
At the beginning of this chapter we showed the formulas for two enantiomeric drugs, Darvon and Novrad. Darvon (also called dextropropoxyphene) is a painkiller. Novrad (levopropoxyphene) is a cough suppressant.



Ibuprofen



Methyldopa



Penicillamine

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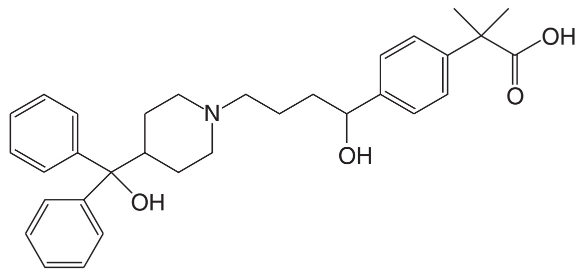
Review Problem 5.16

Write three-dimensional formulas for the (*S*) isomers of **(a)** methyldopa, **(b)** penicillamine, and **(c)** ibuprofen.

Review Problem 5.17

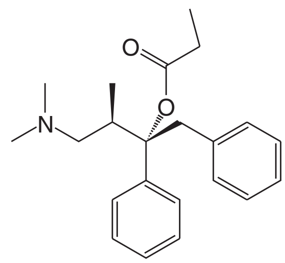
The antihistamine Allegra (fexofenadine) has the following structural formula. For any chirality centers in fexofenadine, draw a substructure that would have an (*R*) configuration.



Fexofenadine (Allegra)

Review Problem 5.18

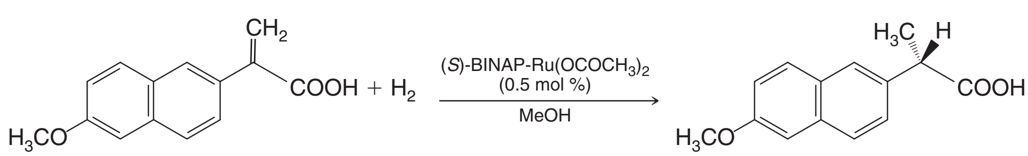
Assign the (*R,S*) configuration at each chirality center in Darvon (dextropropoxyphene).



Darvon

There are many other examples of drugs like these, including drugs where the enantiomers have distinctly different effects. The preparation of enantiomerically pure drugs, therefore, is one factor that makes stereoselective synthesis (Section 5.10B) and the resolution of racemic drugs (separation into pure enantiomers, Section 5.16) major areas of research today.

Underscoring the importance of stereoselective synthesis is the fact that the 2001 Nobel Prize in Chemistry was given to researchers who developed reaction catalysts that are now widely used in industry and academia. William Knowles (Monsanto Company, retired) and Ryoji Noyori (Nagoya University) were awarded half of the prize for their development of reagents used for catalytic stereoselective hydrogenation reactions. The other half of the prize was awarded to Barry Sharpless (Scripps Research Institute) for development of catalytic stereoselective oxidation reactions (see Chapter 11). An important example resulting from the work of Noyori and based on earlier work by Knowles is a synthesis of the anti-inflammatory agent **naproxen,** involving a stereoselective catalytic hydrogenation reaction:



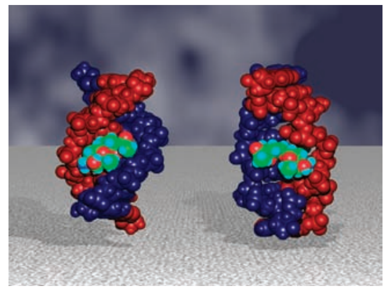
(*S*)-Naproxen
(an anti-inflammatory agent)
(92% yield, 97% ee)

The hydrogenation catalyst in this reaction is an organometallic complex formed from ruthenium and a chiral organic ligand called (*S*)-BINAP. The reaction itself is truly remarkable because it proceeds with excellent enantiomeric excess (97%) and in very high yield (92%). We will have more to say about BINAP ligands and the origin of their chirality in Section 5.18.

THE CHEMISTRY OF . . .

Selective Binding of Drug Enantiomers to Left- and Right-Handed Coiled DNA

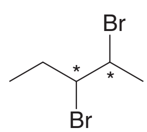
Would you like left- or right-handed DNA with your drug? That's a question that can now be answered due to the recent discovery that each enantiomer of the drug daunorubicin selectively binds DNA coiled with opposite handedness. (+)-Daunorubicin binds selectively to DNA coiled in the typical right-handed conformation (B-DNA). (−)-Daunorubicin binds selectively to DNA coiled in the left-handed conformation (Z-DNA). Furthermore, daunorubicin is capable of inducing conformational changes in DNA from one coiling direction to the other, depending on which coiling form is favored when a given daunorubicin enantiomer binds to the DNA. It has long been known that DNA adopts a number of secondary and tertiary structures, and it is presumed that some of these conformations are involved in turning on or off transcription of a given section of DNA. The discovery of specific interactions between each daunorubicin enantiomer and the left- and right-handed coil forms of DNA will likely assist in design and discovery of new drugs with anticancer or other activities.



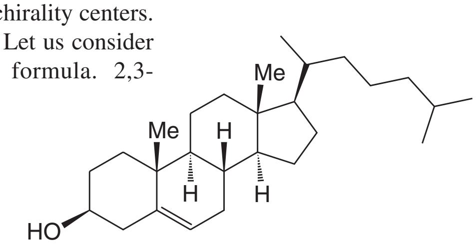
Enantiomeric forms of daunorubicin bind with DNA and cause it to coil with opposite handedness. [Graphic courtesy John O. Trent, Brown Cancer Center, Department of Medicine, University of Louisville, KY. Based on work from Qu, X. Trent, J.O., Fokt, I., Priebe, W., and Chaires, J.B., *Allosteric, Chiral-Selective Drug Building to DNA, Proc. Natl. Acad. Sci. U.S.A.*, 2000 (Oct. 24): 97(22), 12032–12037.]

5.12 *Molecules with More than One Chirality Center*

So far we have mainly considered chiral molecules that contain only one chirality center. Many organic molecules, especially those important in biology, contain more than one chirality center. Cholesterol (Section 23.4B), for example, contains eight chirality centers. (Can you locate them?) We can begin, however, with simpler molecules. Let us consider 2,3-dibromopentane, shown here in a two-dimensional bond-line formula. 2,3-Dibromopentane has two chirality centers:



2,3-Dibromopentane



Cholesterol

A useful rule gives the maximum number of stereoisomers:

- In compounds whose stereoisomerism is due to chirality centers, ***the total number of stereoisomers will not exceed 2^n, where n is equal to the number of chirality centers***.

For 2,3-dibromopentane we should not expect more than four stereoisomers ($2^2 = 4$).

Our next task is to write three-dimensional bond-line formulas for the possible stereoisomers. When doing so it is helpful to follow certain conventions. First, it is generally best to write as many carbon atoms in the plane of the paper as possible. Second, when needing to compare the stereochemistry at adjacent carbon atoms, we usually draw the molecule in a fashion that shows eclipsing interactions, even though this would not be the most stable conformation of the molecule. We do so because, as we shall see later, eclipsed conformations make it easy for us to recognize planes of symmetry when they are present. (We do not mean to imply, however, that eclipsed conformations are the most stable ones—they most certainly are not. It is important to remember that free rotation is possible about single bonds, and that molecules are constantly changing conformations.) Third, if we need to draw the enantiomer

Helpful Hint

Cholesterol, having eight chirality centers, hypothetically could exist in 2^8 (256) stereoisomeric forms, yet biosynthesis via enzymes produces only *one* stereoisomer.

Helpful Hint

Useful conventions when writing three-dimensional formulas

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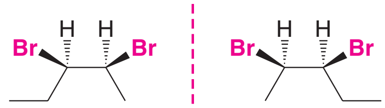
of the first stereoisomer, we can easily do so by drawing a mirror image of the first formula, using as our guide an imaginary mirror perpendicular to the page and *between* the molecules.

The following are two three-dimensional bond-line formulas for 2,3-dibromopentane. Notice that in drawing these formulas we have followed the conventions above.

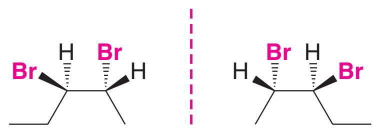


1 **2**

Mirror

Since structures **1** and **2** are not superposable, they represent different compounds. Since structures **1** and **2** differ only in the arrangement of their atoms in space, they represent stereoisomers. Structures **1** and **2** are also mirror images of each other; thus **1** and **2** represent a pair of enantiomers.

Structures **1** and **2** are not the only ones possible for 2,3-dibromopentane, however. If we interchange the bromine and hydrogen at C2 (invert the configuration), we find that we have **3**, which has a different structural formula than either **1** or **2**. Furthermore, we can write a formula for a structure (**4**) that is a nonsuperposable mirror image of **3**, and which is also different from **1** and **2**.



3 **4**

Mirror

Structures **3** and **4** correspond to another pair of enantiomers. Structures **1–4** are all different, so there are, in total, four stereoisomers of 2,3-dibromopentane. Essentially what we have done above is to write all the possible structures that result by successively interchanging two groups at all chirality centers. At this point you should convince yourself that there are no other stereoisomers by writing other structural formulas. You will find that rotation about the single bonds (or of the entire structure) of any other arrangement of the atoms will cause the structure to become superposable with one of the structures that we have written here. Better yet, using different colored balls, make molecular models as you work this out.

The compounds represented by structures **1–4** are all optically active compounds. Any one of them, if placed separately in a polarimeter, would show optical activity.

The compounds represented by structures **1** and **2** are enantiomers. The compounds represented by structures **3** and **4** are also enantiomers. But what is the isomeric relation between the compounds represented by **1** and **3**?

We can answer this question by observing that **1** and **3** *are stereoisomers* and that they *are not mirror images of each other*. They are, therefore, *diastereomers*.

- Diastereomers have different physical properties—different melting points and boiling points, different solubilities, and so forth.

1 **2** **3** **4**

Review Problem 5.19

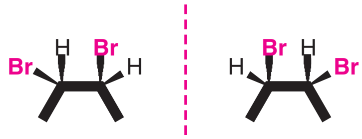
(a) If **3** and **4** are enantiomers, what are **1** and **4**? **(b)** What are **2** and **3**, and **2** and **4**? **(c)** Would you expect **1** and **3** to have the same melting point? **(d)** The same boiling point? **(e)** The same vapor pressure?

5.12A Meso Compounds

A structure with two chirality centers does not always have four possible stereoisomers. Sometimes there are only *three*. As we shall see:

- Some molecules are achiral even though they contain chirality centers.

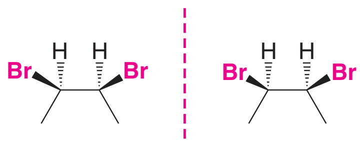
To understand this, let us write stereochemical formulas for 2,3-dibromobutane. We begin in the same way as we did before. We write formulas for one stereoisomer and for its mirror image:



A **B**

Structures **A** and **B** are nonsuperposable and represent a pair of enantiomers.

When we write the new structure **C** (see below) and its mirror image **D**, however, the situation is different. *The two structures are superposable*. This means that **C** and **D** do not represent a pair of enantiomers. Formulas **C** and **D** represent identical orientations of the same compound:



C **D**

Helpful Hint

If a molecule has an internal plane of symmetry it is achiral.

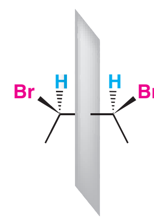


Figure 5.16 The plane of symmetry of *meso*-2,3-dibromobutane. This plane divides the molecule into halves that are mirror images of each other.

The molecule represented by structure **C** (or **D**) is not chiral even though it contains two chirality centers.

- A **meso compound** is an achiral molecule that contains chirality centers. Meso compounds are not optically active.

The ultimate test for molecular chirality is to construct a model (or write the structure) of the molecule and then test whether or not the model (or structure) is superposable on its mirror image. If it is, the molecule is achiral: If it *is not*, the molecule is chiral.

We have already carried out this test with structure **C** and found that it is achiral. We can also demonstrate that **C** is achiral in another way. Figure 5.16 shows that structure **C** *has an internal plane of symmetry* (Section 5.6).

The following two problems relate to compounds **A–D** in the preceding paragraphs.

Review Problem 5.20

Which of the following would be optically active?

(a) A pure sample of **A**

(b) A pure sample of **B**

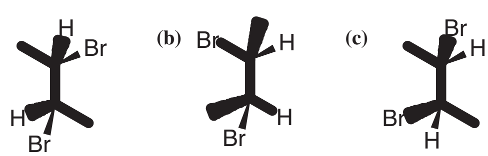
(c) A pure sample of **C**

(d) An equimolar mixture of **A** and **B**

Review Problem 5.21

The following are formulas for three compounds, written in noneclipsed conformations. In each instance tell which compound (**A**, **B**, or **C** above) each formula represents.

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



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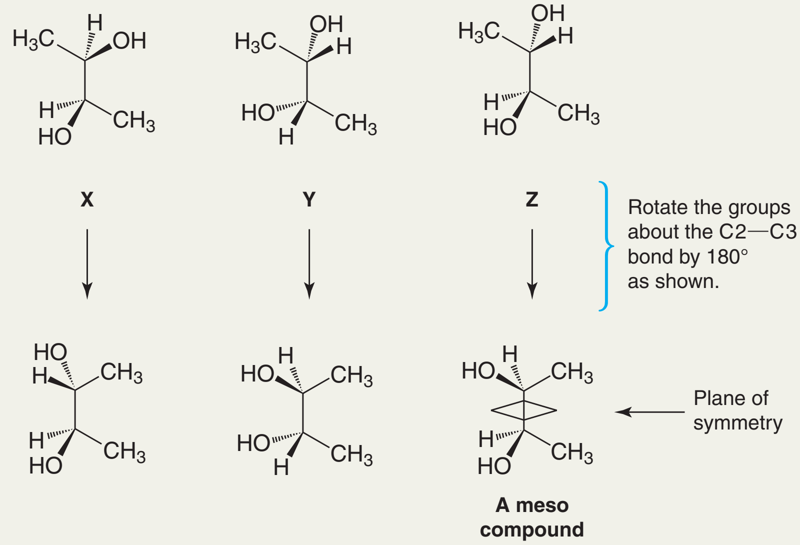
Solved Problem 5.6

Which of the following is a meso compound?

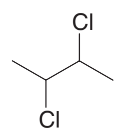
STRATEGY AND ANSWER In each molecule, rotating the groups joined by the C2—C3 bond by 180° brings the two methyl groups into comparable position. In the case of compound Z, a plane of symmetry results, and therefore, Z is a meso compound. No plane of symmetry is possible in X and Y.



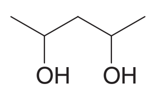
Review Problem 5.22

Write three-dimensional formulas for all of the stereoisomers of each of the following compounds. Label pairs of enantiomers and label meso compounds.

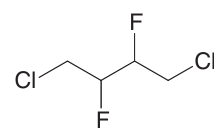
(a)



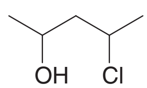
(b)



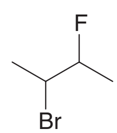
(c)



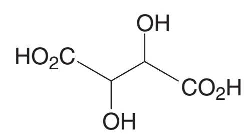
(d)



(e)



(f)

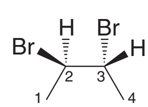


Tartaric acid

5.12B How to Name Compounds with More than One Chirality Center

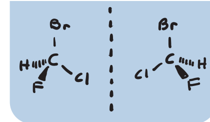
If a compound has more than one chirality center, we analyze each center separately and decide whether it is (*R*) or (*S*). Then, using numbers, we tell which designation refers to which carbon atom.

Consider stereoisomer **A** of 2,3-dibromobutane:

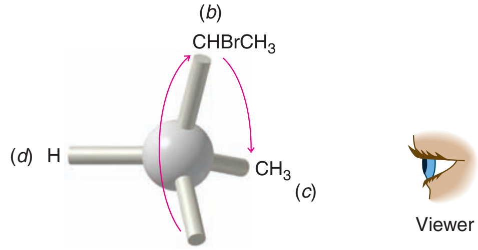


A

2,3-Dibromobutane



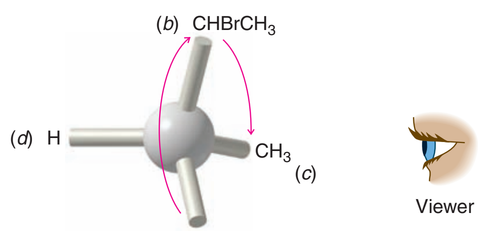
When this formula is rotated so that the group of lowest priority attached to C2 is directed away from the viewer, it resembles the following:



(*R*) Configuration

The order of progression from the group of highest priority to that of next highest priority (from —Br, to —$CHBrCH_3$, to —CH_3) is clockwise. So C2 has the (*R*) configuration.

When we repeat this procedure with C3, we find that C3 also has the (*R*) configuration:



(*R*) Configuration

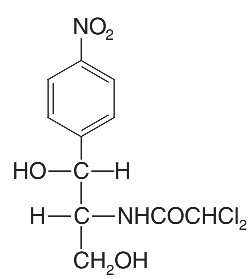
Compound **A**, therefore, is (2*R*,3*R*)-2,3-dibromobutane.

Give names that include (*R*) and (*S*) designations for compounds **B** and **C** in Section 5.12A. *Review Problem 5.23*

Give names that include (*R*) and (*S*) designations for your answers to Review Problem 5.22. *Review Problem 5.24*

Review Problem 5.25

Chloramphenicol (at right) is a potent antibiotic, isolated from *Streptomyces venezuelae*, that is particularly effective against typhoid fever. It was the first naturally occurring substance shown to contain a nitro (—NO_2) group attached to an aromatic ring. Both chirality centers in chloramphenicol are known to have the (*R*) configuration. Identify the two chirality centers and write a three-dimensional formula for chloramphenicol.



Chloramphenicol

5.13 *Fischer Projection Formulas*

So far in writing structures for chiral molecules we have only used formulas that show three dimensions with solid and dashed wedges, and we shall largely continue to do so until we study carbohydrates in Chapter 22. The reason is that formulas with solid and dashed wedges unambiguously show three dimensions, and they can be manipulated on paper in any way that we wish so long as we do not break bonds. Their use, moreover, teaches us to see molecules (in our mind's eye) in three dimensions, and this ability will serve us well.

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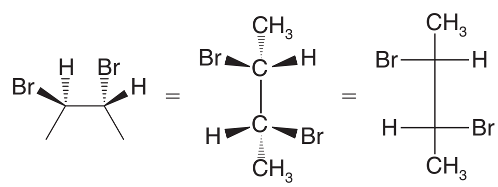
Chemists, however, sometimes use formulas called **Fischer projections** to show three dimensions in chiral molecules such as acyclic carbohydrates. Fischer projection formulas are useful in cases where there are chirality centers at several adjacent carbon atoms, as is often the case in carbohydrates. Use of Fischer projection formulas requires rigid adherence to certain conventions, however. **Used carelessly, these projection formulas can easily lead to incorrect conclusions**.

5.13A How to Draw and Use Fischer Projections

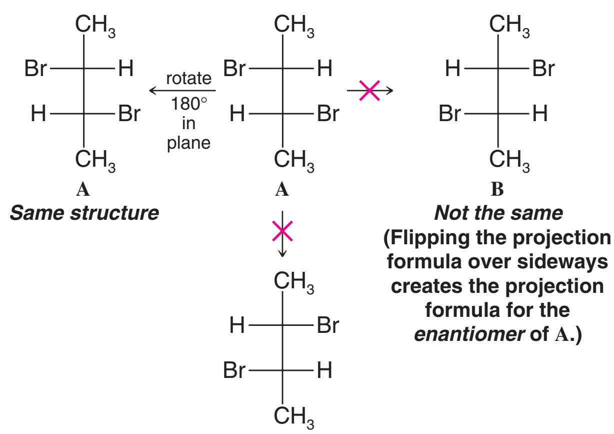
Let us consider how we would relate a three-dimensional formula for 2,3-dibromobutane using solid and dashed wedges to the corresponding Fischer projection formula. First, it is necessary to note that in Fischer projections the carbon chain is always drawn from top to bottom, rather than side to side as is often the case with bond-line formulas. We consider the molecule in a conformation that has eclipsing interactions between the groups at each carbon. For 2,3-dibromobutane we turn the bond-line formula so that the carbon chain runs up and down and we orient it so that groups attached to the main carbon chain project out of the plane like a bow tie. The carbon–carbon bonds of the chain, therefore, lie either in the plane of the paper or project behind it. Then to draw the Fischer projection we simply "project" all of the bonds onto the paper, replacing all solid and dashed wedges with ordinary lines. Having done this, the vertical line of the formula now represents the carbon chain, each point of intersection between the vertical line and a horizontal line represents a carbon atom in the chain, and we understand the horizontal lines to be bonds that project out toward us.



A **A** **A**

Fischer projection formula

To test the superposability of two structures represented by Fischer projections we are allowed to rotate them in the plane of the paper by 180°, *but by no other angle*. We must always keep the Fischer projection formulas in the plane of the paper, and **we are not allowed to flip them over**. If we flip a Fischer projection over, the horizontal bonds project behind the plane instead of in front, and every configuration would be *misrepresented* as the opposite of what was intended.

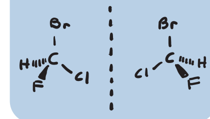


Not the same **(Flipping the projection formula over sideways creates the projection formula for the** ***enantiomer*** **of A.)**

Not the same **(Flipping the projection formula over end for end creates the projection formula for the** ***enantiomer*** **of A.)**

Helpful Hint

Build handheld models of **A** and **B** and relate them to the Fischer projections shown here.



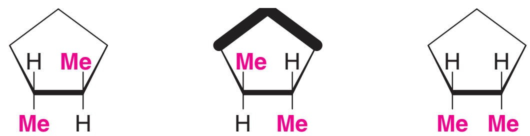
Because Fischer projections must be used with such care, we introduce them now only so that you can understand Fischer projections when you see them in the context of other courses. Our emphasis for most of this book will be on the use of solid and dashed wedges to represent three-dimensional formulas (or chair conformational structures in the case of cyclohexane derivatives), except in Chapter 22 when we will use Fischer projections again in our discussion of carbohydrates. If your instructor wishes to utilize Fischer projections further, you will be so advised.

Review Problem 5.26

(**a**) Give the (*R,S*) designations for each chirality center in compound **A** and for compound **B**. (**b**) Write the Fischer projection formula for a compound **C** that is the diastereomer of **A** and **B**. (**c**) Would **C** be optically active?

5.14 *Stereoisomerism of Cyclic Compounds*

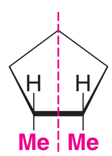
Cyclopentane derivatives offer a convenient starting point for a discussion of the stereoisomerism of cyclic compounds. For example, 1,2-dimethylcyclopentane has two chirality centers and exists in three stereoisomeric forms **5**, **6**, and **7**:



Enantiomers — Meso compound

5 **6** **7**

The trans compound exists as a pair of enantiomers **5** and **6**. *cis*-1,2-Dimethylcyclopentane (**7**) is a meso compound. It has a plane of symmetry that is perpendicular to the plane of the ring:



Plane of symmetry

7

Review Problem 5.27

(a) Is *trans*-1,2-dimethylcyclopentane (**5**) superposable on its mirror image (i.e., on compound **6**)? **(b)** Is *cis*-1,2-dimethylcyclopentane (**7**) superposable on its mirror image? **(c)** Is *cis*-1,2-dimethylcyclopentane a chiral molecule? **(d)** Would *cis*-1,2-dimethylcyclopentane show optical activity? **(e)** What is the stereoisomeric relationship between **5** and **7**? **(f)** Between **6** and **7**?

Review Problem 5.28

Write structural formulas for all of the stereoisomers of 1,3-dimethylcyclopentane. Label pairs of enantiomers and meso compounds if they exist.

5.14A Cyclohexane Derivatives

1,4-Dimethylcyclohexanes If we examine a formula of 1,4-dimethylcyclohexane, we find that it does not contain any chirality centers. However, it does have two stereogenic centers. As we learned in Section 4.13, 1,4-dimethylcyclohexane can exist as cis–trans isomers. The cis and trans forms (Fig. 5.17) are *diastereomers*. Neither compound is chiral and, therefore, neither is optically active. Notice that both the cis and trans forms of 1,4-dimethylcyclohexane have a plane of symmetry.

Helpful Hint

Build handheld molecular models of the 1,4-, 1,3-, and 1,2-dimethylcyclohexane isomers discussed here and examine their stereochemical properties. Experiment with flipping the chairs and also switching between cis and trans isomers.

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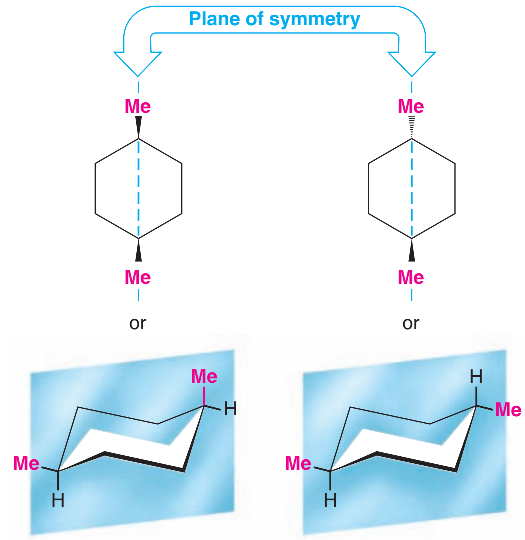


***cis*-1,4-Dimethylcyclohexane** | ***trans*-1,4-Dimethylcyclohexane**

Figure 5.17 The cis and trans forms of 1,4-dimethylcyclohexane are diastereomers of each other. Both compounds are achiral, as the internal plane of symmetry (blue) shows for each.

1,3-Dimethylcyclohexanes 1,3-Dimethylcyclohexane has two chirality centers; we can, therefore, expect as many as four stereoisomers ($2^2 = 4$). In reality there are only three. *cis*-1,3-Dimethylcyclohexane has a plane of symmetry (Fig. 5.18) and is achiral.

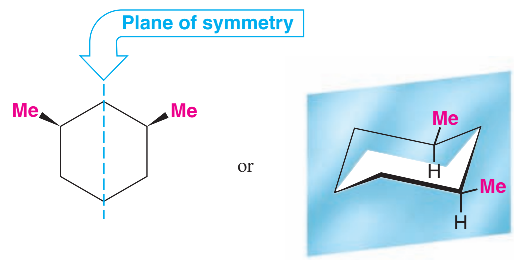
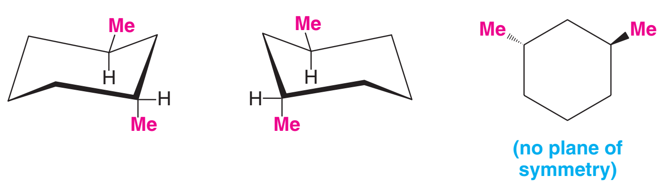


Figure 5.18 *cis*-1,3-Dimethylcyclohexane has a plane of symmetry, shown in blue, and is therefore achiral.

trans-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers (Fig. 5.19). You may want to make models of the *trans*-1,3-dimethylcyclohexane enantiomers. Having done so, convince yourself that they cannot be superposed as they stand and that they cannot be superposed after one enantiomer has undergone a ring flip.



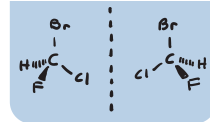
(*a*) (*b*) (*c*)

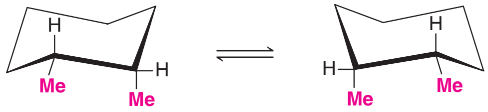
Figure 5.19 *trans*-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers. The two structures *(a* and *b)* shown here are not superposable as they stand, and flipping the ring of either structure does not make it superposable on the other. *(c)* A simplified representation of *(b)*.

1,2-Dimethylcyclohexanes 1,2-Dimethylcyclohexane also has two chirality centers, and again we might expect as many as four stereoisomers. Indeed there are four, but we find that we can *isolate* only *three* stereoisomers. *trans*-1,2-Dimethylcyclohexane (Fig. 5.20) exists as a pair of enantiomers. Its molecules do not have a plane of symmetry.

(*a*) (*b*)

Figure 5.20 *trans*-1,2-Dimethylcyclohexane has no plane of symmetry and exists as a pair of enantiomers (*a* and *b*). [Notice that we have written the most stable conformations for *(a)* and *(b)*. A ring flip of either *(a)* or *(b)* would cause both methyl groups to become axial.]





(*c*) (*d*)

Figure 5.21 *cis*-1,2-Dimethylcyclohexane exists as two rapidly interconverting chair conformations *(c)* and *(d)*.

cis-1,2-Dimethylcyclohexane, shown in Fig. 5.21, presents a somewhat more complex situation. If we consider the two conformational structures (*c*) and (*d*), we find that these two mirror-image structures are not identical. Neither has a plane of symmetry and each is a chiral molecule, *but they are interconvertible by a ring flip*. Therefore, although the two structures represent enantiomers, *they cannot be separated* because they rapidly interconvert even at low temperature. They simply represent *different conformations of the same compound*. Therefore, structures (*c*) and (*d*) are not configurational stereoisomers; they are **conformational stereoisomers** (see Section 4.9A). This means that at normal temperatures there are only three *isolable stereoisomers* of 1,2-dimethylcyclohexane.

As we shall see later, there are some compounds whose conformational stereoisomers *can* be isolated in enantiomeric forms. Isomers of this type are called atropisomers (Section 5.18).

Review Problem 5.29

Write formulas for all of the isomers of each of the following. Designate pairs of enantiomers and achiral compounds where they exist.

(a) 1-Bromo-2-chlorocyclohexane **(b)** 1-Bromo-3-chlorocyclohexane

(c) 1-Bromo-4-chlorocyclohexane

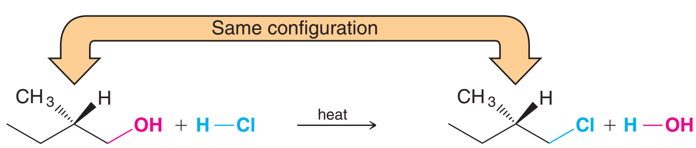
Review Problem 5.30

Give the (*R,S*) designation for each compound given as an answer to Review Problem 5.29.

5.15 *Relating Configurations through Reactions in Which No Bonds to the Chirality Center Are Broken*

- **If a reaction takes place in a way so that no bonds to the chirality center are broken**, the product will of necessity have the same general configuration of groups around the chirality center as the reactant.

Such a reaction is said **to proceed with retention of configuration**. Consider as an example the reaction that takes place when (*S*)-(−)-2-methyl-1-butanol is heated with concentrated hydrochloric acid:



(*S*)-(−)-2-Methyl-1-butanol **$[\alpha]_D^{25}$ = −5.756**

(*S*)-(+)-1-Chloro-2-methylbutane **$[\alpha]_D^{25}$ = +1.64**

We do not need to know now exactly how this reaction takes place to see that the reaction must involve breaking the CH_2—OH bond of the alcohol because the —OH group is replaced by a —Cl. There is no reason to assume that any other bonds are broken. (We shall study how this reaction takes place in Section 11.8A.) Since no bonds to the chirality center are broken, the reaction must take place with retention of configuration, and the product of the reaction *must have the same configuration of groups around the chirality center that the reactant had*. By saying that the two compounds have the same configuration, we simply mean that comparable or identical groups in the two compounds occupy the same relative positions in space around the chirality center. (In this instance the —CH_2OH group and the —CH_2Cl are comparable, and they occupy the same relative position in both compounds; all the other groups are identical and they occupy the same positions.)

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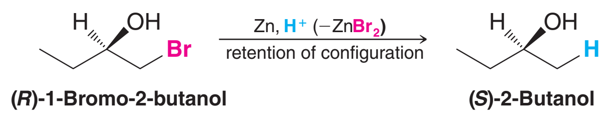
Notice that in this example while the (*R,S*) designation *does not change* [both reactant and product are (*S*)], the direction of optical rotation *does change* [the reactant is (−) and the product is (+)]. Neither occurrence is a necessity when a reaction proceeds with retention of configuration. In the next section we shall see examples of reactions in which configurations are retained and where the direction of optical rotation does not change. The following reaction is one that proceeds with retention of configuration but involves a change in the (*R,S*) designation:

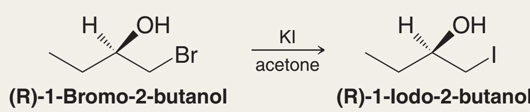


In this example the (*R,S*) designation changes because the —CH_2Br group of the reactant changes to a —CH_3 group in the product (—CH_2Br has a higher priority than —CH_2CH_3, and —CH_3 has a lower priority than —CH_2CH_3).

Solved Problem 5.7

When (*R*)-1-bromo-2-butanol reacts with KI in acetone the product is 1-iodo-2-butanol. Would the product be (*R*) or (*S*)?

STRATEGY AND ANSWER No bonds to the chirality center would be broken, so we can reason that the product would be the following.

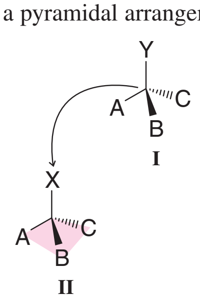


The configuration of the product would still be (*R*) because replacing the bromine at C1 with an iodine atom does not change the relative priority of C1.

5.15A Relative and Absolute Configurations

Reactions in which no bonds to the chirality center are broken are useful in relating configurations of chiral molecules. That is, they allow us to demonstrate that certain compounds have the same relative configuration. In each of the examples that we have just cited, the products of the reactions have the same *relative configurations* as the reactants.

- Chirality centers in different molecules have the same **relative configuration** if they share three groups in common and if these groups **with** the central carbon can be superposed in a pyramidal arrangement.

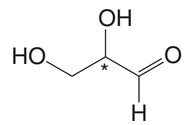


The chirality centers in **I** and **II** have the same relative configuration. Their common groups and central carbon can be superposed.

Before 1951 only relative configurations of chiral molecules were known. No one prior to that time had been able to demonstrate with certainty what the actual spatial arrangement of groups was in any chiral molecule. To say this another way, no one had been able to determine the absolute configuration of an optically active compound.

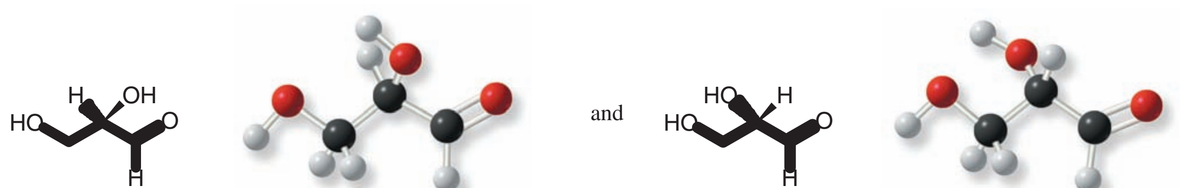
- The **absolute configuration** of a chirality center is its (*R*) or (*S*) designation, which can only be specified by knowledge of the actual arrangement of groups in space at the chirality center.

Prior to any known absolute configurations, the configurations of chiral molecules were related to each other *through reactions of known stereochemistry*. Attempts were also made to relate all configurations to a single compound that had been chosen arbitrarily to be the standard. This standard compound was glyceraldehyde:



Glyceraldehyde

Glyceraldehyde has one chirality center; therefore, glyceraldehyde exists as a pair of enantiomers:

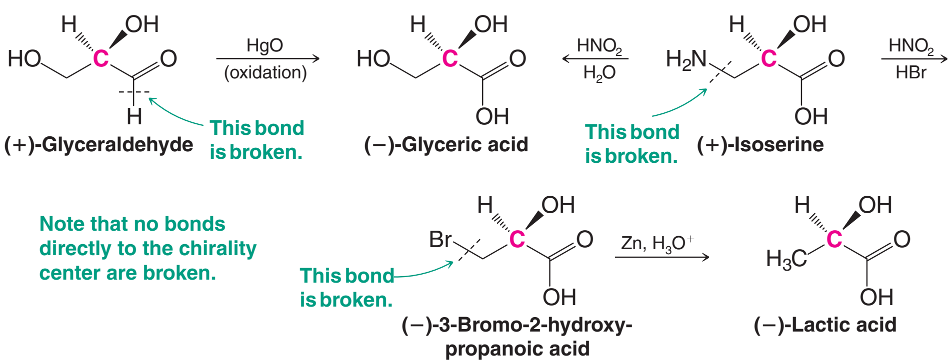


(*R*)-Glyceraldehyde and **(*S*)-Glyceraldehyde**

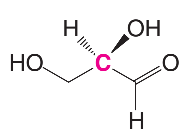
In one system for designating configurations, (*R*)-glyceraldehyde is called D-glyceraldehyde and (*S*)-glyceraldehyde is called L-glyceraldehyde. This system of nomenclature is used with a specialized meaning in the nomenclature of carbohydrates. (See Section 22.2B.)

One glyceraldehyde enantiomer is dextrorotatory (+) and the other, of course, is levorotatory (−). Before 1951 no one was sure, however, which configuration belonged to which enantiomer. Chemists decided arbitrarily to assign the (*R*) configuration to the (+)-enantiomer. Then, configurations of other molecules were related to one glyceraldehyde enantiomer or the other through reactions of known stereochemistry.

For example, the configuration of (−)-lactic acid can be related to (+)-glyceraldehyde through the following sequence of reactions in which no bond to the chirality center is broken:



The stereochemistry of all of these reactions is known. Because none of the bonds to the chirality center (shown in red) has been broken during the sequence, its original configuration is retained. If the assumption is made that (+)-glyceraldehyde is the (*R*) stereoisomer, and therefore has the following configuration,



(*R*)-(+)-Glyceraldehyde

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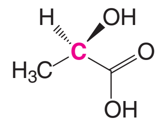
then (−)-lactic acid is also an (*R*) stereoisomer and its configuration is

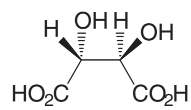


(*R*)-(−)-Lactic acid

Review Problem 5.31

Write bond-line three-dimensional formulas for the starting compound, the product, and all of the intermediates in a synthesis similar to the one just given that relates the configuration of (−)-glyceraldehyde with (+)-lactic acid. Label each compound with its proper (*R*) or (*S*) and (+) or (−) designation.

The configuration of (−)-glyceraldehyde was also related through reactions of known stereochemistry to (+)-tartaric acid:



(+)-Tartaric acid

In 1951 J. M. Bijvoet, the director of the van't Hoff Laboratory of the University of Utrecht in the Netherlands, using a special technique of X-ray diffraction, was able to show conclusively that (+)-tartaric acid had the absolute configuration shown above. This meant that the original arbitrary assignment of the configurations of (+)- and (−)-glyceraldehyde was also correct. It also meant that the configurations of all of the compounds that had been related to one glyceraldehyde enantiomer or the other were now known with certainty and were now **absolute configurations**.

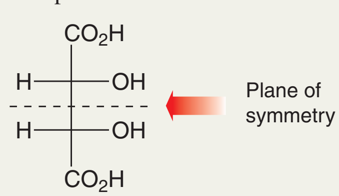
Review Problem 5.32

Fischer projection formulas are often used to depict compounds such as glyceraldehyde, lactic acid, and tartaric acid. Draw Fischer projections for both enantiomers of (**a**) glyceraldehyde, (**b**) tartaric acid, and (**c**) lactic acid, and specify the (*R*) or (*S*) configuration at each chirality center. [Note that in Fischer projection formulas the terminal carbon that is most highly oxidized is placed at the top of the formula (an aldehyde or carboxylic acid group in the specific examples here).]

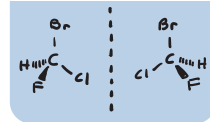
Solved Problem 5.8

Write a Fischer projection formula for a tartaric acid isomer that is not chiral.

STRATEGY AND ANSWER We reason that because tartaric acid has two chirality centers, the achiral isomer must have a plane of symmetry and be a meso compound.



***meso*-Tartaric acid**
(achiral)



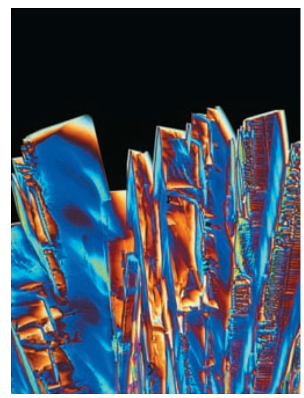
5.16 *Separation of Enantiomers: Resolution*

So far we have left unanswered an important question about optically active compounds and racemic forms: How are enantiomers separated? Enantiomers have identical solubilities in ordinary solvents, and they have identical boiling points. Consequently, the conventional methods for separating organic compounds, such as crystallization and distillation, fail when applied to a racemic form.

5.16A Pasteur's Method for Separating Enantiomers

It was, in fact, Louis Pasteur's separation of a racemic form of a salt of tartaric acid in 1848 that led to the discovery of the phenomenon called enantiomerism. Pasteur, consequently, is often considered to be the founder of the field of stereochemistry.

(+)-Tartaric acid is one of the by-products of wine making (nature usually only synthesizes one enantiomer of a chiral molecule). Pasteur had obtained a sample of racemic tartaric acid from the owner of a chemical plant. In the course of his investigation Pasteur began examining the crystal structure of the sodium ammonium salt of racemic tartaric acid. He noticed that two types of crystals were present. One was identical with crystals of the sodium ammonium salt of (+)-tartaric acid that had been discovered earlier and had been shown to be dextrorotatory. Crystals of the other type were *non*superposable mirror images of the first kind. The two types of crystals were actually chiral. Using tweezers and a magnifying glass, Pasteur separated the two kinds of crystals, dissolved them in water, and placed the solutions in a polarimeter. The solution of crystals of the first type was dextrorotatory, and the crystals themselves proved to be identical with the sodium ammonium salt of (+)-tartaric acid that was already known. The solution of crystals of the second type was levorotatory; it rotated plane-polarized light in the opposite direction and by an equal amount. The crystals of the second type were of the sodium ammonium salt of (−)-tartaric acid. The chirality of the crystals themselves disappeared, of course, as the crystals dissolved into their solutions, *but the optical activity* remained. Pasteur reasoned, therefore, that the molecules themselves must be chiral.



Tartaric acid crystals

Pasteur's discovery of enantiomerism and his demonstration that the optical activity of the two forms of tartaric acid was a property of the molecules themselves led, in 1874, to the proposal of the tetrahedral structure of carbon by van't Hoff and Le Bel.

Unfortunately, few organic compounds give chiral crystals as do the (+)- and (−)-tartaric acid salts. Few organic compounds crystallize into separate crystals (containing separate enantiomers) that are visibly chiral like the crystals of the sodium ammonium salt of tartaric acid. Pasteur's method, therefore, is not generally applicable to the separation of enantiomers.

5.16B Current Methods for Resolution of Enantiomers

One of the most useful procedures for separating enantiomers is based on the following:

- When a racemic mixture reacts with a single enantiomer of another compound, a mixture of diastereomers results, and diastereomers, because they have different melting points, boiling points, and solubilities, can be separated by conventional means.

Diastereomeric recrystallization is one such process. We shall see how this is done in Section 20.3F. Another method is **resolution** by enzymes, whereby an enzyme selectively converts one enantiomer in a racemic mixture to another compound, after which the unreacted enantiomer and the new compound are separated. The reaction by lipase in Section 5.10B is an example of this type of resolution. Chromatography using chiral media is also widely used to resolve enantiomers. This approach is applied in high-performance liquid chromatography (HPLC) as well as in other forms of chromatography. Diastereomeric interactions between molecules of the racemic mixture and the chiral chromatography medium cause enantiomers of the racemate to move through the chromatography apparatus at different rates. The enantiomers are then collected separately as they elute from the chromatography device. (See "*The Chemistry of* . . . HPLC Resolution of Enantiomers," Section 20.3.)

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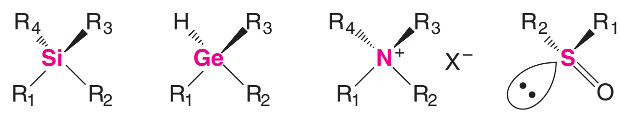
5.17 Compounds with Chirality Centers Other than Carbon

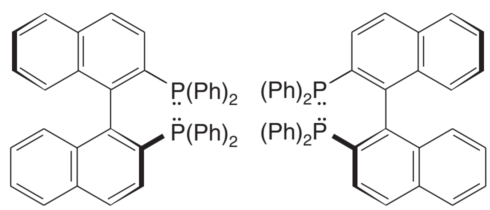
Any tetrahedral atom with four different groups attached to it is a chirality center. Shown here are general formulas of compounds whose molecules contain chirality centers other than carbon. Silicon and germanium are in the same group of the periodic table as carbon. They form tetrahedral compounds as carbon does. When four different groups are situated around the central atom in silicon, germanium, and nitrogen compounds, the molecules are chiral and the enantiomers can, in principle, be separated. Sulfoxides, like certain examples of other functional groups where one of the four groups is a nonbonding electron pair, are also chiral. This is not the case for amines, however (Section 20.2B):



5.18 Chiral Molecules That Do Not Possess a Chirality Center

A molecule is chiral if it is not superposable on its mirror image. The presence of a tetrahedral atom with four different groups is only one type of chirality center, however. While most of the chiral molecules we shall encounter have chirality centers, there are other structural attributes that can confer chirality on a molecule. For example, there are compounds that have such large rotational barriers between conformers that individual conformational isomers can be separated and purified, and some of these conformational isomers are stereoisomers.

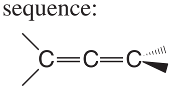
Conformational isomers that are stable, isolable compounds are called **atropisomers**. The existence of chiral atropisomers has been exploited to great effect in the development of chiral catalysts for stereoselective reactions. An example is BINAP, shown below in its enantiomeric forms:



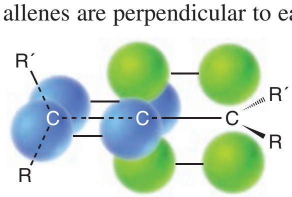
***(S)*-BINAP** ***(R)*-BINAP**

The origin of chirality in BINAP is the restricted rotation about the bond between the two nearly perpendicular naphthalene rings. This torsional barrier leads to two resolvable enantiomeric conformers, (*S*)- and (*R*)-BINAP. When each enantiomer is used as a ligand for metals such as ruthenium and rhodium (bound by unshared electron pairs on the phosphorus atoms), chiral organometallic complexes result that are capable of catalyzing stereoselective hydrogenation and other important industrial reactions. The significance of chiral ligands is highlighted by the industrial synthesis each year of approximately 3500 *tons* of (−)-menthol using an isomerization reaction involving a rhodium (*S*)-BINAP catalyst.

Allenes are compounds that also exhibit stereoisomerism. Allenes are molecules that contain the following double-bond sequence:



The planes of the π bonds of allenes are perpendicular to each other:



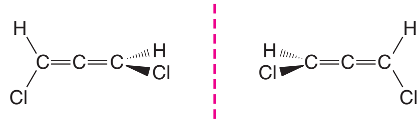


Figure 5.22 Enantiomeric forms of 1,3-dichloroallene. These two molecules are nonsuperposable mirror images of each other and are therefore chiral. They do not possess a tetrahedral atom with four different groups, however.

This geometry of the π bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes, and, because of this, allenes with different substituents on the end carbon atoms are chiral (Fig. 5.22). (Allenes do not show cis–trans isomerism.)

In This Chapter

In this chapter you learned that the handedness of life begins at the molecular level. Molecular recognition, signaling, and chemical reactions in living systems often hinge on the handedness of chiral molecules. Molecules that bear four different groups at a tetrahedral carbon atom are chiral if they are nonsuperposable with their mirror image. The atoms bearing four different groups are called chirality centers.

Mirror planes of symmetry have been very important to our discussion. If we want to draw the enantiomer of a molecule, one way to do so is to draw the molecule as if it were reflected in a mirror. If a mirror plane of symmetry exists *within* a molecule, then it is achiral (not chiral), even if it contains chirality centers. Using mirror planes to test for symmetry is an important technique.

In this chapter you learned how to give unique names to chiral molecules using the Cahn–Ingold–Prelog *R,S*–system. You have also exercised your mind's eye in visualizing molecular structures in three dimensions, and you have refined your skill at drawing three-dimensional molecular formulas. You learned that pairs of enantiomers have identical physical properties except for the equal and opposite rotation of plane-polarized light, whereas diastereomers have different physical properties from one another. Interactions between each enantiomer of a chiral molecule and any other chiral material lead to diastereomeric interactions, which lead to different physical properties that can allow the separation of enantiomers.

Chemistry happens in three dimensions. Now, with the information from this chapter building on fundamentals you have learned about molecular shape and polarity in earlier chapters, you are ready to embark on your study of the reactions of organic molecules. Practice drawing molecules that show three dimensions at chirality centers, practice naming molecules, and label their regions of partial positive and negative charge. Paying attention to these things will help you learn about the reactivity of molecules in succeeding chapters. Most important of all, do your homework!

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

CHIRALITY AND STEREOISOMERISM

5.33 Which of the following are chiral and, therefore, capable of existing as enantiomers?

(a) 1,3-Dichlorobutane
(b) 1,2-Dibromopropane
(c) 1,5-Dichloropentane
(d) 3-Ethylpentane
(e) 2-Bromobicyclo[1.1.0]butane
(f) 2-Fluorobicyclo[2.2.2]octane
(g) 2-Chlorobicyclo[2.1.1]hexane
(h) 5-Chlorobicyclo[2.1.1]hexane

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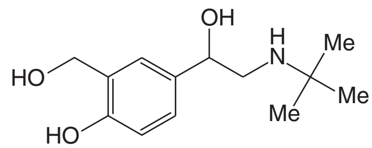
5.34 **(a)** How many carbon atoms does an alkane (not a cycloalkane) need before it is capable of existing in enantiomeric forms? **(b)** Give correct names for two sets of enantiomers with this minimum number of carbon atoms.

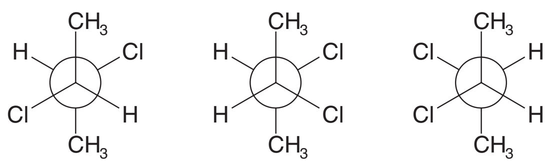
5.35 Albuterol, shown here, is a commonly prescribed asthma medication. For either enantiomer of albuterol, draw a three-dimensional formula using dashes and wedges for bonds that are not in the plane of the paper. Choose a perspective that allows as many carbon atoms as possible to be in the plane of the paper, and show all unshared electron pairs and hydrogen atoms (except those on the methyl groups labeled Me). Specify the (*R,S*) configuration of the enantiomer you drew.



Albuterol

5.36 **(a)** Write the structure of 2,2-dichlorobicyclo[2.2.1]heptane. **(b)** How many chirality centers does it contain? **(c)** How many stereoisomers are predicted by the 2^n rule? **(d)** Only one pair of enantiomers is possible for 2,2-dichlorobicyclo[2.2.1]heptane. Explain.

5.37 Shown below are Newman projection formulas for (*R,R*)-, (*S,S*)-, and (*R,S*)-2,3-dichlorobutane. **(a)** Which is which? **(b)** Which formula is a meso compound?

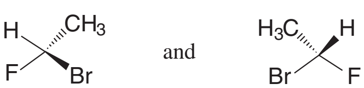


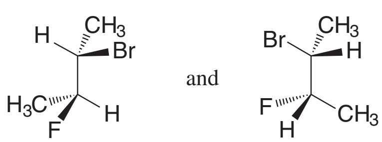
A B C

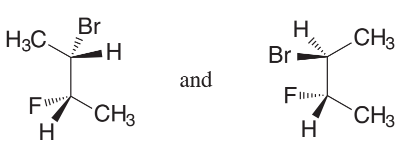
5.38 Write appropriate structural formulas for **(a)** a cyclic molecule that is a constitutional isomer of cyclohexane, **(b)** molecules with the formula C_6H_{12} that contain one ring and that are enantiomers of each other, **(c)** molecules with the formula C_6H_{12} that contain one ring and that are diastereomers of each other, **(d)** molecules with the formula C_6H_{12} that contain no ring and that are enantiomers of each other, and **(e)** molecules with the formula C_6H_{12} that contain no ring and that are diastereomers of each other.

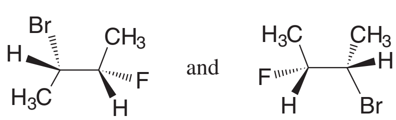
5.39 Consider the following pairs of structures. Designate each chirality center as (*R*) or (*S*) and identify the relationship between them by describing them as representing enantiomers, diastereomers, constitutional isomers, or two molecules of the same compound. Use handheld molecular models to check your answers.

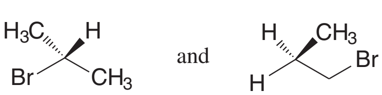
(a) 

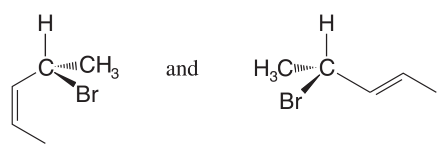
(b) 

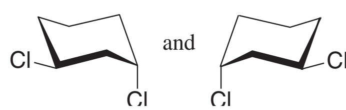
(c) 

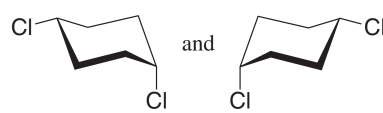
(d) 

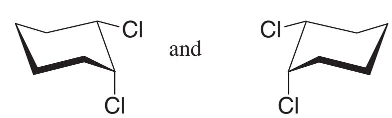
(e) 

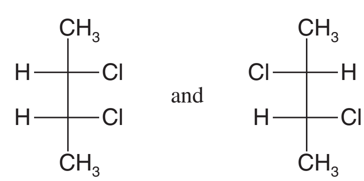
(f) 

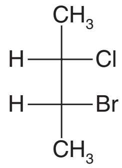
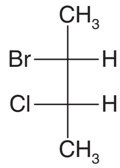
(g) 

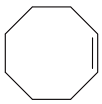
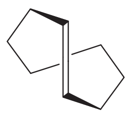
(h) 

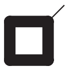
(i) 

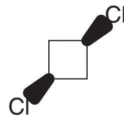
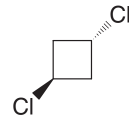
(j) 

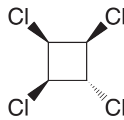
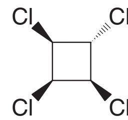
(k) 

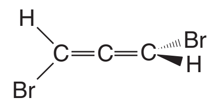
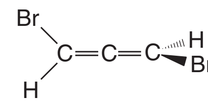
(l)  and 

(m)  and 

(n)  and 

(o)  and 

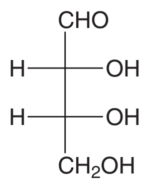
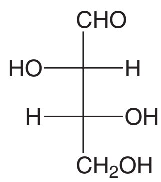
(p)  and 

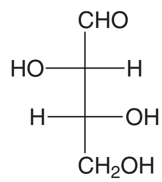
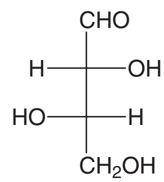
(q)  and 

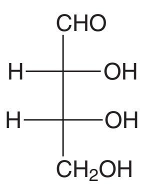
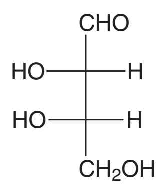
5.40 Discuss the anticipated stereochemistry of each of the following compounds.

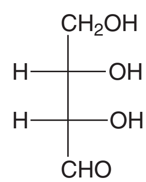
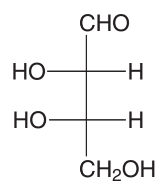
(a) ClCH=C=C=CHCl **(b)** CH_2=C=C=CHCl **(c)** ClCH=C=C=CCl_2

5.41 Tell whether the compounds of each pair are enantiomers, diastereomers, constitutional isomers, or not isomeric.

(a)  and 

(b)  and 

(c)  and 

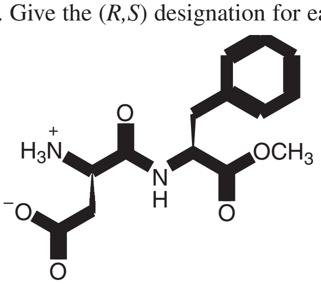
(d)  and 

5.42 A compound **D** with the molecular formula C_6H_{12} is optically inactive but can be resolved into enantiomers. On catalytic hydrogenation, **D** is converted to **E** (C_6H_{14}) and **E** is optically inactive. Propose structures for **D** and **E**.

5.43 Compound **F** has the molecular formula C_5H_8 and is optically active. On catalytic hydrogenation **F** yields **G** (C_5H_{12}) and **G** is optically inactive. Propose structures for **F** and **G**.

5.44 Compound **H** is optically active and has the molecular formula C_6H_{10}. On catalytic hydrogenation **H** is converted to **I** (C_6H_{12}) and **I** is optically inactive. Propose structures for **H** and **I**.

5.45 Aspartame is an artificial sweetener. Give the (*R,S*) designation for each chirality center of aspartame.



Aspartame

5.46 There are four dimethylcyclopropane isomers. **(a)** Write three-dimensional formulas for these isomers. **(b)** Which of the isomers are chiral? **(c)** If a mixture consisting of 1 mol of each of these isomers were subjected to simple gas chromatography (an analytical method that can separate compounds according to boiling point), how many fractions would be obtained and which compounds would each fraction contain? **(d)** How many of these fractions would be optically active?

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5.47 (Use models to solve this problem.) **(a)** Write a conformational structure for the most stable conformation of *trans*-1,2-diethylcyclohexane and write its mirror image. **(b)** Are these two molecules superposable? **(c)** Are they interconvertible through a ring "flip"? **(d)** Repeat the process in part (a) with *cis*-1,2-diethylcyclohexane. **(e)** Are these structures superposable? **(f)** Are they interconvertible?

5.48 (Use models to solve this problem.) **(a)** Write a conformational structure for the most stable conformation of *trans*-1,4-diethylcyclohexane and for its mirror image. **(b)** Are these structures superposable? **(c)** Do they represent enantiomers? **(d)** Does *trans*-1,4-diethylcyclohexane have a stereoisomer, and if so, what is it? **(e)** Is this stereoisomer chiral?

5.49 (Use models to solve this problem.) Write conformational structures for all of the stereoisomers of 1,3-diethylcyclohexane. Label pairs of enantiomers and meso compounds if they exist.

Challenge Problems

5.50 Tartaric acid [$HO_2CCH(OH)CH(OH)CO_2H$] was an important compound in the history of stereochemistry. Two naturally occurring forms of tartaric acid are optically inactive. One optically inactive form has a melting point of 210–212°C, the other a melting point of 140°C. The inactive tartaric acid with a melting point of 210–212°C can be separated into two optically active forms of tartaric acid with the same melting point (168–170°C). One optically active tartaric acid has $[\alpha]_D^{25} = +12$, and the other, $[\alpha]_D^{25} = -12$. All attempts to separate the other inactive tartaric acid (melting point 140°C) into optically active compounds fail. **(a)** Write the three-dimensional structure of the tartaric acid with melting point 140°C. **(b)** Write structures for the optically active tartaric acids with melting points of 168–170°C. **(c)** Can you determine from the formulas which tartaric acid in (b) has a positive rotation and which has a negative rotation? **(d)** What is the nature of the form of tartaric acid with a melting point of 210–212°C?

5.51 **(a)** An aqueous solution of pure stereoisomer X of concentration 0.10 g mL^{-1} had an observed rotation of $-30°$ in a 1.0-dm tube at 589.6 nm (the sodium D line) and 25°C. What do you calculate its $[\alpha]_D$ to be at this temperature?

(b) Under identical conditions but with concentration 0.050 g mL^{-1}, a solution of X had an observed rotation of $+165°$. Rationalize how this could be and recalculate $[\alpha]_D$ for stereoisomer X.

(c) If the optical rotation of a substance studied at only one concentration is zero, can it definitely be concluded to be achiral? Racemic?

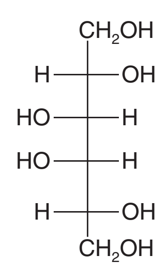
5.52 If a sample of a pure substance that has two or more chirality centers has an observed rotation of zero, it could be a racemate. Could it possibly be a pure stereoisomer? Could it possibly be a pure enantiomer?

5.53 Unknown Y has a molecular formula of $C_3H_6O_2$. It contains one functional group that absorbs infrared radiation in the 3200–3550-cm^{-1} region (when studied as a pure liquid; i.e., "neat"), and it has no absorption in the 1620–1780-cm^{-1} region. No carbon atom in the structure of Y has more than one oxygen atom bonded to it, and Y can exist in two (and only two) stereoisomeric forms. What are the structures of these forms of Y?

Learning Group Problems

1. Streptomycin is an antibiotic that is especially useful against penicillin-resistant bacteria. The structure of streptomycin is shown in Section 22.17. **(a)** Identify all of the chirality centers in the structure of streptomycin. **(b)** Assign the appropriate (*R*) or (*S*) designation for the configuration of each chirality center in streptomycin.

2. D-Galactitol is one of the toxic compounds produced by the disease galactosemia. Accumulation of high levels of D-galactitol causes the formation of cataracts. A Fischer projection for D-galactitol is shown at right:

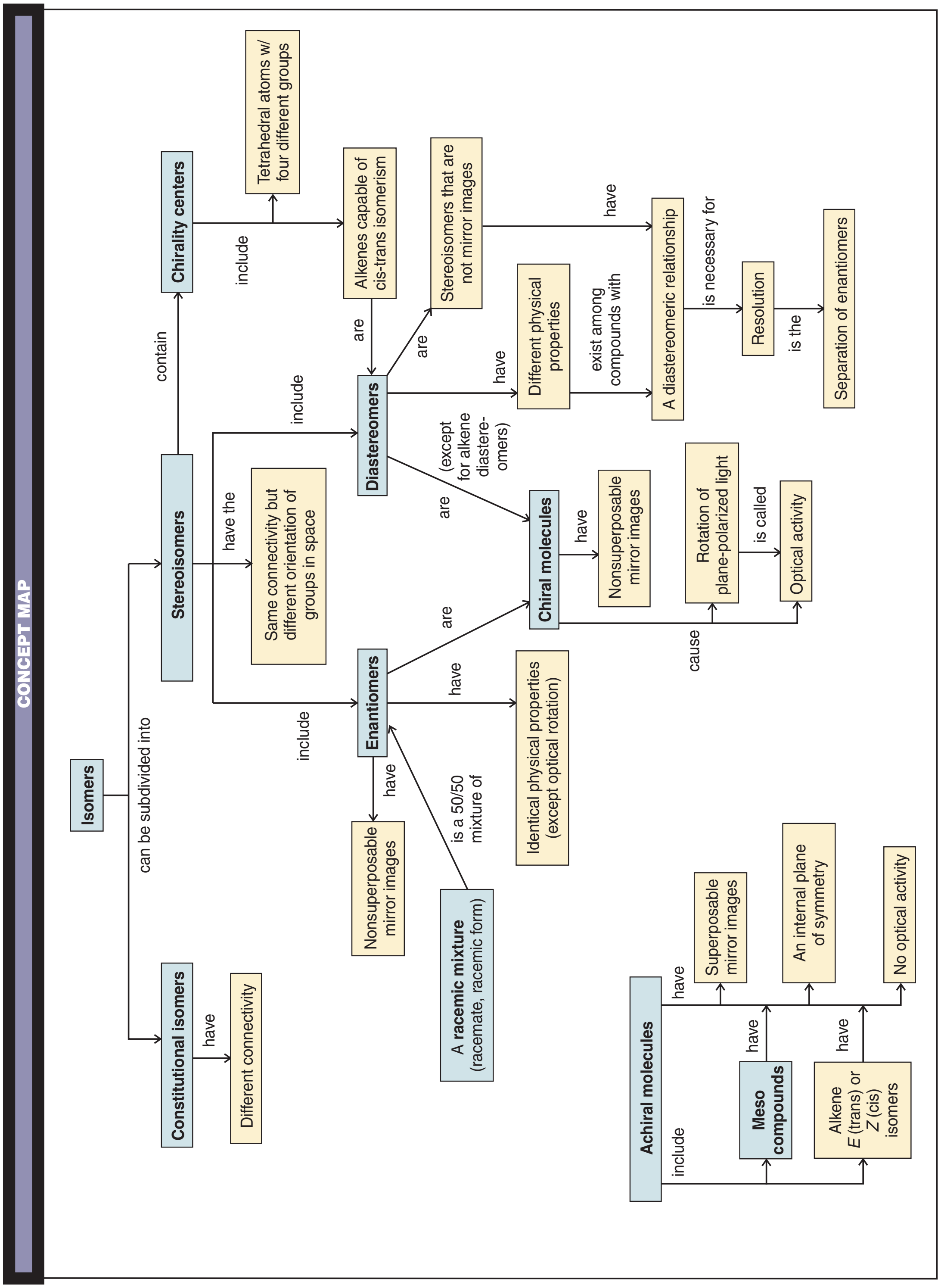


(a) Draw a three-dimensional structure for D-galactitol.

(b) Draw the mirror image of D-galactitol and write its Fischer projection formula.

(c) What is the stereochemical relationship between D-galactitol and its mirror image?

3. Cortisone is a natural steroid that can be isolated from the adrenal cortex. It has anti-inflammatory properties and is used to treat a variety of disorders (e.g., as a topical application for common skin diseases). The structure of cortisone is shown in Section 23.4D. **(a)** Identify all of the chirality centers in cortisone. **(b)** Assign the appropriate (*R*) or (*S*) designation for the configuration of each chirality center in cortisone.



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