25

STEREOCHEMISTRY OF ORGANIC COMPOUNDS

WHAT'S AHEAD

25.1 | Stereochemistry in Organic Chemistry

Stereochemistry is about the three-dimensional shape of a molecule. This may sometimes be of crucial importance in determining the physical properties of a compound. Recall that coordination compounds that exhibit stereochemistry give rise to different properties such as color. Stereochemistry may also play a role in the chemical reactions of a compound. This is most clearly seen when an organic molecule interacts with a complex biological molecule such as an enzyme.

For example, the compound limonene is responsible for the distinct smells of both oranges and lemons. Limonene is a colorless liquid hydrocarbon containing 10 carbon atoms, yet it can adopt two different shapes. These shapes are mirror images of one another—rather like a right hand and a left hand—and this subtle difference in shape results in a different interaction with the smell receptors in our noses. One mirror image form smells of lemons and the other of oranges.

When you finish this section, you should be able to:

- Understand the relationship between different classes of isomers

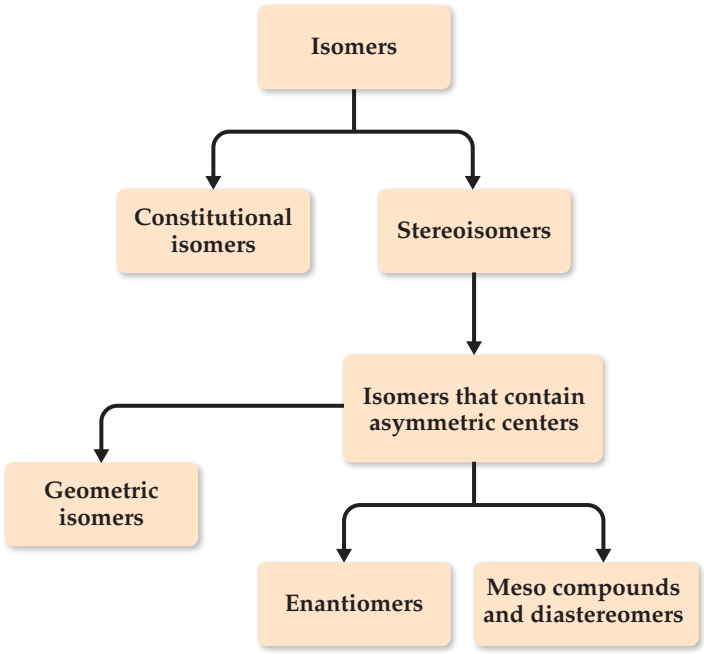
We have already discussed the dimensionality of simple organic molecules and seen that structure is responsible for a compound's physical properties, such as melting point, boiling point and density. As we see in this chapter, and again in Chapter 31, the three-dimensional structure of a molecule is also important for its chemical properties, especially in a biological environment.

The term *isomers* is used to describe molecules with the same molecular formula but some difference in structure **Figure 25.1** illustrates the relationship between the different classes of isomers. Constitutional isomers have a different bonding arrangement; for example, a straight-chain and a branched-chain alkane both of the formula C_6H_{14}.

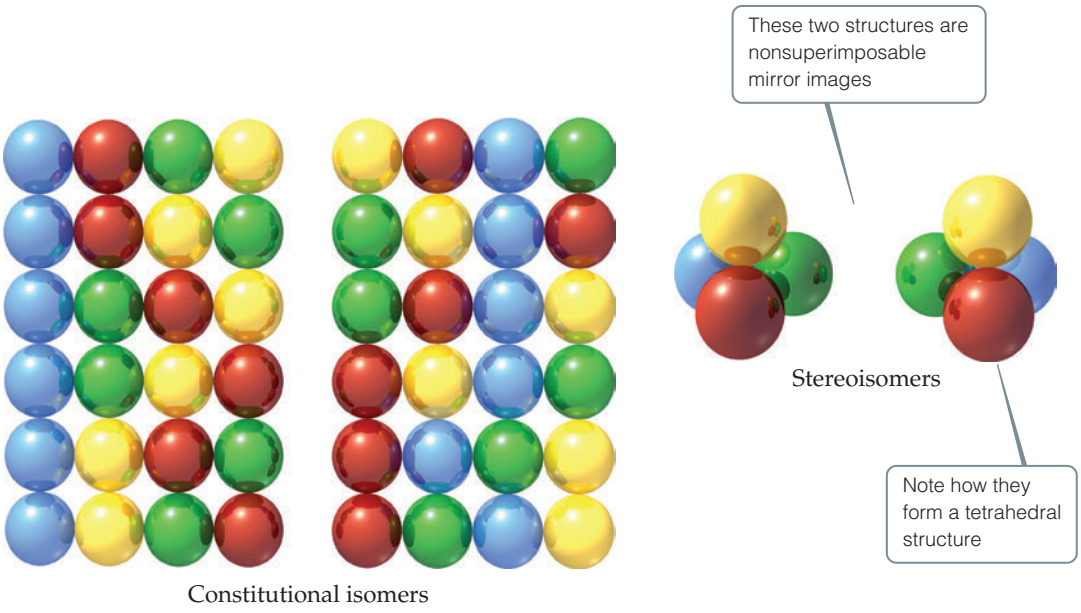
Stereoisomers have the same molecular formula and the same connectivity of atoms, but may be quite different in their physical and chemical properties. Stereoisomers can exist in several forms. Of these forms, there are three distinct classes: **geometric isomers**, **enantiomers**, and **diastereomers** (also called diastereoisomers). Stereoisomers cannot be interconverted without the breaking and remaking of a covalent bond.

We can begin our understanding of stereochemistry by considering simple representations of atoms, such as four colored balls—blue, green, red, and yellow. When the balls are laid in a row, there are 12 possible permutations, taking into account the ability to read from right to left or left to right (**Figure 25.2**). The relationship between any or all permutations can be described as *constitutional isomers*. In essence, the balls act as building blocks, in the same way as we described atoms or groups of atoms in Table 24.8. You can

Go Figure Can propane demonstrate constitutional isomerism?



▲ **Figure 25.1 There are several different forms of isomerism.** Although constitutional, geometric and diastereomers vary in their physical properties, enantiomers vary only when in a chiral environment.



▲ **Figure 25.2 Understanding isomerism.** Orientation of colored balls can be used as imagery to describe constitutional isomerism and stereoisomerism.

see from this example how easy it is to build up a library of compounds with the same molecular formula.

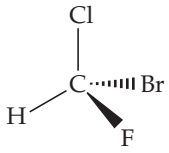
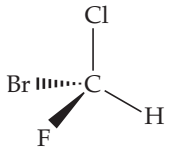
What happens when we change from a pseudo one-dimensional shape of the four balls, as occurs in a row, to one that is three-dimensional, such as a pyramid? The answer is a simplification in the number of permutations to just two. Notice that there is no way of superimposing the two pyramidal structures in Figure 25.2 onto one another—they are different. The two structures represented are, in fact, mirror images of each other. In chemical terms, they are stereoisomers and, more specifically, *enantiomers*.

Self-Assessment Exercise

25.1 Which of the pairs of structures represent stereoisomers?

(a) $CH_3CH_2CH_2CH_3$ and $CH_3CH_2CH_2CH_2CH_3$

(b) $CH_3CHCH_2CH_3$ (with CH_3 branch) and $CH_3CH_2CHCH_3$ (with CH_3 branch)

(c)  and 

(d) CH_3OCH_3 and CH_3CH_2OH

Answers to Self-Assessment Exercise

25.1 (c)

25.2 | *Cis–Trans* Isomerism in Cycloalkanes

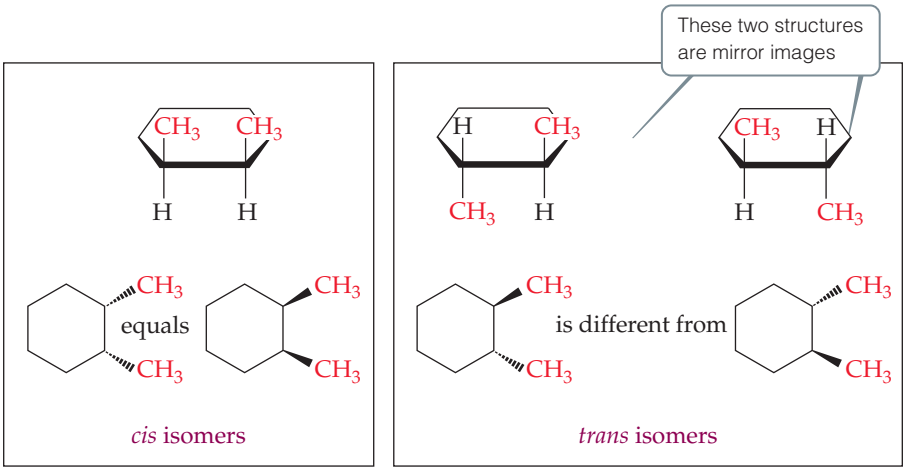
Inositol is a type of sugar that has a ring of six carbon atoms, each bearing an —OH group. It is important in the synthesis of neurotransmitter molecules and has been sold as a health supplement to improve brain function. There are eight geometries with different relative positions of the alcohol groups, only one of which is active in the body. In this section, we will look at the isomers possible in a cyclic compound with just two substituents.

When you finish this section, you should be able to:

- Identify the geometric isomers of a disubstituted cyclic compound

The three isomers of 1,2-dimethylcyclohexane shown in **Figure 25.3** differ in the relative locations of their methyl groups. These three compounds are *stereoisomers*. That is, they are compounds that have the same molecular formula and the same connectivity between atoms but differ in the spatial arrangement of these groups. Thus, the ***cis*** isomer of 1,2-dimethylcyclohexane has the two methyl groups orientated on the same side of the plane of the ring, whereas the ***trans*** isomers have the methyl groups orientated on opposite sides.

The three-dimensional orientation of groups within a structural formula or line drawing can be described using bold and dashed wedges, as shown in Figure 25.3. The notation employs the two-dimensional plane of the paper to draw a three-dimensional object. A bold wedge (▬) indicates that this bond extends towards you out of the plane of the



▶ **Figure 25.3 Geometric isomerism in disubstituted cycloalkanes.** *Cis* and *trans* isomerism is a feature of cycloalkanes. The easiest way to remember which isomer is which is to remember that *trans* (as in transpacific or transport) means "across".

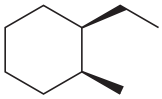
paper. A dashed wedge (·····) indicates that this bond is directed into the paper. This symbolism will become important in Section 25.3, where we investigate three-dimensional structure in more detail.

Despite the ability of C—C bonds to rotate under normal conditions, their ability to do so in a cycloalkane is greatly restricted by ring strain. Hence, the three stereoisomers shown in Figure 25.3 cannot be interconverted without breaking and remaking C—C bonds.

Sample Exercise 25.1

Naming *cis* and *trans* Isomers

Write the systematic name for the following cycloalkane:



SOLUTION

Analyze We are given the structure of a cycloalkane bearing two substituents and asked to name it, taking into account stereochemistry.

Plan Understand the type of cycloalkane, the names of the substituents and their relative orientation to each other using the wedged nature of the bonds.

Solve The cycloalkane has six carbons associated with the ring structure, so the full name is derived from cyclohexane. The two substituent groups are an ethyl group at position 1 and a methyl group at position 2 based on nomenclature rules.

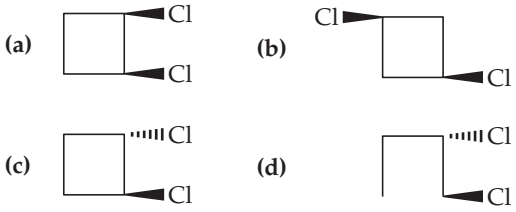
The name for this alkane would be 1-ethyl-2-methylcyclohexane. However, this name tells us nothing about the relative orientations of the alkyl substituents. These two groups are *cis* to one another because the symbolism used in the line drawing has both substituents extending out of the page in the same direction. Hence, a full systematic name would be cis-1-ethyl-2-methylcyclohexane.

Practice Exercise

Write the systematic name for the following cycloalkane:

Self-Assessment Exercises

25.2 Which structure represents *cis*-1,2-dichlorocyclobutane?



25.3 Give the correct name, including the stereochemical descriptor, for:

(a) 1,4-dimethylcyclohexane

(b) *cis*-1,4-dimethylcyclohexane

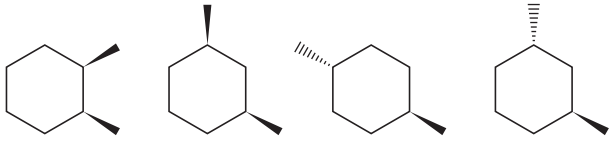
(c) *trans*-1,4-dimethylcyclohexane

Exercises

25.4 Write the systematic name for the following cycloalkane:

25.5 Draw the structure of *cis*-1,2-dimethylcycloheptane.

25.6 Which pair of structures represent geometric isomers?



Answers to Self-Assessment Exercises

25.2 (a) 25.3 (c)

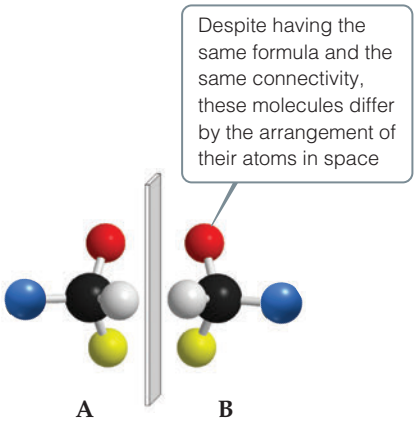
25.3 | Chirality in Organic Compounds

In 1875, a book by Charles Darwin was published titled *On the Movements and Habits of Climbing Plants*. One observation Darwin made was that some species of vines always twisted up a stake in a clockwise direction, while other species adopted an anti-clockwise direction. The two different spirals are mirror images of one another. There are many instances in nature of this sort of symmetry and a preference to adopt one form over the other. Our hands are an example of a mirror-image pair in which the two elements are not superimposable on one another. The very specific interactions this may lead to are shown by pulling on a pair of gloves and finding it is impossible to wear the glove that is not matched to the correct hand. Certain molecules possess non-superimposable mirror images and are called *optical isomers*.

When you finish this section, you should be able to:

- Identify the stereogenic center in a chiral molecule
- Draw the mirror-image structures of a chiral molecule

Let us begin our discussion of **optical isomers** in organic chemistry by looking at Figure 25.4. Molecule **A** consists of a tetrahedral carbon atom with four different groups attached, represented by the white, blue, red, and yellow balls. Is **A** identical to its mirror image, **B**? This question is best explored by making three-dimensional models and trying to overlay them; alternatively, try to imagine rotating **A** by 180° and placing it on top of **B**. What happens? The blue, black and white balls align, but the red and yellow are reversed. In fact, any way you try to overlay these two molecules, the result is the same—three of the balls are superimposable but the other two are not.



▲ **Figure 25.4 Mirror images.** These two molecules are non-superimposable mirror images. Being able to move molecules around mentally in three-dimensional space to prove two molecules are non-superimposable is extremely difficult and will require practice before it is mastered.

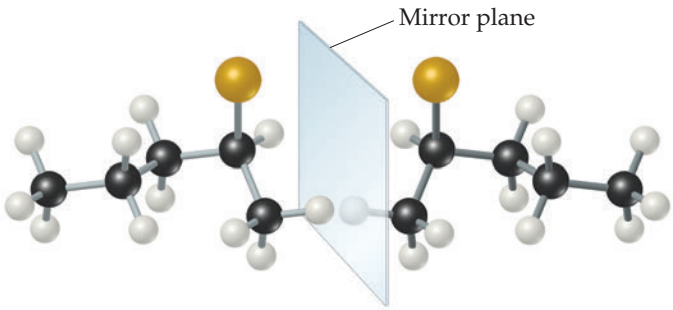
Molecules possessing non-superimposable mirror images, such as **A** and **B**, are termed **chiral** (Greek *cheir*, "hand"; pronounced *ky-ral*)—that is, they show handedness. In fact, *all molecules containing a single carbon atom bearing four different groups are chiral*. The fact that molecules **A** and **B** cannot be overlaid demonstrates that they are *different substances*. The relationship between two molecules that are non-superimposable mirror images is described by the term **enantiomer**. Hence, molecules **A** and **B** are enantiomers. For example, Figure 25.5 shows the two enantiomers of 2-bromopentane.

All enantiomers have a **chiral center** (also known as a **stereogenic center** or simply a **stereocenter**)—an atom (usually carbon) to which four different groups are attached.

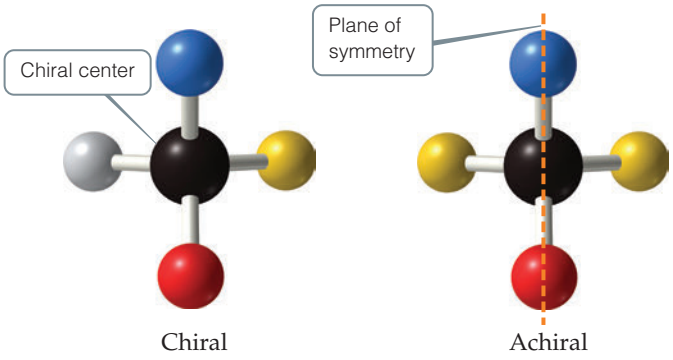
Molecules that have superimposable mirror images are **achiral**, meaning *not chiral*. Achiral molecules can usually be identified because they possess a plane of symmetry (Figure 25.6).

We can make the following general rules at this point:

1. *Stereocenters within any compound can be recognized because they have four different groups bonded to them.*
2. *The presence of one or more stereocenters always results in stereoisomers.*



◀ **Figure 25.5 The two enantiomeric forms of 2-bromopentane.** The mirror-image isomers are not superimposable with each other.

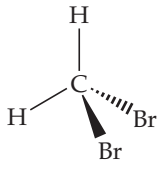


◀ **Figure 25.6 Chiral and achiral.** A molecule that contains one chiral center (stereocenter) is chiral (left). If a plane of symmetry exists, as in the molecule on the right, that molecule is said to be achiral.

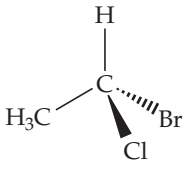
Sample Exercise 25.2

Predicting Chirality

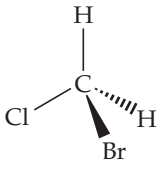
Determine which of the following structures is chiral:



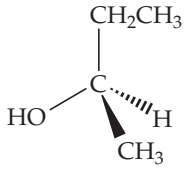
I



II



III



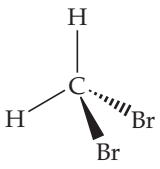
IV

SOLUTION

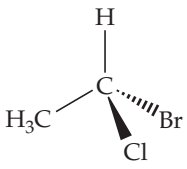
Analyze We are given four structures containing wedged bonds and are asked to determine which are chiral.

Plan Identify any planes of symmetry among the structures to determine achiral molecules. If there is no plane of symmetry, identify the stereogenic center to determine chirality.

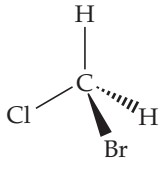
Solve Two compounds are chiral: II and IV. Compounds I and III have at least one plane of symmetry—in fact, compound I has two planes of symmetry. Note that methyl and ethyl groups are classed as different groups, as are the halogens, chlorine, and bromine. Remember, the alternative (and sometimes easier) way to determine whether a molecule is chiral or not is to check each carbon atom to see whether it is a stereocenter.



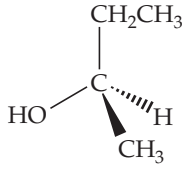
I
achiral



II
chiral



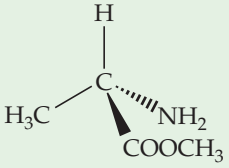
III
achiral

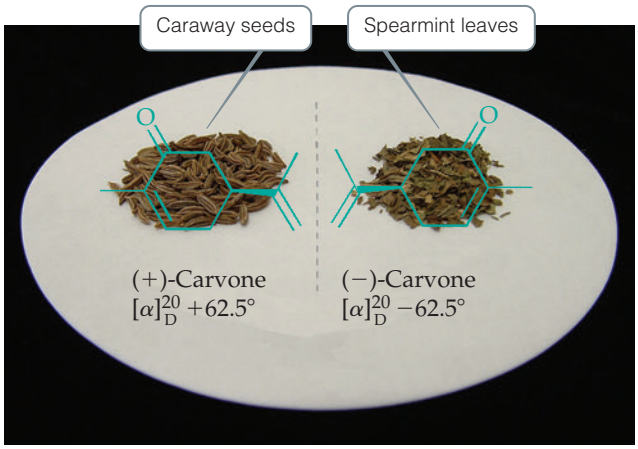


IV
chiral

Practice Exercise

Identify the chiral center in the following molecule and label it with an asterisk. Draw the molecule's mirror image.





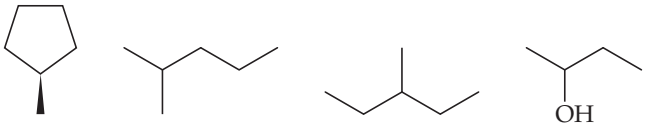
▶ **Figure 25.7 Enantiomers of carvone.** Caraway seeds smell very different from spearmint leaves or oil. The difference is a result of how each molecule interacts with the chiral receptors in the nose.

Most of the physical and chemical properties of enantiomers are identical because each enantiomer contains the same functional groups and the same non-bonding interactions. Enantiomers, such as the two forms of 2-bromopentane shown in Figure 25.5, have identical physical properties, such as melting and boiling points, and identical chemical properties when they react with achiral reagents. The properties of two enantiomers *differ only if they are in a chiral environment*. An easy way of demonstrating the differences between enantiomers in a chiral environment is to purchase caraway seeds and spearmint leaves from your local supermarket. Each product contains a different enantiomer of carvone (**Figure 25.7**). Now smell them and note the stark difference.

The difference in their smell is a result of the chirality of the receptors contained within your nose. Each enantiomer fits into the receptor's binding site in a similar way to how our right or left hands would fit into a left-hand glove. For one enantiomer, the fit is perfect, leading to a maximum interaction between the molecule and receptor. The other enantiomer fits awkwardly, leading to less than perfect binding and a different response, perhaps a different smell or taste.

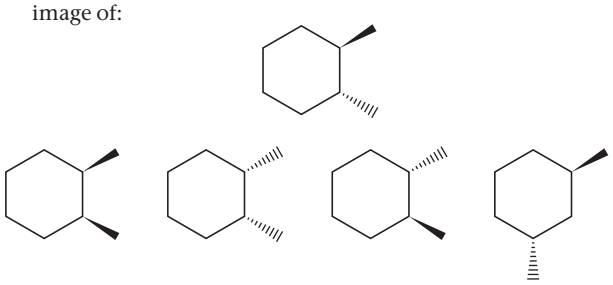
Self-Assessment Exercises

25.7 Which structure represents a chiral molecule—contains a stereocenter?



(a) (b) (c) (d)

25.8 Identify the structure that is a non-superimposable mirror image of:

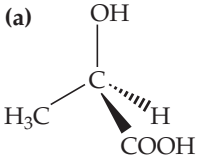


(a) (b) (c) (d)

Exercises

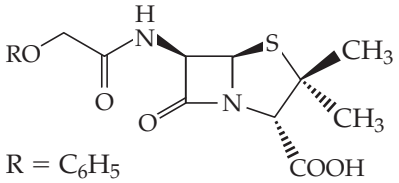
25.9 Locate the chiral carbon atoms, if any, in each of the following natural products:

(a)



lactic acid

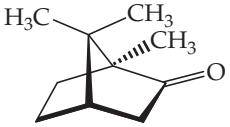
(b)



R = C_6H_5

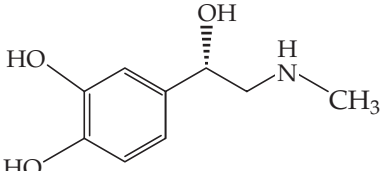
penicillin V

(c)



camphor

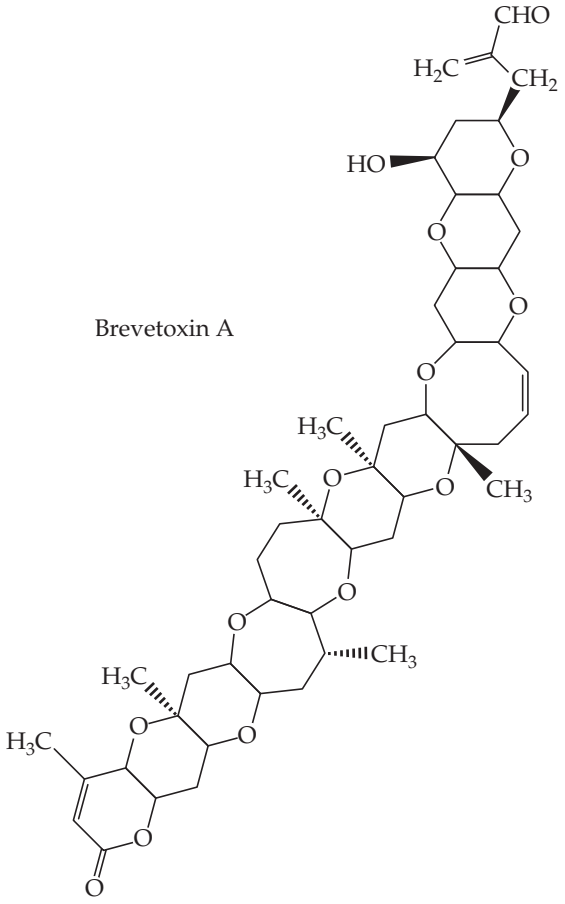
(d)



epinephrine

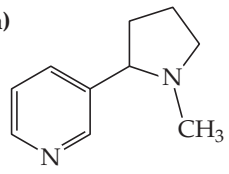
26.10 Brevetoxin A, a cyclic polyether made up of 11 rings, is a potent neurotoxin. It is named from the *brevis* family of algae from which it was extracted. Locate all the stereocenters in Brevetoxin A.

Brevetoxin A



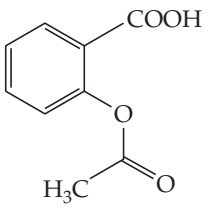
26.11 Which of the following molecules are chiral?

(a)



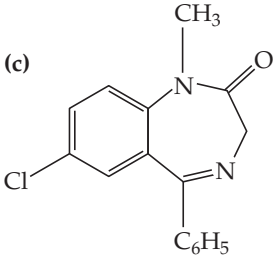
nicotine

(b)



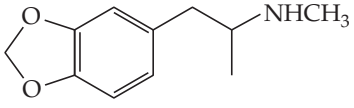
aspirin

(c)



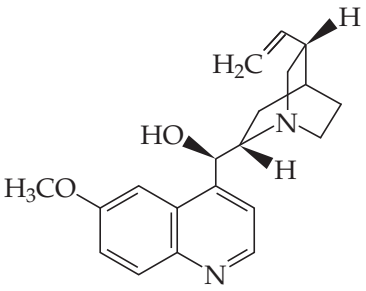
valium

(d)



ecstasy

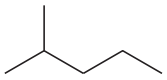
26.12 Quinine is a well-know antimalarial drug. How many chiral centers exist in quinine?



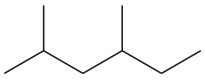
(quinine—an antimalarial drug)

26.13 Which of the following molecules contain stereogenic centers?

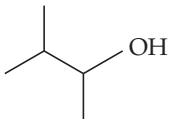
(a)



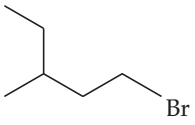
(b)



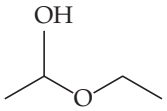
(c)



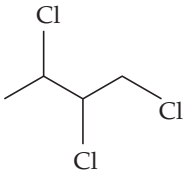
(d)



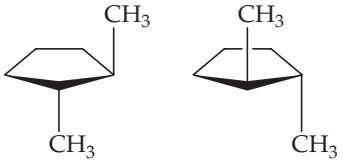
(e)



(f)



26.14 **(a)** What type of isomeric relationship exists between pentane and 2-methylbutane? **(b)** What is the relationship between these two *trans*-structures?



Answers to Self-Assessment Exercises

25.7 (d) **25.8** (c)

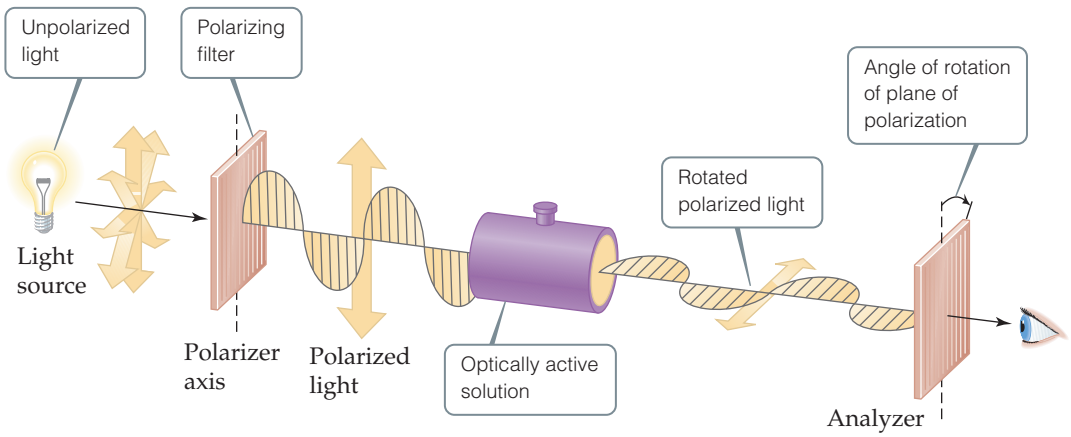
25.4 Measuring Optical Activity

Louis Pasteur (1822–1895) was a French chemist and biologist. He was responsible for some of the most important concepts and applications of modern science, including the discovery of the science of microbiology, the process of pasteurization, and molecular asymmetry. In 1848, Pasteur noticed that a saturated solution of sodium ammonium tartrate crystallized to form crystals that were mirror images of one another. He separated "right-handed" crystals from "left-handed" crystals using a microscope and a pair of tweezers. Dissolving the two crystalline forms in water and subjecting them to plane-polarized light, Pasteur was able to demonstrate that the optical activity of the mirror image crystals was opposite to one another. White wines contain a relatively high concentration of tartaric acid and crystals of calcium tartrate may sometimes be seen on corks of wine after long cellaring.

In this section, we will learn about the optical properties of chiral compounds and, by the end, you will:

- Understand the relationship between non-superimposable mirror images and rotation of plane polarized light.

Chiral molecules are said to be optically active because of their effect on plane-polarized light. If light is polarized—for example, by passage through a polarizing filter—the light in only one particular plane is allowed to pass through, as shown in **Figure 25.8**. If the



▲ **Figure 25.8 Optical activity.** Effect of an optically active solution on the plane of polarization of plane-polarized light. The unpolarized light is passed through a polarizer. The resultant polarized light then passes through a solution containing a dextrorotatory optical isomer. As a result, the plane of polarization of the light is rotated to the right relative to an observer looking towards the light source and so the optically active compound is dextrorotatory.

plane-polarized light is passed through a solution containing one enantiomer, this plane is rotated through an angle a, measured in degrees, to the right (clockwise, or +) or to the left (anticlockwise, or −) as viewed by an observer. The isomer that rotates plane-polarized light to the right is **dextrorotatory** (Latin *dexter*, "right"); it is labelled the (+)-isomer. Its enantiomer rotates plane-polarized light to the left and is called **levorotatory** (Latin *laevus*, "left"); it is labelled the (−)-isomer.

Figure 25.7 provides information on the results of the plane-polarized light experiment for the enantiomers of carvone. Notice that one enantiomer rotates light in a positive direction while the other rotates light in a negative direction. The term $[\alpha]_D$ is known as the **specific rotation** (Equation 25.1) and takes into account the concentration of the sample c (g cm^{-3}) and the path length l of the sample (dm, 1 dm = 0.1 m) confined within a solution cell, as well as the observed rotation α (degrees). The specific rotation is usually expressed in degrees, even though the units formally should be ° cm^3 dm^{-1} g^{-1}.

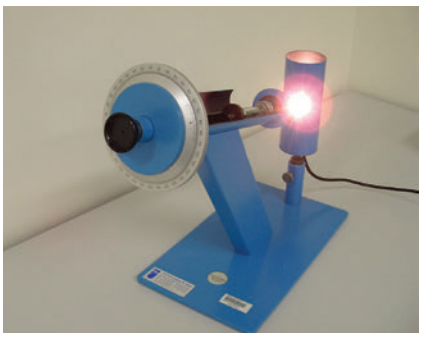
$$[\alpha]_D^{20} = \frac{\alpha}{c \times l} \qquad [25.1]$$

The subscript D refers to the source of monochromatic radiation used for the measurement (typically the sodium-D line, λ = 589 nm). The superscript 20 above the D refers to the temperature (in degrees Celsius) of the measurement, as optical activity is temperature dependent. Note that the magnitudes of the specific rotation for (+)- and (−)-carvone are identical—only the sign changes. An example of the instrument used to perform this optical experiment, called a **polarimeter**, as well as the type of solution cell used, is shown in Figure 25.9.

Optical rotation is a useful way of determining whether a compound is **enantiomerically pure**—that is, contains a single enantiomer. Failure to obtain the same specific rotation for a compound prepared in the laboratory as that reported in the literature most often happens because some of the other enantiomer is present. Often, no rotation can be observed for a substance whose molecules contain a chiral center. This usually means a 50 : 50 mixture of the two enantiomers has formed under the reaction conditions. A mixture with an equal amount of both enantiomers is called a **racemic mixture**, or *racemate*. A racemic mixture of enantiomers does not rotate plane-polarized light because the two enantiomeric forms rotate the light to equal extents in opposite directions, cancelling out any optical effect. Since a racemic mixture contains equal amounts of the (+) and (−) enantiomer it is often designated (±) or (*dl*).

Table 25.1 lists the specific rotation for several well-known organic compounds. Note that *specific rotation is an experimental quantity* and neither the magnitude nor the sign is easily predicted from the structure. An example of the difficulties in prediction is shown in the acid hydrolysis of sucrose, a compound that contains nine stereogenic centers. Here we need not concentrate so much on the complex sugar structures as on the sign and magnitudes of the specific rotation of starting materials and products.

Sucrose, $[\alpha]_D^{25}$ = +65°, is hydrolysed (broken up by the addition of water) under acidic conditions to give glucose, $[\alpha]_D^{25}$ = +53°, and fructose, $[\alpha]_D^{25}$ = −89.5° (Figure 25.10). The 1 : 1 mixture of glucose and fructose that is obtained upon the hydrolysis of sucrose is called *invert sugar* because the specific rotation of the mixture is dominated by the negative rotation of fructose. Since the total specific rotation is effectively the sum of individual specific



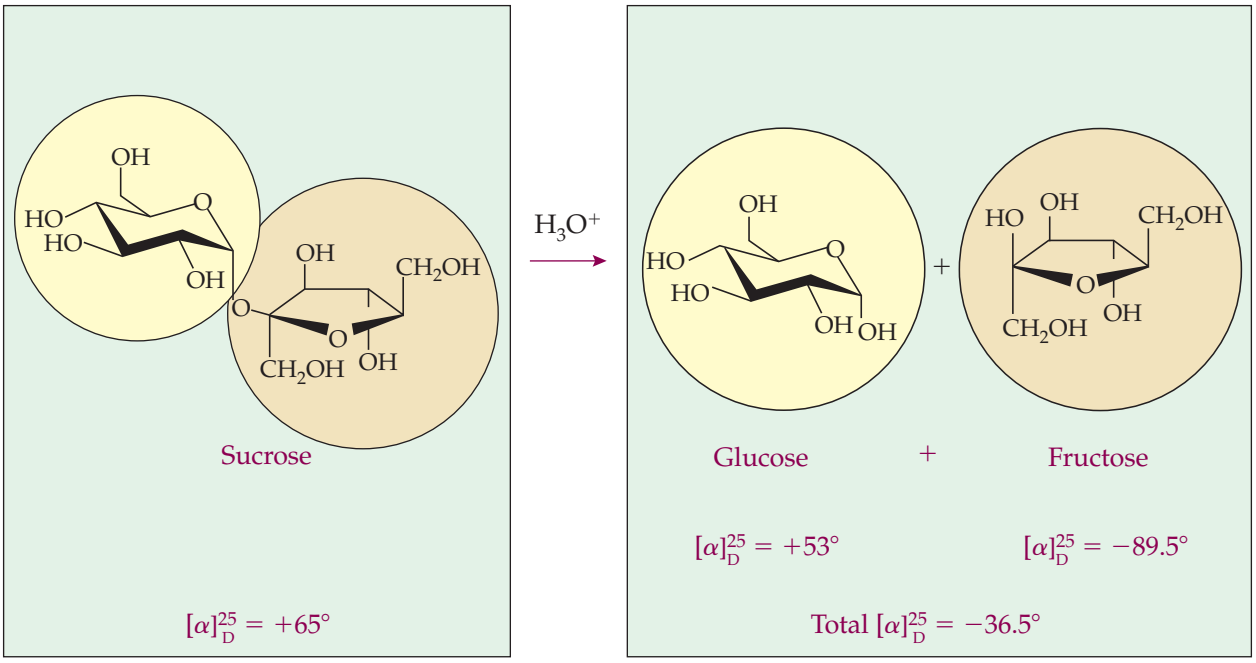
(a)

(b)

▲ **Figure 25.9 A polarimeter and solution cell.** A polarimeter (a) is used to measure the rotation of plane-polarized light as it passes through a sample contained within a 1 dm cell (b).

TABLE 25.1 Specific rotations, $[\alpha]_D$, of some common organic compounds

Compound	$[\alpha]_D$ (°)	Compound	$[\alpha]_D$ (°)
Cholesterol	−39	*d*-Camphor	+44
Penicillin-V	+233	*l*-lactic acid	−4
Sucrose	+66.5	Quinine	−178
Morphine	−132	*d*-Tartaric acid	+12
Strychnine	−139	Maltose	+141
Fructose	−92	Glucose	+53



▲ **Figure 25.10 Forming invert sugar.** The complete hydrolysis of sucrose gives glucose and fructose as products. Complete hydrolysis of sucrose yields a specific rotation of −36.5°. Fructose is the sweetest common sugar, being about twice as sweet as sucrose; consequently, invert sugar is sweeter than sucrose. The enzyme *invertase*, which bees use in making honey, accomplishes the same chemical result as the acid-catalysed hydrolysis of sucrose.

rotations, hydrolysis changes the optical properties of the solution from rotating light clockwise (+) to anticlockwise (−), despite very little molecular difference between the two sides of the equation. Hence, specific rotation is extremely sensitive to molecular structure.

Sample Exercise 25.3

Specific Rotation

The specific rotation of (−)-carvone is −62.5°, measured at 20 °C. Calculate the observed rotation at 20 °C for a solution prepared by dissolving 1000 mg of (−)-carvone in 30 cm^3 of ethanol and placing it in a solution cell 10 cm long.

SOLUTION

Analyze We are given the specific rotation, temperature, concentration and path length and asked to determine the observed rotation.

Plan These variables are all related by Equation 25.1, where $[\alpha]_D = -62.5$, $l = 10\text{ cm} = 1\text{ dm}$, $c = 1/30\text{ g cm}^{-3}$. We can solve for α.

Solve Substituting into Equation 25.1 yields

$$-62.5 = \frac{30\alpha}{1 \times 1}$$

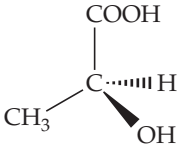
$$\alpha = -2.1°$$

Practice Exercise

The observed rotation of a solution of camphor prepared by dissolving 1.6 g in 20 cm^3 of hexane was +2.4°. Determine the specific rotation of this sample, which was contained in a 1 dm-long cell, and use Table 25.1 to conclude whether the sample is that of a single enantiomer.

Self-Assessment Exercise

25.15 Lactic acid is a chiral molecule with the structure:



One enantiomer has a specific rotation of +2.6°. What is the specific rotation of the other (mirror image) enantiomer?

(a) 0.0°.

(b) −2.6°.

(c) +2.6°.

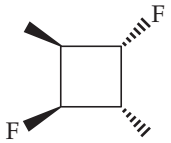
(d) It is impossible to tell from the data given

Exercises

25.16 Is it possible to determine the sign and magnitude of the optical rotation from the structure of the molecule?

25.17 Does 3-chloro-3-methylhexane have optical isomers? Why or why not?

25.18 Is the following compound optically active?



25.19 An 8 g sample of sucrose, $[\alpha]_D = +65°$, was dissolved in 25 cm^3 of water and placed in a solution cell of 5 cm length. What was the observed rotation? Is sucrose levorotatory or dextrorotatory?

25.20 The specific rotation, $[\alpha]_D$, of a pure compound obtained from plant material was found to be $-20°$. Explain the symbolism used to describe specific rotation and comment on what the result means.

Answers to Self-Assessment Exercise

25.15 (b)

25.5 | Absolute Stereochemistry

Using Priority Rules to Find a Stereocenter's Absolute Configuration

The "Hammerhead ribozyme" shown in the picture carries out a simple reaction but at a very specific site in RNA. This is a complex molecule, but even a molecule with one stereocenter, in a biological system, may show reactions of one enantiomer that are very different from its pair. While we can measure optical activity for the enantiomers, we need a system to describe the actual shape of each mirror image. The British chemists Robert Cahn (1899–1981) and Christopher Ingold (1893–1970), together with Vladimir Prelog (1906–1998), a Yugoslav chemist based in Switzerland, proposed a set of rules in 1956 to bring some order to the complex world of organic stereochemistry. Prelog was awarded the Nobel Prize in Chemistry in 1975 (jointly with Australian-born Sir John Cornforth) for his work on stereochemistry and complex naturally occurring chemical products.

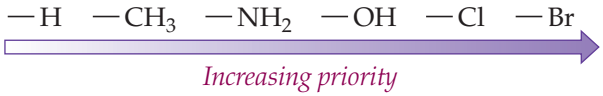
By the end of this section, you will be able to:

- Assign the configuration to a stereocenter using the nomenclature *R* or *S*.

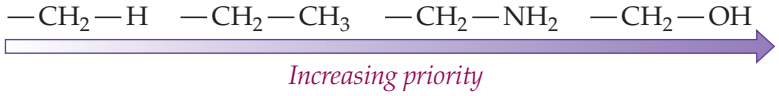
Although the (+)- and (−)-notation yields important experimental information about a compound, it tells us nothing about the **absolute configuration** (that is, the exact three-dimensional structure) of the molecule. To remove any ambiguity when describing the absolute configuration at a stereocenter, the **Cahn–Ingold–Prelog *R,S* notation** has been employed. The Cahn–Ingold–Prelog notation uses **sequence priority rules** to determine a stereocenter's absolute configuration.

We can use the following steps to determine the absolute configuration of a stereocenter:

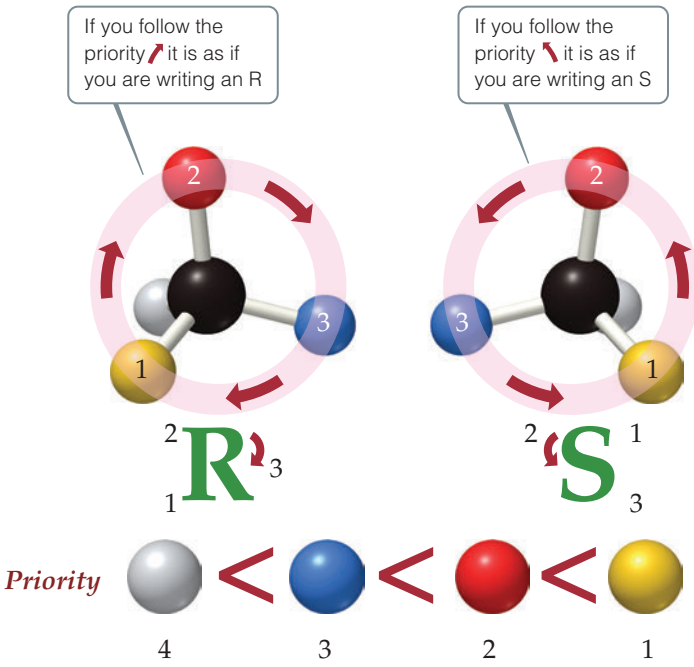
1. Locate the stereocenter.
2. Assign a priority to each substituent from 1 (highest) to 4 (lowest) based on the *atomic number* of the four atoms directly attached to the stereocenter. The higher the atomic number, the higher the priority. A representative set of groups in increasing priority order is



   If two atoms are identical in terms of priority, you need to move out along the respective chains until a difference in priority is encountered. Continue to reapply rule 2 to determine priority or until the end of the group is reached. If no difference is found, the molecule has symmetry and is therefore achiral. Examples of increasing priority fragments are



3. Orient the molecule so that the group with the lowest priority (often hydrogen) is directed away from you, that is, it is connected to the stereocenter by a dashed wedge (·····).



4. Read the three groups orientated towards you in order from highest (1) to lowest (3) priority.
5. If the numbers increase from 1–3 in a clockwise manner, the configuration is *R* (from the Latin *rectus*, "straight, correct, right"). If the numbers increase in an anticlockwise manner, the configuration is *S* (from the Latin *sinister*, "left").
6. If the compound containing the stereocenter is *R*, then its enantiomer is *S*, and *vice versa*.

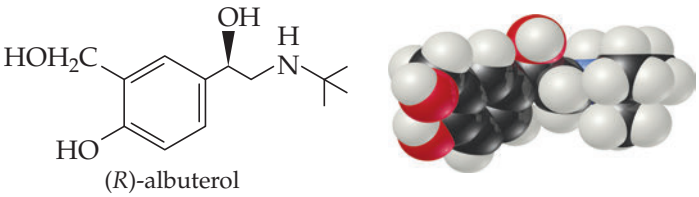
CHEMISTRY AND LIFE Chiral Drugs

Many drugs of importance in medicine are chiral substances. When a drug is prepared, sold and administered as a racemic mixture, it often turns out that only one of the enantiomers has beneficial results. The other enantiomer is either inert or nearly so, or may even have a harmful effect. For the last reason, a great deal of attention has been given in recent years to methods for synthesising the desired enantiomer of chiral drugs. Chemical research directed at understanding how to control the stereochemistry of a reaction has led to new synthetic methods that make it not only possible, but relatively cost-effective, to produce chiral molecules in *enantiomerically pure* form. Worldwide sales of single-enantiomer drugs amounts to over $225 billion annually.

Albuterol is a good example of the different physiological behaviour of enantiomers. The drug (*R*)-albuterol (Figure 25.11) is an effective bronchodilator used to relieve the symptoms of asthma. Its enantiomer, (*S*)-albuterol, is not only ineffective as a bronchodilator but actually counters the effects of (*R*)-albuterol.

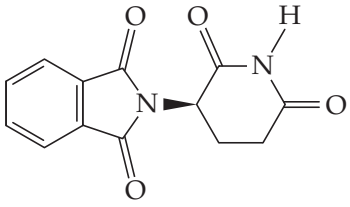
The non-steroidal analgesic ibuprofen (marketed under the trade names Advil™ and Nurofen™) is a chiral molecule usually sold as a racemic mixture. The more active enantiomer, (*S*)-ibuprofen (Figure 25.12), relieves pain and reduces inflammation, whereas the weakly active *R* enantiomer, which isn't as easily utilized, is actually converted by enzymes within the body to the active S form.

In the 1950s and 1960s the drug thalidomide was administered to pregnant women as an anti-emetic to combat morning sickness. It was found to be teratogenic, being responsible for severe deformities in over 12 000 foeteuses worldwide. The case against thalidomide has two sides, however. First, rigorous testing of all chiral drug candidates has now been made mandatory for both enantiomers after the thalidomide experience. The *R* enantiomer of thalidomide was active in preventing morning sickness during pregnancy, whereas the *S* enantiomer was responsible for the terrible side-effects in humans. Unfortunately, racemization of (*R*)-thalidomide (to form the *S* enantiomer) occurs easily within the body, so even the useful *R* enantiomer has no therapeutic use for pregnant women. Thalidomide has also been approved by the US Food and Drug Administration for the treatment of leprosy. Trials are also under way for epilepsy and HIV.



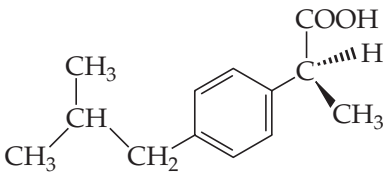
(*R*)-albuterol

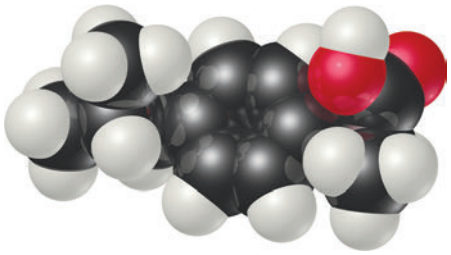
▲ **Figure 25.11 (*R*)-Albuterol.** This compound acts as a bronchodilator in patients with asthma. In contrast, (*S*)-albuterol counters this effect.



(*R*)-thalidomide

Go Figure Locate the chiral center in Ibuprofen. What evidence immediately drew you to that choice?



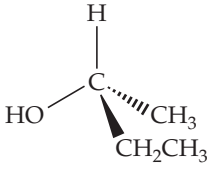


▲ **Figure 25.12 (*S*)-Ibuprofen.** For relieving pain and reducing inflammation, the ability of this enantiomer far outweighs that of the *R* enantiomer.

Sample Exercise 25.4

R and *S* Notation

Assign the absolute configuration as *R* or *S* to the following compound:



SOLUTION

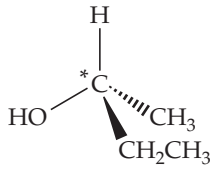
Analyze We are asked to identify this molecule as *R* or *S*.

Plan Follow the sequence priority rules after identifying the stereocenter.

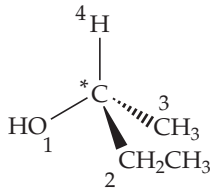
Continued

Solve

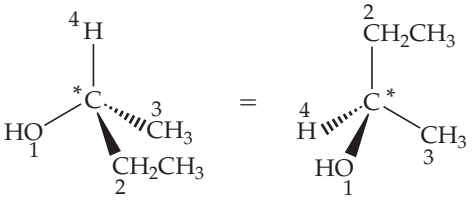
Step 1



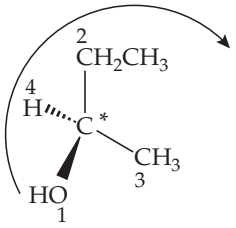
Step 2



Step 3



Step 4



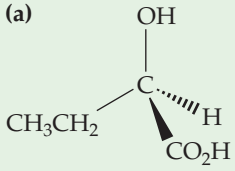
Step 5 *R* configuration

Name (*R*)-2-butanol

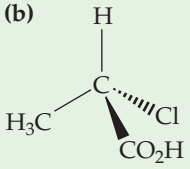
Practice Exercise

Assign the absolute configuration as *R* or *S* to the following:

(a)

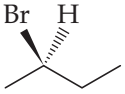


(b)



Self-Assessment Exercise

25.21 Give the full systematic name of the following molecule:

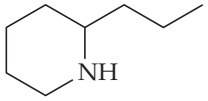


(a) (*R*)-2-bromobutane

(b) (*S*)-2-bromobutane

Exercises

25.22 Coniine is the active natural ingredient in the poison hemlock. Locate the stereocenter in this structure and assign priorities to each of the substituents.



coniine

25.23 Draw the structure for 2-bromo-2-chloro-3-methyl-pentane, and indicate any stereogenic centers in the molecule.

25.24 Assign priorities to the following sets of substituents:

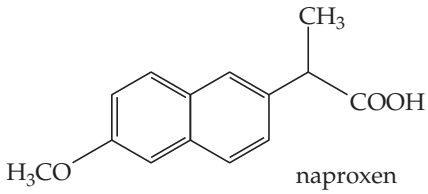
(a) $-Br$, $-CH_2CH_3$, $-CH_3$, $-OH$

(b) $-COOH$, $-CH(CH_3)_2$, $-H$, $-OCH_3$

(c) $-CH_2CH_2CH_2COOH$, $-NH_2$, $-COOH$, $-H$

(d) $-COOH$, $-COOCH_3$, $-CH_2OH$, $-OH$

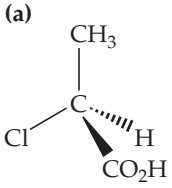
25.25 The *S* enantiomer of naproxen is a potent antiinflammatory agent whereas the *R* enantiomer is a harmful liver toxin. Draw the *S* enantiomer of naproxen and its mirror image.



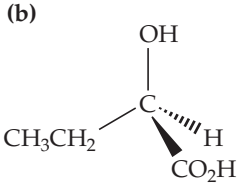
naproxen

25.26 Assign an *R*,*S* configuration to each stereocenter.

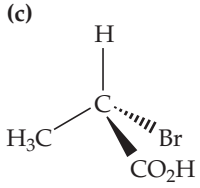
(a)



(b)



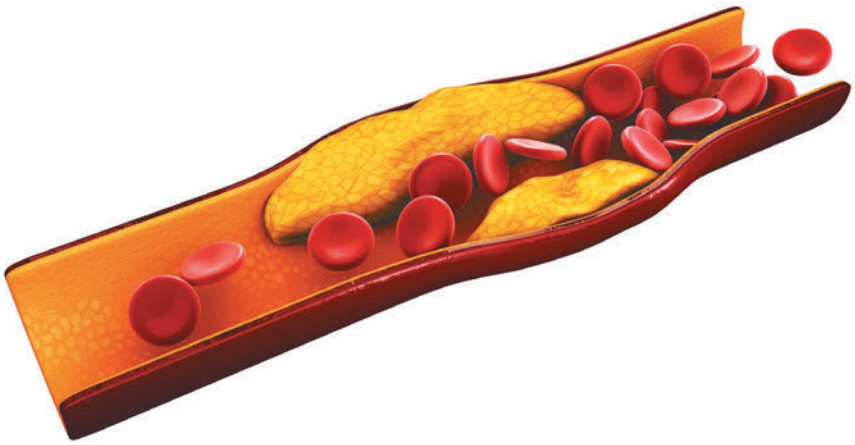
(c)



Answers to Self-Assessment Exercise

25.21 (a)

25.6 Molecules with More than One Stereocenter



A diet rich in saturated fat can result in an excess of cholesterol in the body. When this surplus is deposited on the walls of arteries, it can restrict the flow of blood to vital organs such as the heart or brain and lead to heart attack or stroke. Cholesterol is a chiral molecule with eight stereocenters and a possible 256 different stereoisomers. Remarkably, only one of these isomers is produced naturally.

In this section, we examine molecules containing two stereocenters, and by the end, you will:

- Recognize the relationship between different isomers of the same molecule
- Appreciate one method by which enantiomers may be separated

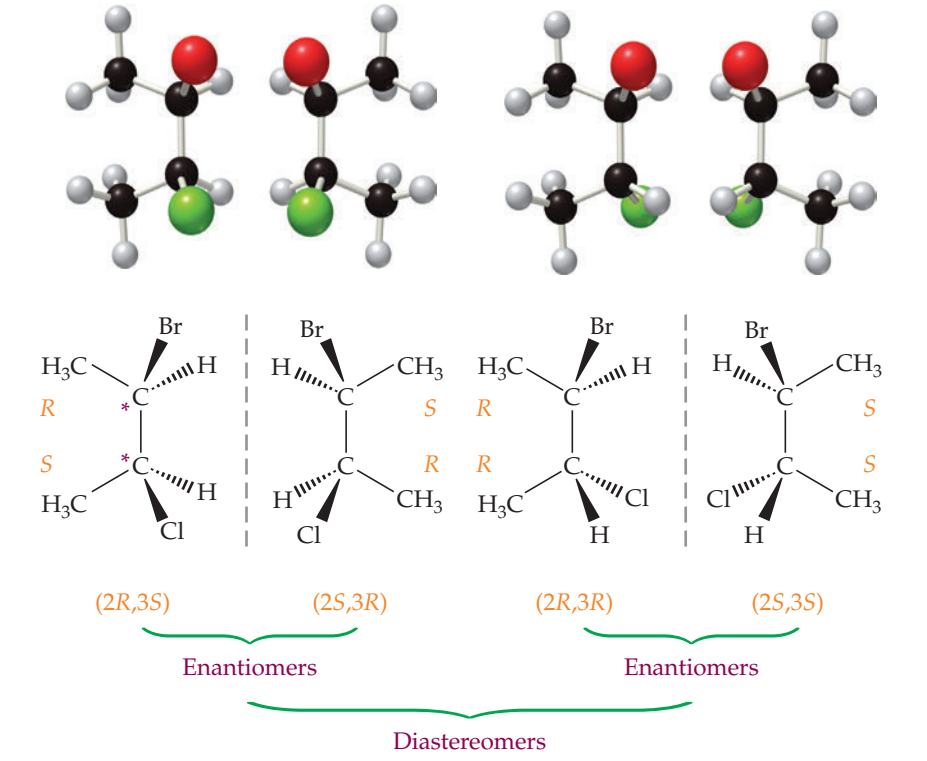
A chiral molecule with one stereocenter can exist as one of two enantiomers, *R* or *S*. Generally, for a molecule with *n* stereocenters, the maximum number of stereoisomers possible is given by Equation 25.2

$$\text{Number of stereoisomers} = 2^n \qquad [25.2]$$

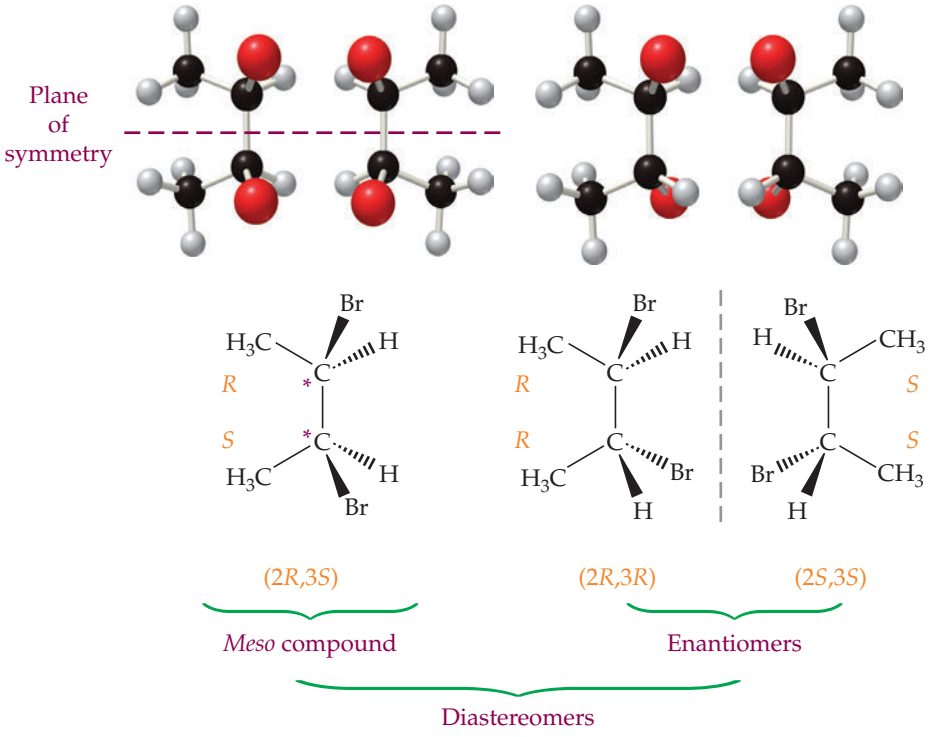
Let us consider a molecule with two stereocenters—that is, a molecule that can exist as a maximum of four stereoisomers. All the possible stereoisomeric permutations for the compound 2-bromo-3-chlorobutane are shown in **Figure 25.13**. This compound contains two stereocenters (labelled with an asterisk) and so can exist in (2*R*,3*S*), (2*S*,3*R*), (2*R*,3*R*), (2*S*,3*S*) forms. This notation is used to describe the stereochemistry at each stereocenter: the number represents the position of the chiral carbon atom on the longest chain and the *R*,*S* notation is used to describe the absolute stereochemistry at that position.

Each of the chiral molecules in Figure 25.13 is related to the other three. Notice that two pairs of enantiomers exist. Thus, one pair of enantiomers is labelled (*R*,*R*) and (*S*,*S*), while the other pair will be labelled (*R*,*S*) and (*S*,*R*). The two pairs of enantiomers are also related (for example, compare (*R*,*S*) and (*R*,*R*)). They are neither non-superimposable nor mirror images and are called **diastereomers**. Diastereomers, by definition, are any set of stereoisomers that are not enantiomers. *Whereas enantiomers have identical physical and chemical properties in an achiral environment, diastereomers always have different chemical and physical properties*.

Let's now consider 2,3-dibromobutane as an example (**Figure 25.14**). This compound has two stereocenters. However, a plane of symmetry exists through the C—C single bond between the two stereocenters in the (*R*,*S*) form, making it identical to the (*S*,*R*) form. The two forms are now superimposable and so are not enantiomers. From our earlier definition, a molecule possessing a plane of symmetry is not chiral. An achiral compound possessing two or more stereocenters is known as a ***meso* compound**.



▶ **Figure 25.13 Enantiomers and diastereomers.** Compounds with two stereocenters have a maximum of four stereoisomers. These stereoisomers have a relationship to each other. The name describing the relationship differs if the two molecules in question are non-superimposable mirror images (enantiomers) or not (diastereomers).



▶ **Figure 25.14 *Meso* compounds.** Despite possessing two stereocenters, 2,3-dibromobutane has only three stereoisomers. The *meso* form is achiral because it contains a plane of symmetry.

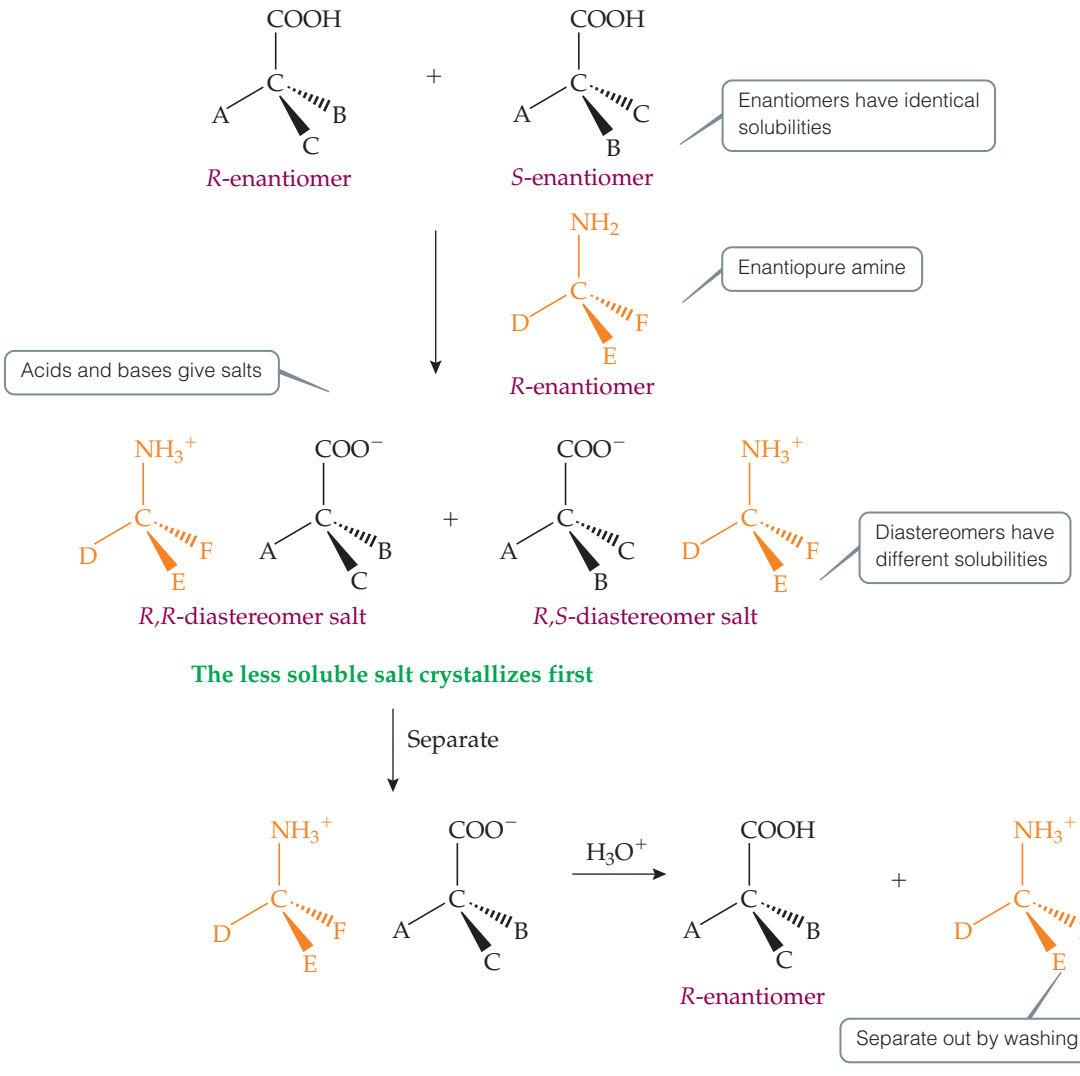
Resolution: Separating Enantiomers

Separating a racemic mixture into two enantiomers with high optical purity is extremely difficult to do without the aid of a chiral auxiliary. Pasteur was indeed fortunate that the racemic tartaric salts crystallized in such a way as to contain a single enantiomer within one crystalline form. More often than not, the two enantiomers co-crystallize to form crystals that are indistinguishable from each other. Even with the aid of chiral separating agents, this process of separating enantiomers (called **resolution**) is extremely

expensive and time-consuming. We can, however, use the different chemical and physical properties of diastereomers to perform a clever experiment to resolve two enantiomers. The trick is to convert the enantiomers into diastereomers in order to separate them.

The resolution process is explained schematically in **Figure 25.15**. Whenever possible, the chemical reactions involved in the formation of diastereomers and their conversion into separate enantiomers are acid–base reactions. The reason for this is simple: organic salts crystallize well in almost any solvent (including water) and the acid–base chemistry employed is uncomplicated. For example, a racemic mixture of a chiral carboxylic acid is reacted with a single enantiomer of an amine such as (*R*)-α-methylbenzylamine (RAMBA). The two salts that form are diastereomeric because they each contain two chiral centers, yet are not mirror images. Separation of one diastereomeric salt from the other is typically achieved by crystallization methods. In order to maximize enantiomeric purity, the crystallization is repeated several times. The pure enantiomer is subsequently liberated by treatment with aqueous acid.

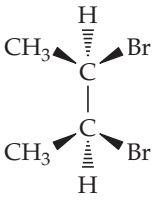
The method described in Figure 25.15 is also widely used for the resolution of chiral amines, using an *enantiopure* carboxylic acid such as the naturally occurring carboxylic acid, (*S*)-malic acid. Other methods, depending on the functionality present within the *racemate*, have also been developed. One of the more interesting methods involves an enzymatic resolution. Since biological systems such as enzymes are highly specific for a particular enantiomer, they can be conveniently used to perform simple derivatizations to a single enantiomer in a racemic mix. Derivatization (for example, hydrolysis of an ester functionality) changes both the physical and chemical properties, allowing for easy separation and hence resolution.



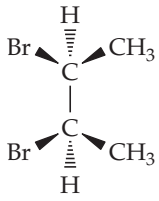
◀ **Figure 25.15**
Resolution. Enantiomers, especially those containing a carboxylic acid functionality, can be separated by converting them into diastereomeric salts. Typically, crystallization leads to the separation of one diastereomeric salt over the other. Conversion of the salt back to the carboxylic acid yields a purified enantiomer.

Self-Assessment Exercises

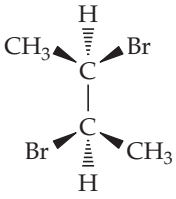
25.27 Consider the following structures of 2,3-dibromobutane:



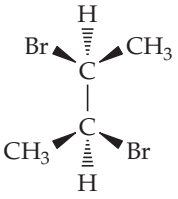
A



B



C



D

What is the relationship between the following pairs of structures?

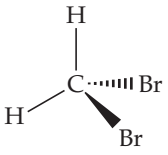
(a) **A** and **B** are enantiomers; **C** and **D** are enantiomers

(b) **A** and **B** are identical (the *meso* form); **C** and **D** are enantiomers

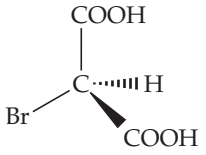
(c) **A** and **C** are diastereomers; **C** and **D** are identical (the *meso* form)

(d) **A** and **B** are identical (the *meso* form); **C** and **D** are diastereomers

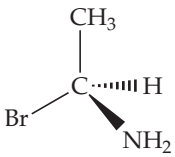
25.28 Which of the following molecules could be used to resolve a racemic mixture of a chiral amines?



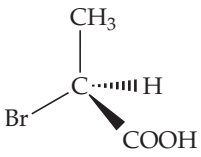
(a)



(b)



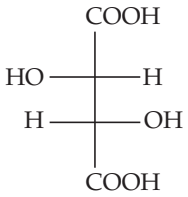
(c)



(d)

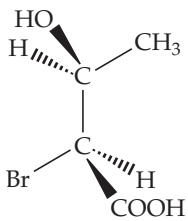
Exercises

25.29 Draw all possible stereoisomers of tartaric acid and comment on their relationship. Identify any *meso* compounds.

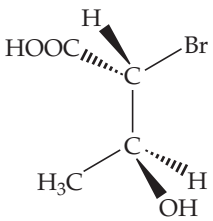


25.30 Assign *R* or *S* configurations to each stereocenter in the following molecules:

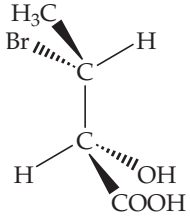
(a)



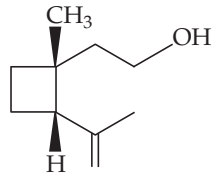
(b)



(c)

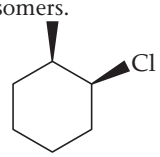


25.31 Grandisol is a pheromone of the male cotton boll weevil. What is the maximum number of stereoisomers that could exist for this molecule?

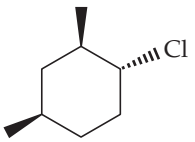


25.32 Indicate whether each of the following pairs of compounds are identical, enantiomers, diasteromers or constitutional isomers.

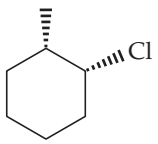
(a)



and



(b)



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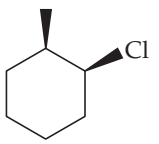

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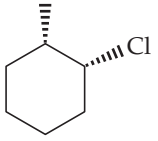

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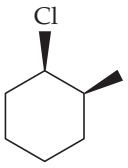
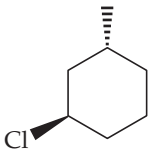
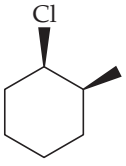


(d)



and



25.33 Revisit the stereoisomers shown in Figure 25.3 for 1,2-dimethylcyclohexane. Identify the stereocenters present as *R* or *S* and relate pairs of structures in terms of enantiomers and diastereomers.

25.34 Briefly explain how the resolution of a racemic carboxylic acid may be carried out.

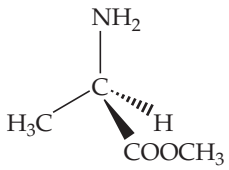
Answers to Self-Assessment Exercises

25.27 (b) 25.28 (d)

Sample Integrative Exercise

Putting Concepts Together

Alanine is one of the 20 most common naturally occurring amino acids. A methyl ester derivative ($RCOOCH_3$), prepared in the laboratory, had the following stereochemistry:



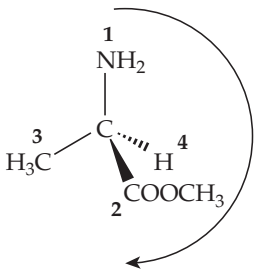
alanine methyl ester

(a) Identify the chiral center in alanine methyl ester. How many possible stereoisomers exist for alanine? **(b)** List the groups attached to this chiral center in *decreasing order* of sequence rule priority, then state whether the compound has the *R* or *S* configuration about this center. **(c)** Draw the other enantiomer of alanine methyl ester. **(d)** Describe how a pure sample of this compound may be obtained from a racemic mixture.

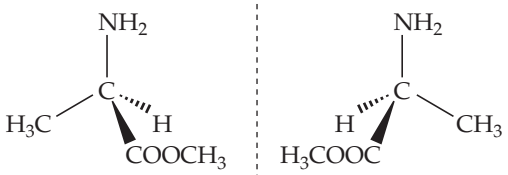
SOLUTION

(a) The central carbon atom in alanine methyl ester is the only chiral center since it has four different groups attached to it. Having only one stereocenter means that only two stereoisomers are possible.

(b) Using the sequence priority rules in Section 25.5, $NH_2 > COOCH_3 > CH_3 > H$. Since the lowest-priority group is already oriented back into the page, this compound has an *R* configuration.



(c)



(d) It is very difficult to separate enantiomers directly, and in quantity. Since this compound contains an amine functional group, the best way to achieve resolution would be to react it with a single enantiomer of a chiral carboxylic acid such as (*S*)-malic acid. This would form the *R,S* and *S,S* diastereomeric salts, which can be separated by fractional crystallization. Once isolated, addition of base would re-generate the amine, which could be separated by extraction from the water-soluble carboxylate salt and dried. Removing the solvent leaves the pure enantiomer.

(See also Exercise 25.40.)

Chapter Summary and Key Terms

SECTION 25.1 **Stereoisomers** are isomers with the same connectivity of atoms (bonding) but different arrangement of their atoms in space. The most common forms of stereoisomerism are **geometric isomers**, **enantiomers** and **diastereomers**.

SECTION 25.2 Two substituents on a cycloalkane can be ***cis*** or ***trans*** to each other. *Cis* and *trans* isomers are called geometric isomers. Geometric isomers differ from one another in their chemical and physical properties.

SECTION 25.3 **Optical isomers** are non-superimposable mirror images of one another. They are molecules that contain a **stereocenter**. Optical isomers, or enantiomers, are **chiral**, meaning that they have a specific "handedness" and their physical and chemical properties differ only in the presence of a chiral environment. Molecules that are superimposable are **achiral**, meaning not chiral.

SECTION 25.4 Optical isomers can be distinguished from each other by their interactions with **plane-polarized light**; solutions of one

enantiomer rotate the plane of polarization to the right (**dextrorotatory**, +) and solutions of its mirror image rotate the plane to the left (**levorotatory**, −) with the same magnitude. Chiral molecules, therefore, are **optically active**. A **polarimeter** is used to determine the **specific rotation** of a chiral sample. A compound that is **enantiomerically pure** contains a single enantiomer. A mixture with an equal amount of two enantiomers is called a **racemic mixture**, or *racemate*.

SECTION 25.5 The **absolute configuration** around a stereocenter can be described with the **Cahn–Ingold–Prelog *R,S* notation**. This notation uses a set of **sequence priority rules** to assign priority to each group around a stereocenter.

SECTION 25.6 Molecules with two or more chiral centers can form enantiomers and *diastereomers*. Diastereomers have different physical and chemical properties, a trait that can be used in the **resolution** of enantiomers from a *racemic mixture* to yield an enantiomerically pure compound. An achiral compound possessing two or more stereocenters is known as a ***meso* compound**.

Key Skills

- Be able to draw three-dimensional structures in two dimensions using bold and dashed wedges. (Sections 25.1 and 25.3)
- Understand the concept of chirality and be able to identify a chiral center. (Section 25.3)
- Use the Cahn–Ingold–Prelog rules to describe unambiguously the absolute configuration of a stereocenter. (Section 25.5)
- Calculate the number of potential stereoisomers based on the number of chiral centers. (Section 25.6)

Key Equations

- Specific rotation

$$[\alpha]_D^{20} = \frac{\alpha}{c \times l} \qquad [25.1]$$

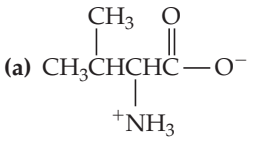
- Maximum number of stereoisomers for a compound with n stereocenters

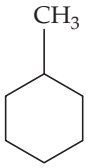
$$\text{No. of stereoisomers} = 2^n \qquad [25.2]$$

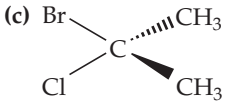
Exercises

Visualizing concepts

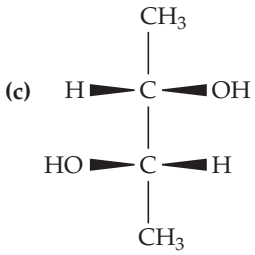
25.35 Which of the following compounds is capable of possessing isomerism? In each case where isomerism is possible, identify the type or types of isomerism.

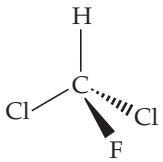
(a) 

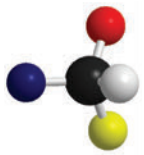
(b) 

(c) 

(d) $CH_3CH_2CH_2CH_3$

(c) 

(d) 

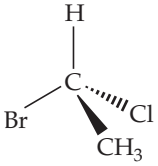
(e) 

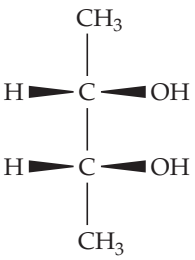
(f) 

Stereochemistry In Organic Chemistry (Section 25.1)

25.36 List some of the many items used in everyday life that are chiral.

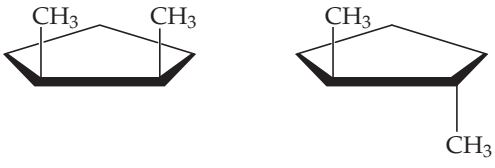
25.37 Which of the following have a non-superimposable mirror image?

(a) 

(b) 

Cis–Trans Isomerism in Cycloalkanes (Section 25.2)

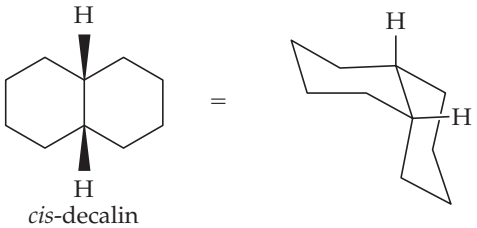
25.38 **(a)** Give the systematic or IUPAC name for each structure, assigning absolute stereochemistry to each center. Are any of these compounds achiral?



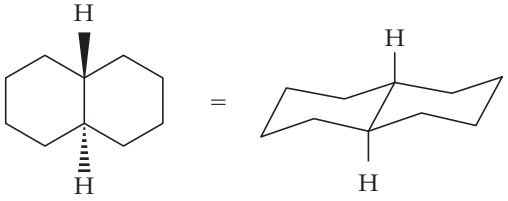
(b) Draw a *trans*-1,2-disubstituted cyclohexane in the chair conformation with your choice of alkyl substituent. What

do you notice about the position of the two substituents? Are both substituents axial, or equatorial, or is there one of each? Is this general? Explain. **(c)** Systematically name the structure you drew in part (b), taking into account absolute stereochemistry.

25.39 Decalin is a C_{10} compound composed of two fused six-membered rings. It is often used as a model to describe conformations in steroids, such as cholesterol. Two geometric isomers are possible, *cis*-decalin and *trans*-decalin. Which of these two isomers is the most stable? Explain your answer.



cis-decalin

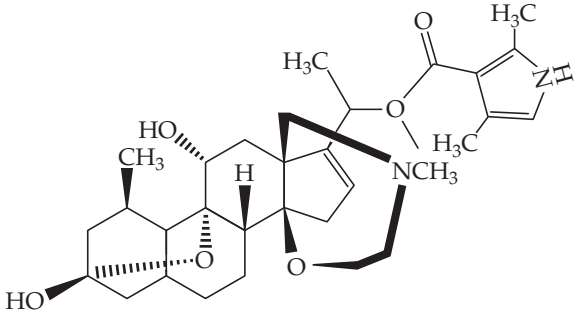


trans-decalin

Chirality in Organic Compounds (Section 25.3)

25.40 **(a)** What conditions are necessary for an organic molecule to be classed as optically active? **(b)** What is a *racemic mixture*, and why doesn't it rotate plane-polarized light?

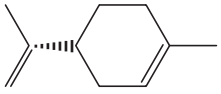
25.41 Batrachotoxin is one of the most potent toxins ever discovered. The poison is secreted from the skin of frogs and is used to coat the tip of blow darts. Only 200 μg is needed to kill a healthy adult. Locate all the stereocenters in batrachotoxin.



batrachotoxin

Measuring Optical Activity (Section 25.4)

25.42 You are very familiar with limonene. (+)-Limonene gives oranges and lemons their odour.



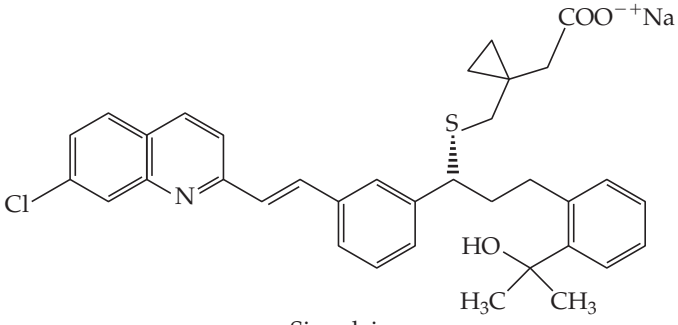
(+)-limonene

(a) Is it possible to tell the absolute configuration of (+)-limonene from its name? **(b)** Identify the chiral center in (+)-limonene. **(c)** Draw the mirror image of (+)-limonene. **(d)** Indicate the absolute stereochemistry of (+)-limonene.

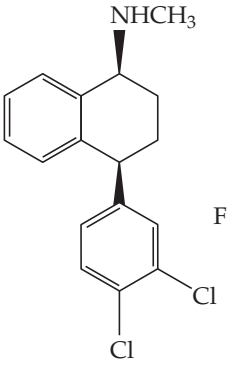
25.43 The specific rotation $[\alpha]_D$ of enantiomerically pure *d*-lactic acid is +4°. Calculate the observed rotation of a 5 cm^3 solution of lactic acid containing 6 g of *d*-lactic acid and 2 g of *l*-lactic acid in a standard 10 cm solution cell.

Absolute Stereochemistry (Section 25.5)

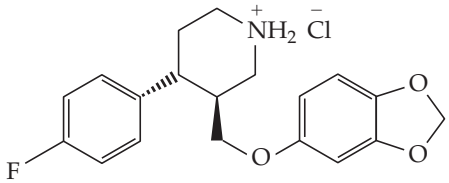
25.44 The fastest growing new treatment for asthma is the single-enantiomer drug Singulair (montelukast sodium) from Merck. Sales of the product in 2001 were worth $1.4 billion worldwide. Antidepressants such as GlaxoSmithKline's Paxil (paroxetine hydrochloride) and Pfizer's Zoloft (sertraline) had sales worth over $2 billion worldwide in 2005. Assign an *R,S* configuration to each stereocenter in each drug.



Singulair



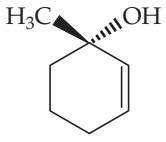
zoloft



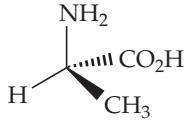
Paxil

25.45 Assign the configuration (*R* or *S*) to the stereogenic center(s) in the following compounds.

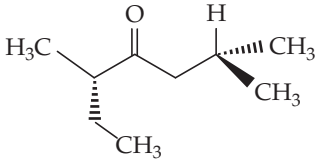
(a)



(b)



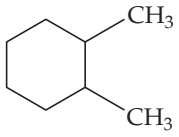
(c)



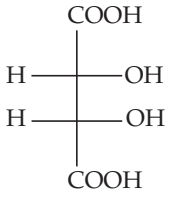
Molecules with More than One Stereocenter (Section 25.6)

25.46 Draw the *meso* form of each of the following molecules:

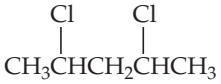
(a)



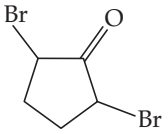
(b)



(c)



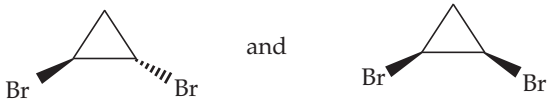
(d)



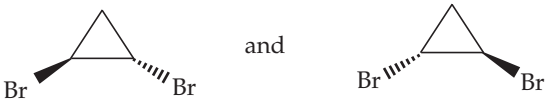
25.47 **(a)** Draw the structure of (2*R*,3*S*)-2-chloro-3-methyl pentane. **(b)** How many different 2,3-dichlorobutanes are there?

25.48 Indicate whether each of the following pairs of compounds are identical, enantiomers, diasteromers or constitutional isomers.

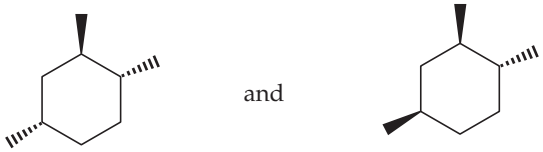
(a)



(b)

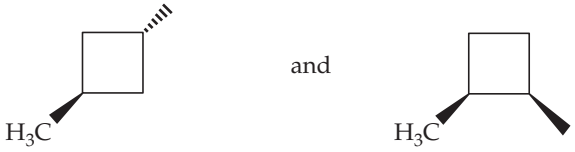


(c)



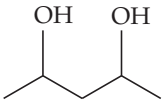
(d)

(e)

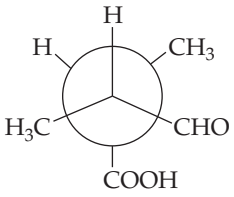


Additional Exercises

25.49 What stereoisomers exist for pentane-2,4-diol?

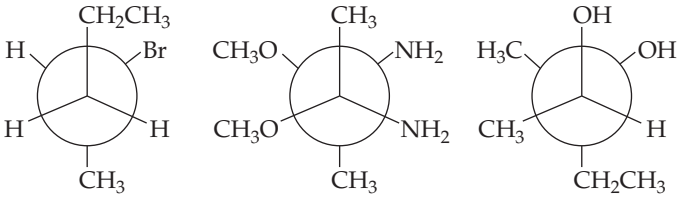


25.50 **(a)** Determine the stereochemistry at the two stereocenters within the Newman projection shown here. **(b)** Draw a Newman projection that is enantiomeric with the one shown here. **(c)** What relationship in specific rotation exists between these two structures?



25.51 Convert the following Newman projections into their standard structural formula, retaining stereochemistry.

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



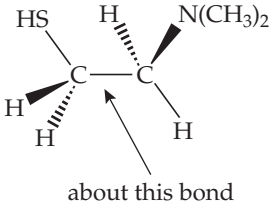
25.52 Draw the structure for 2-bromo-2-chloro-3-methylpentane, and indicate any stereogenic centers in the molecule.

25.53 Does 3-chloro-3-methylhexane have optical isomers? Why or why not?

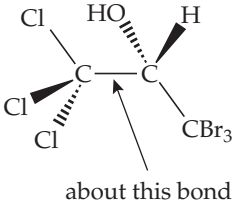
Integrative Exercises

25.54 Using Newman projections, draw the most stable staggered form of the following compounds:

(a)

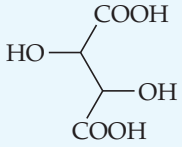


(b)



Design an Experiment

Tartaric acid occurs naturally in grapes and plays an important role in the wine industry. It also has other industrial uses such as a chelate ligand in the formation of complexes that, when enantiopure, are used in the chiral synthesis of many natural products and pharmaceuticals.



Tartaric Acid

The form of tartaric acid obtained from grapes has a configuration of (2*R*, 3*R*) and rotates plane polarized light in a (+) direction (see Table 25.1). The synthesis of tartaric acid in the lab typically produces a mixture of all possible stereoisomers. You are tasked with separating a sample of laboratory-made tartaric acid into the different isomers and identifying which is which. You have at your disposal a polarimeter and the enantiomerically pure amine, (+)-cinchonine, as well as standard laboratory glassware and reagents.

(a) How many stereocenters are there in tartaric acid? Draw out the isomers and assign the configuration at each stereocenter. **(b)** What is the expected direction of optical rotation of the isomers? **(c)** Outline the experimental procedure you would use to resolve the sample of tartaric acid. **(d)** How could you check whether the samples you obtain are pure? **(e)** Finally, how do you link your samples with the absolute configuration of the tartaric acid stereoisomers?