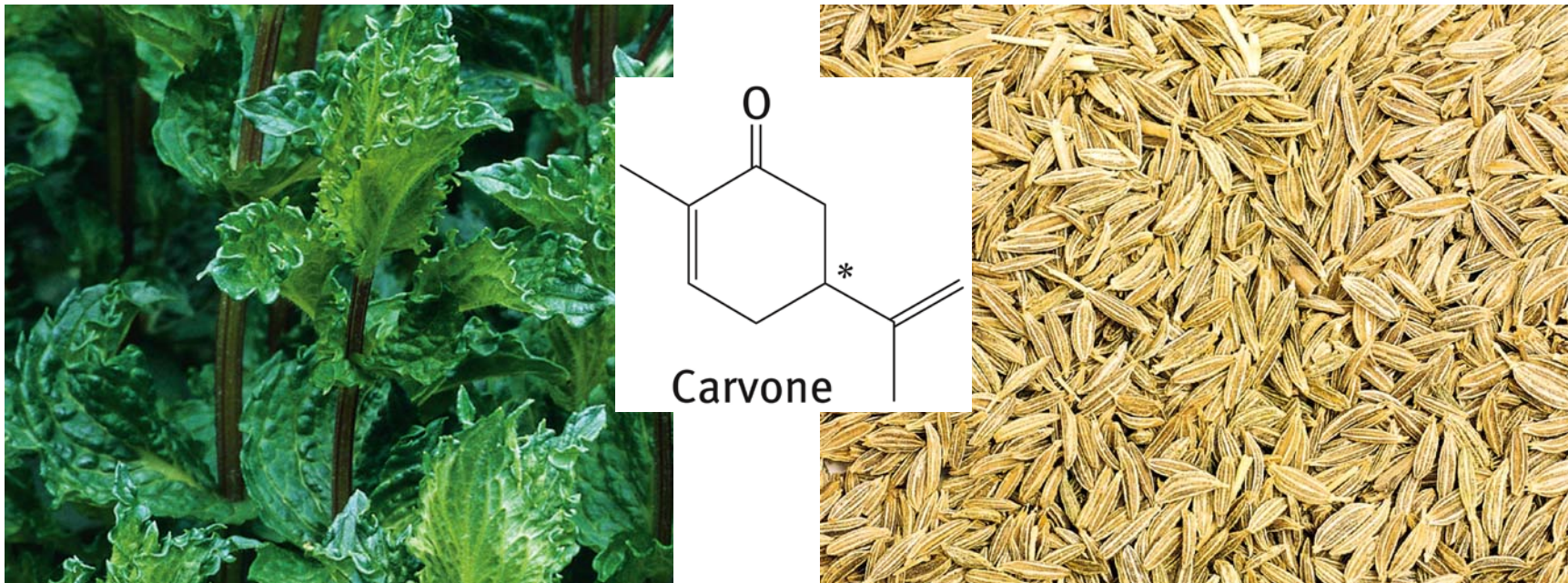


# Chapter 5: Stereoisomerism

**Stereoisomers** are compounds that have the same structural formula in terms of order of attachment, but differ in arrangements of the atoms in space.



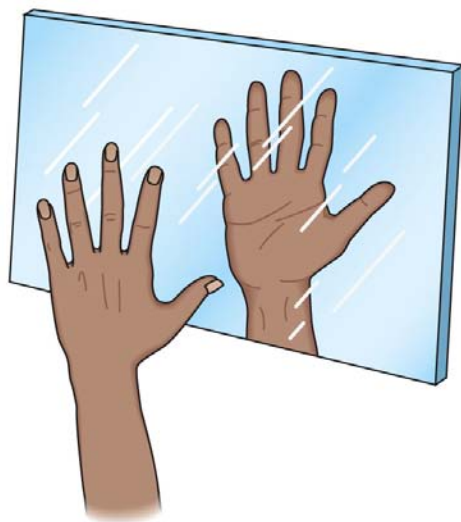
The difference in odor between caraway seeds and mint leaves arises from two stereoisomers of carvone due to different arrangement of atoms at the carbon (\*)

# 5.1 Chirality and Enantiomers

- A molecule (or object) is either chiral or achiral. The word chiral, pronounced “kairal” to rhyme with spiral, comes from the Greek (cheir, hand). A chiral molecule (or object) is one that exhibits the property of handedness. An achiral molecule does not have this property.
- What test can we apply to tell whether a molecule (or object) is chiral or achiral?
- We examine the molecule (or object) and its mirror image. The mirror image of a chiral molecule cannot be superimposed on the molecule itself. The mirror image of an achiral molecule, however, is identical to or superimposable on the molecule itself.

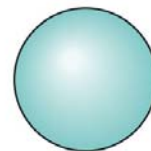
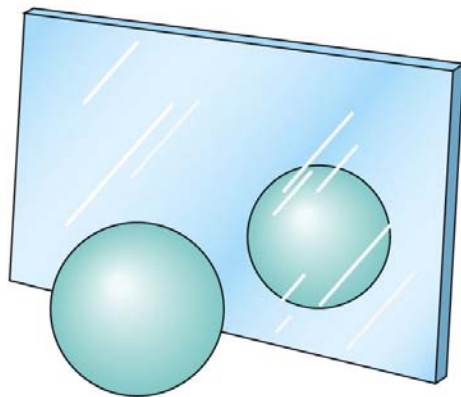
# Mirror-image relationship of chiral and achiral objects

The mirror image of a left hand is not a left hand, but a right hand.

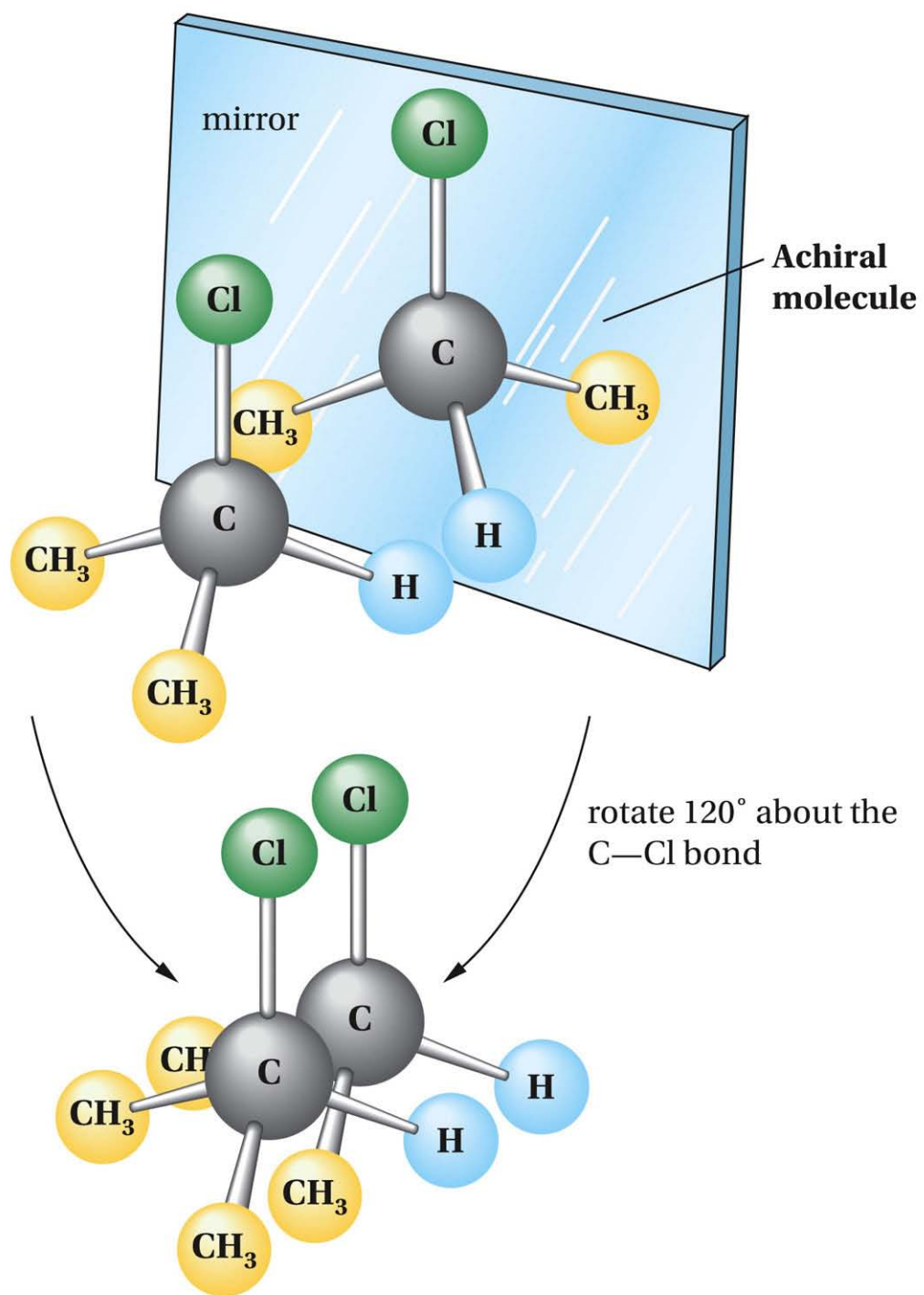


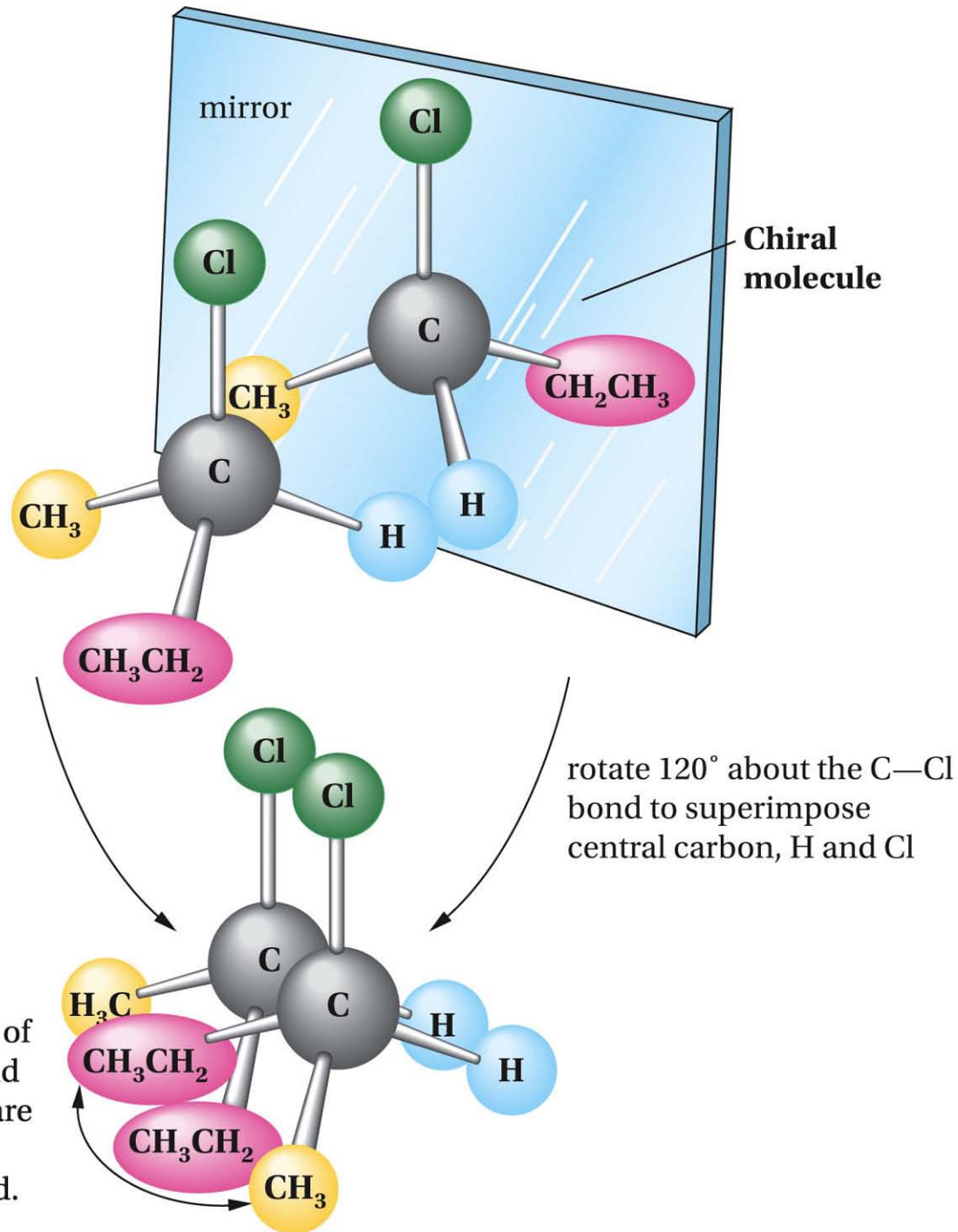
**Chiral object**

The mirror image of a ball is identical with the object itself.



**Achiral object**





The positions of the methyl and ethyl groups are *not* superimposed.

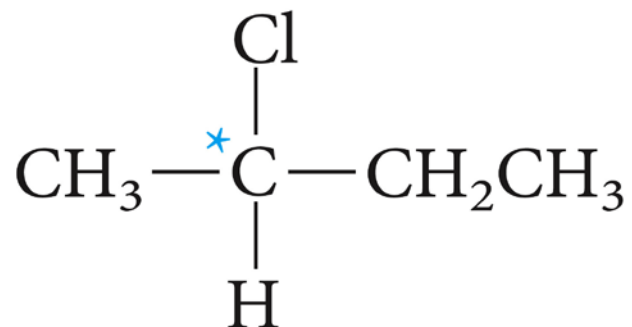
***Stereoisomers*** have the same order of attachment of atoms but different spatial arrangements of atoms.

***Chiral*** molecules possess the property of handedness.

***Achiral*** molecules do not possess the property of handedness.

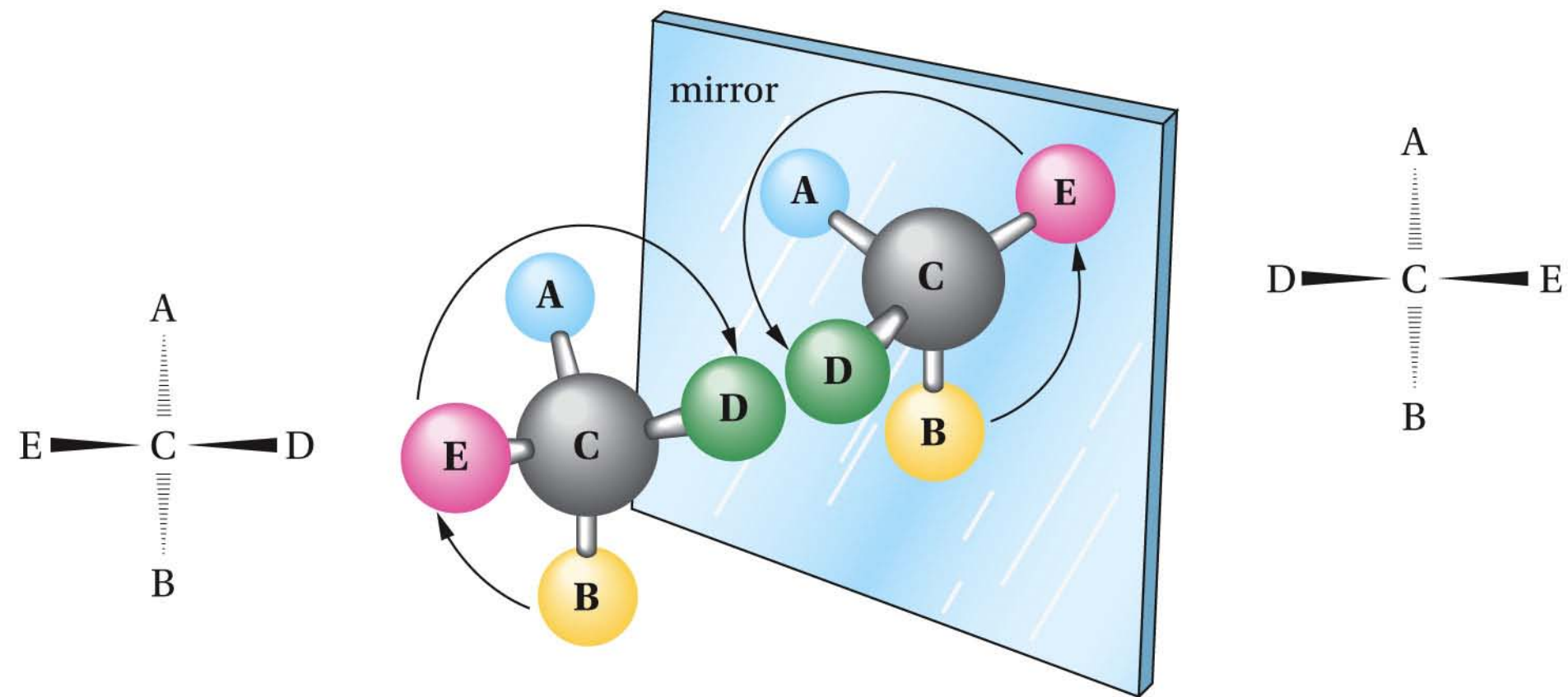
***Enantiomers*** are a pair of molecules related as nonsuperimposable mirror images.

## 4.2 Stereogenic Centers: the Stereogenic Carbon Atom

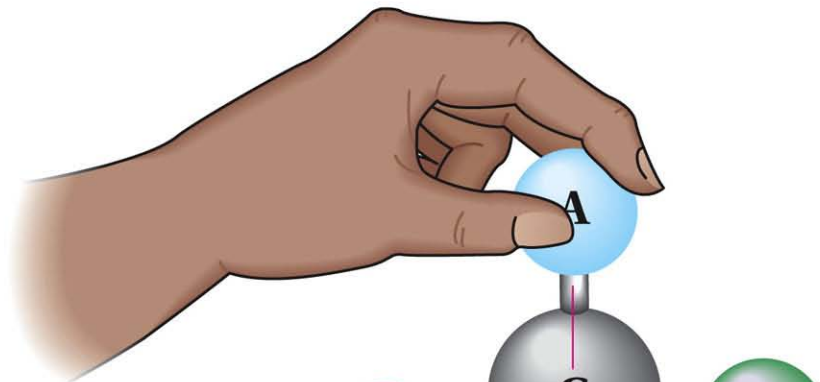


Carbon atoms with four different groups attached to them are called **stereogenic carbon** atoms (also called chiral carbon)

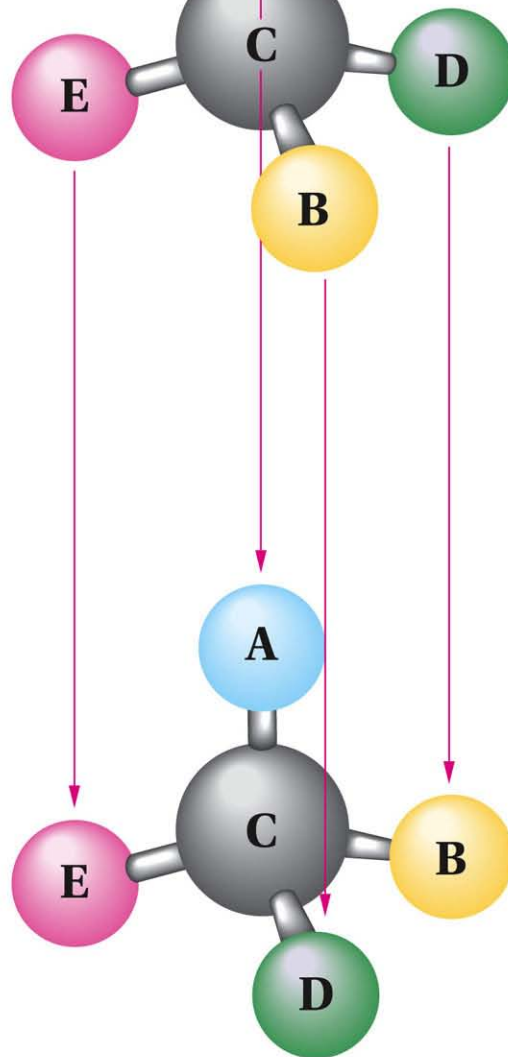
More general case for stereogenic center



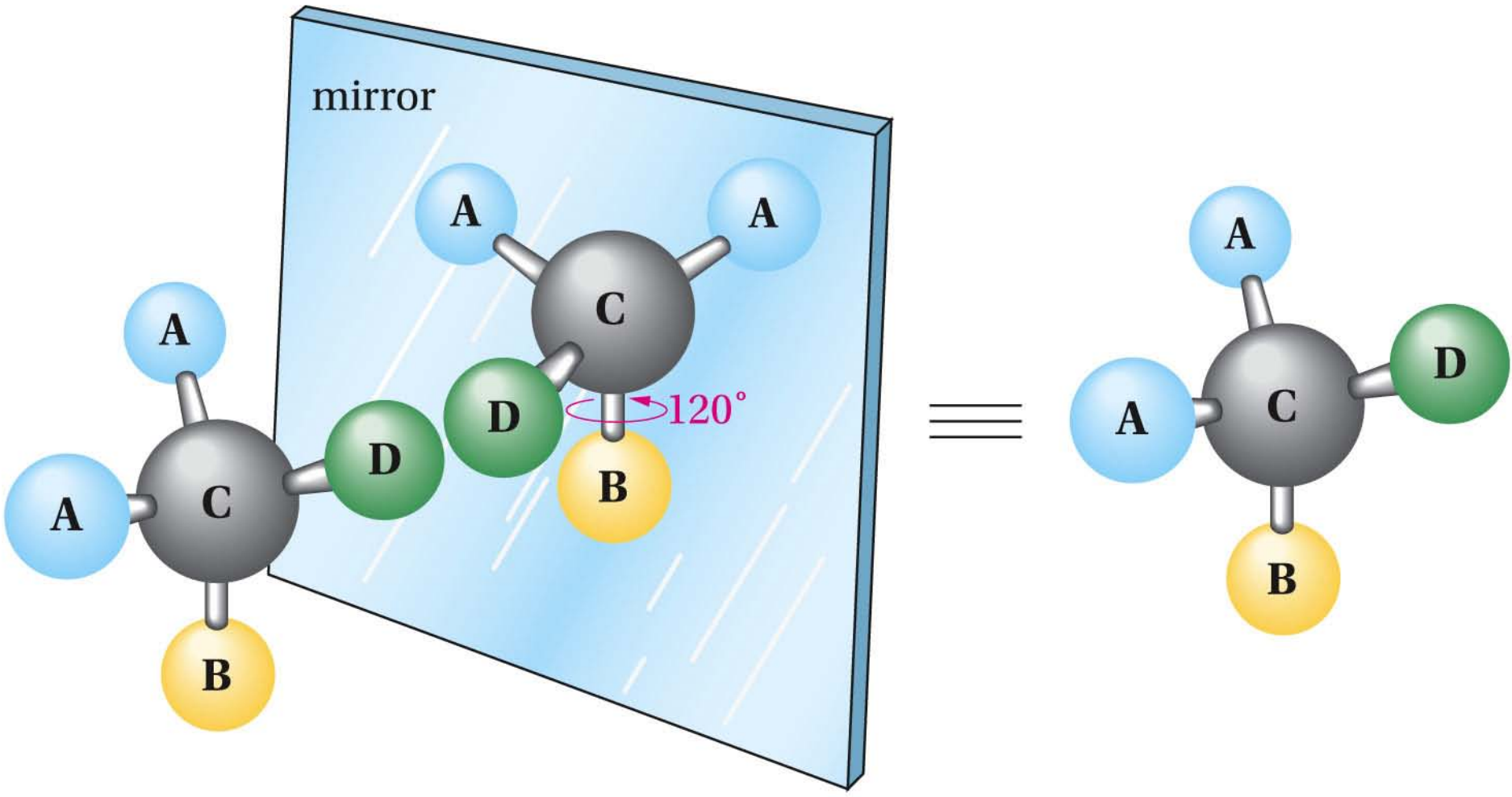


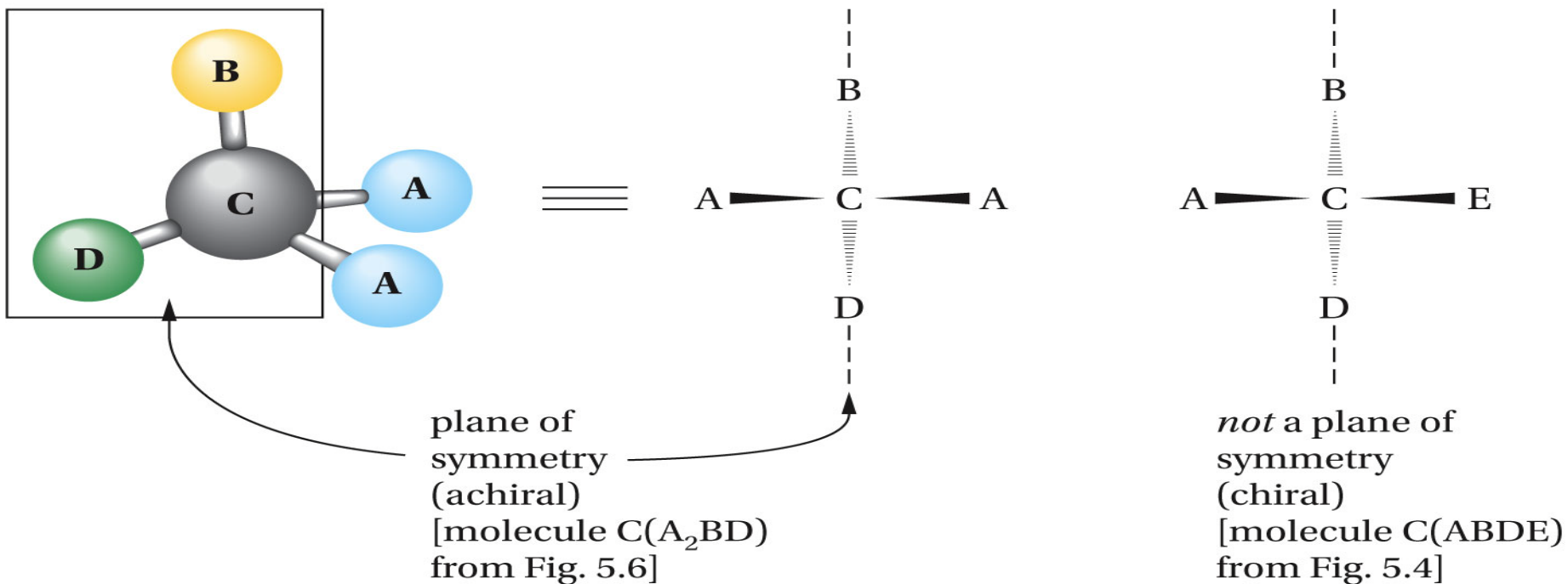


molecule in the  
mirror in Figure 5.4



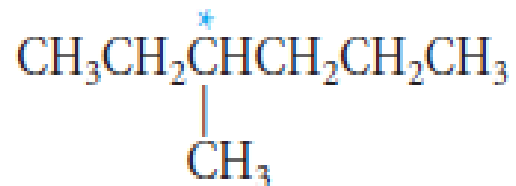
molecule to left of mirror  
in Figure 5.4



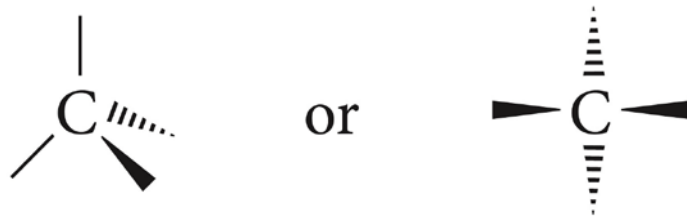


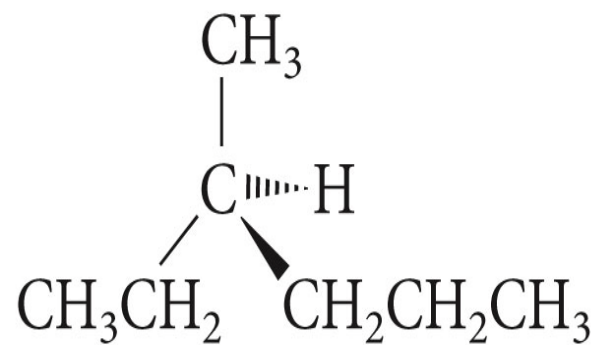
**Plane of symmetry** (sometimes called a mirror plane) is a plane that passes through a molecule (or object) in such a way that what is on one side of the plane is the exact reflection of what is on the other side. Any molecule with a plane of symmetry is achiral. Chiral molecules do not have a plane of symmetry

How many stereogenic carbons does 3-methylhexane have?

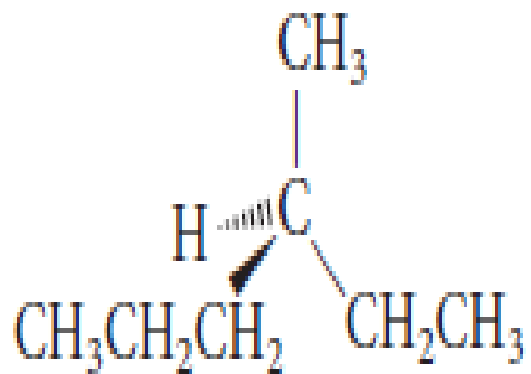
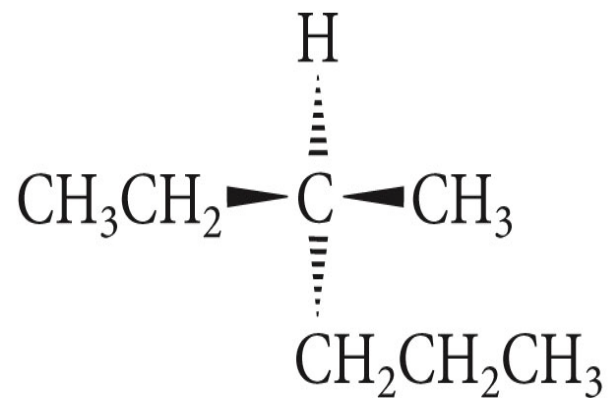


Draw the two enantiomers of 3-methylhexane.?

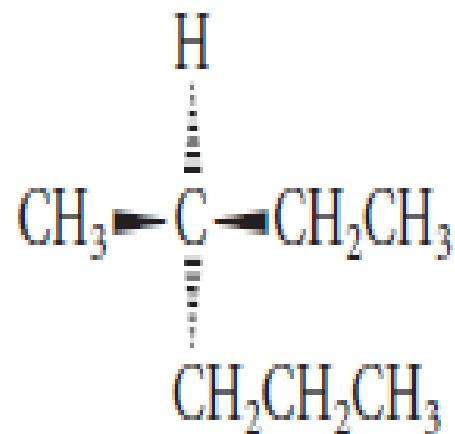




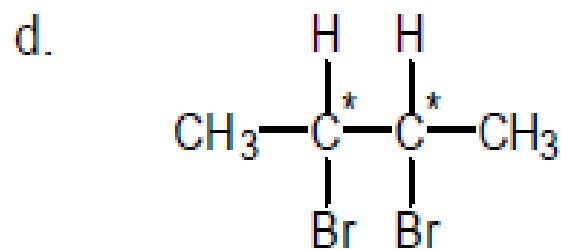
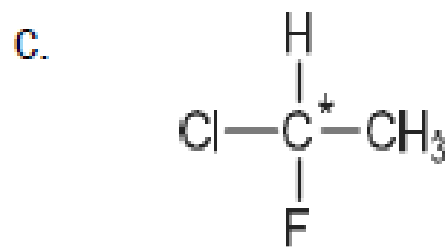
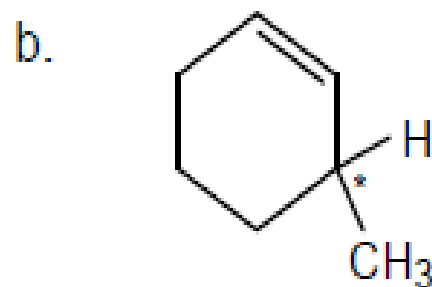
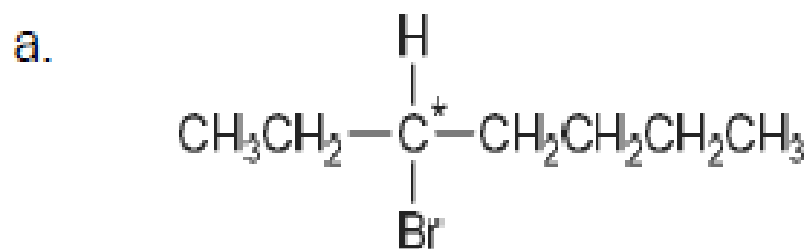
or



or



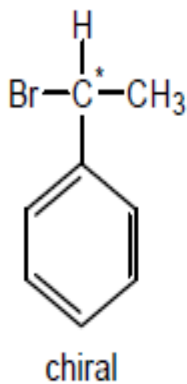
**PROBLEM 5.2** Find the stereogenic centers in



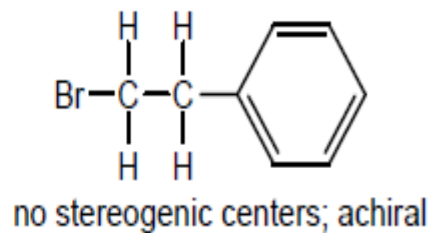
**PROBLEM 5.3** Which of the following compounds is chiral?

- a. 1-bromo-1-phenylethane b. 1-bromo-2-phenylethane

a.

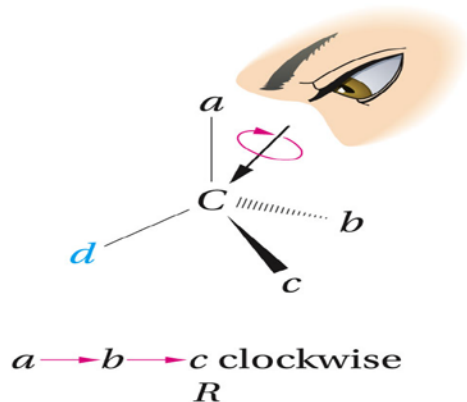


b.

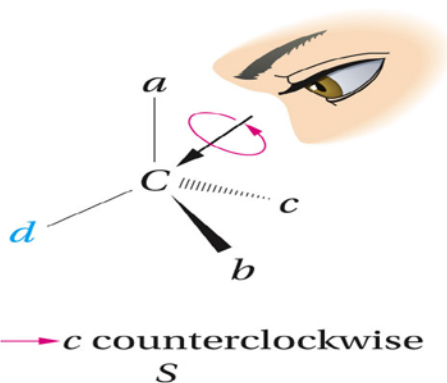
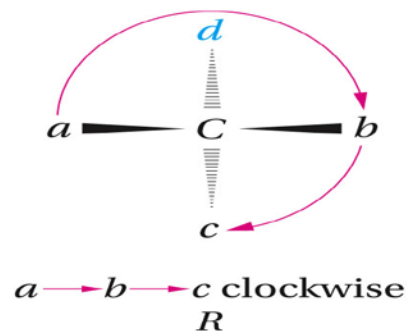


## 4.3 Configuration and the *R-S* Convention

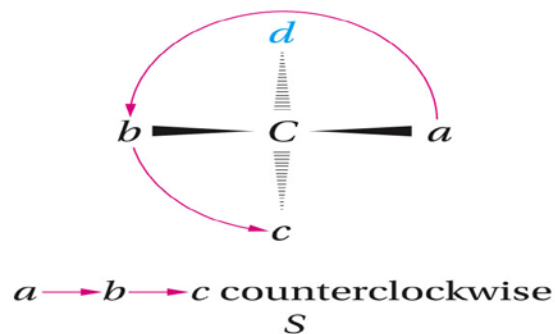
Enantiomers differ in the arrangement of the groups attached to the stereogenic center. This arrangement of groups is called the **configuration** of the stereogenic center. *Enantiomers* are another type of configurational isomer; they are said to have opposite configurations.



or



or



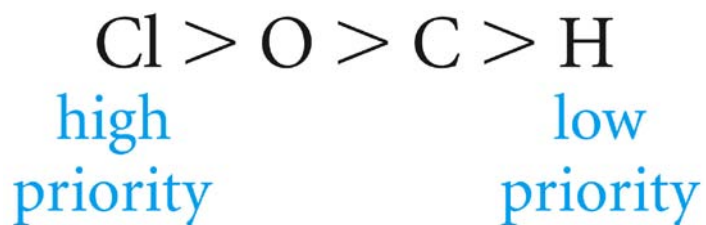


## **R-S or Cahn–Ingold–Prelog System**

The priority order of the four groups is set in the following way:

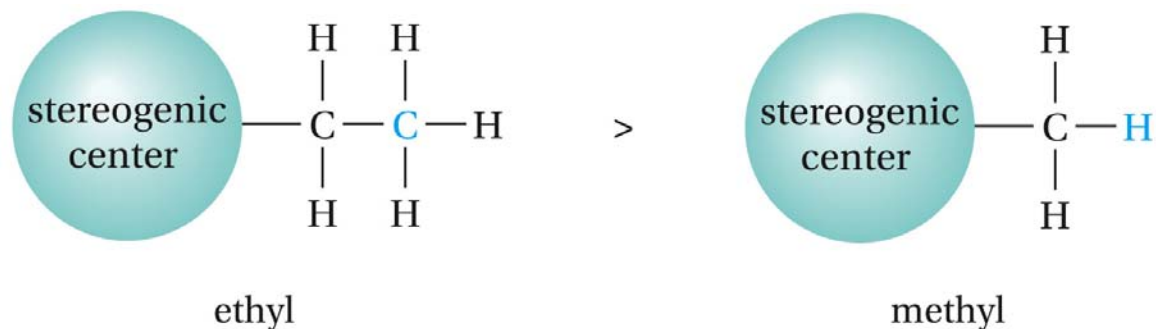
### *Rule 1*

The atoms directly attached to the stereogenic center are ranked according to atomic number. The higher the atomic number, the higher the priority



## Rule 2

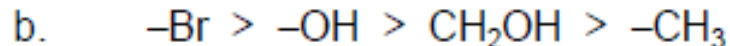
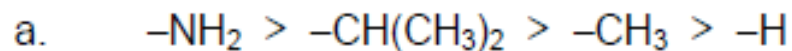
If a decision cannot be reached with rule 1, work outward from the stereogenic center until a decision is made. Example of ethyl and methyl below.



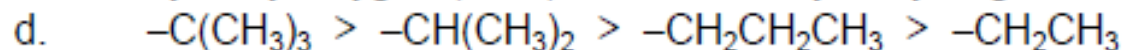
**PROBLEM 5.8** Assign a priority order to each of the following sets of groups:

- $-\text{CH}(\text{CH}_3)_2$ ,  $-\text{CH}_3$ ,  $-\text{H}$ ,  $-\text{NH}_2$
- $-\text{OH}$ ,  $-\text{Br}$ ,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$
- $-\text{OCH}_3$ ,  $-\text{NH}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{NH}_2$ ,  $-\text{OH}$
- $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}(\text{CH}_3)_2$

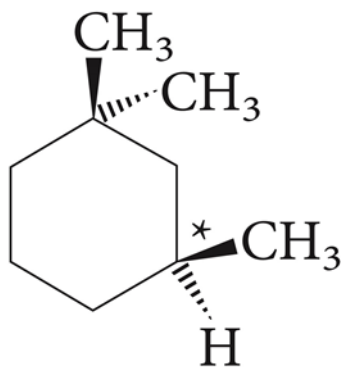
In each case, proceed from high to low priority.



The oxygen in the methoxy group ( $-\text{OCH}_3$ ) is bonded to carbon, whereas the hydroxyl oxygen ( $-\text{OH}$ ) is bonded only to hydrogen.



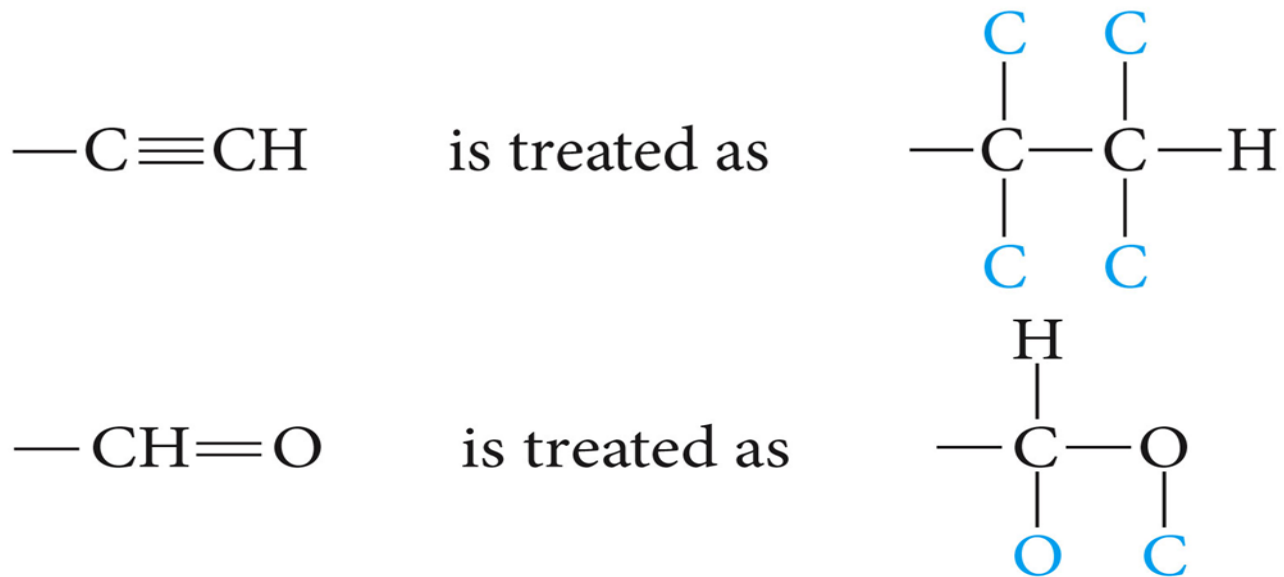
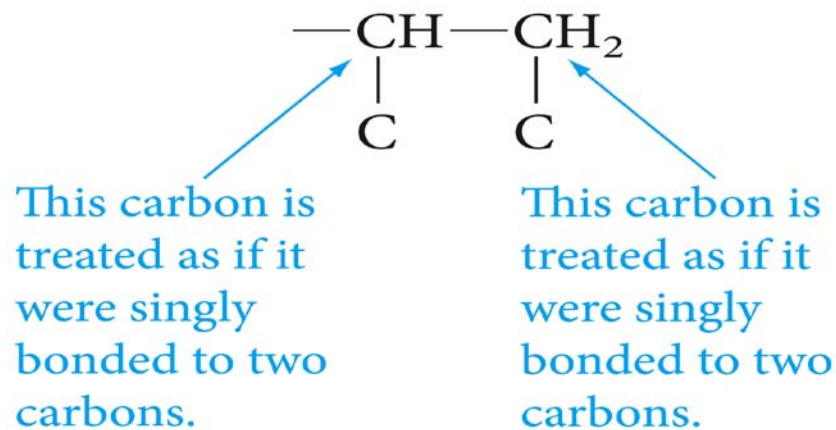
For stereogenic centers in cyclic compounds, the same rule for assigning priorities is followed



1,1,3-trimethylcyclohexane

### Rule 3

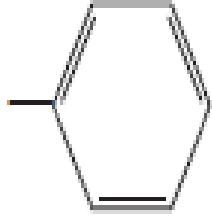
Multiple bonds are treated as if they were an equal number of single bonds.



Which group has the higher priority, isopropyl or vinyl?

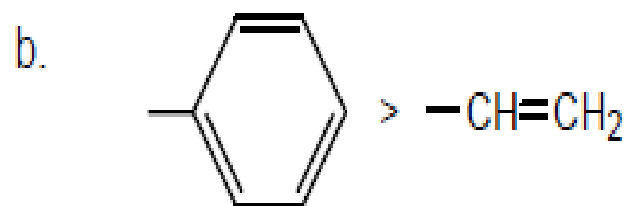


**PROBLEM 5.9** Assign a priority order to

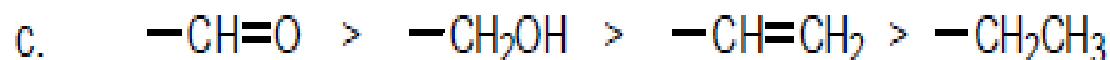
- a.  $\text{---C}\equiv\text{CH}$  and  $\text{---CH=CH}_2$       b.  $\text{---CH=CH}_2$  and 
- c.  $\text{---CH=O}$ ,  $\text{---CH=CH}_2$ ,  $\text{---CH}_2\text{CH}_3$ , and  $\text{---CH}_2\text{OH}$



The acetylenic carbon ( $-\text{C}\equiv$ ) is treated as though it is bonded to three carbons, while the olefinic carbon ( $-\text{CH}=\text{}$ ) is treated as though it is bonded to two carbons and a hydrogen (see Sec. 5.3).

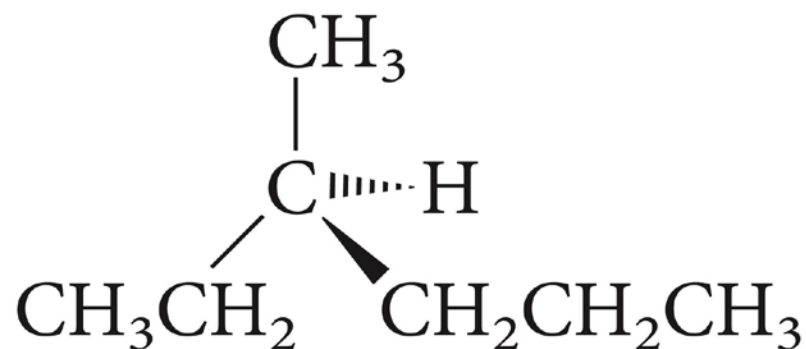


The phenyl carbon is treated as though it is bonded to three carbons.



The aldehyde carbon is treated as though it is bonded to two oxygens.

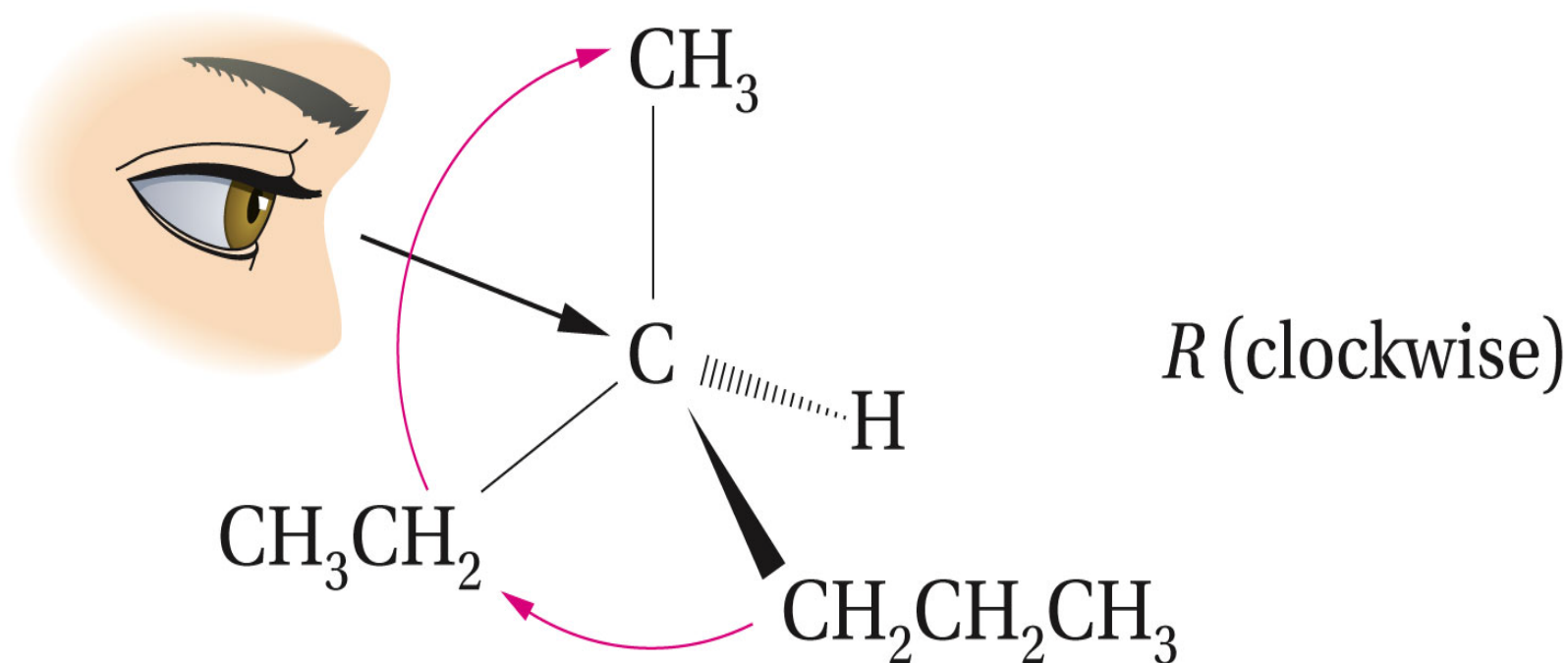
Assign the configuration (R or S) to the following enantiomer of 3-methylhexane



First assign the priority order to the four different groups attached to the stereogenic center.

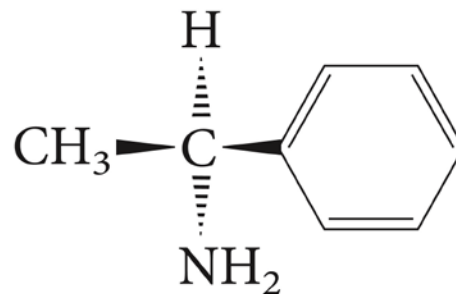
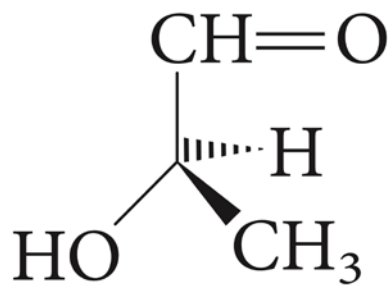


Now view the molecule from the side opposite the lowest-priority group (-H) and determine whether the remaining three groups, *from high to low priority, form a clockwise (R) or counterclockwise (S) array.*

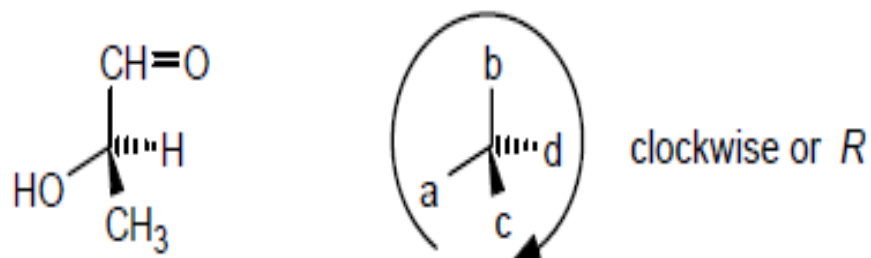




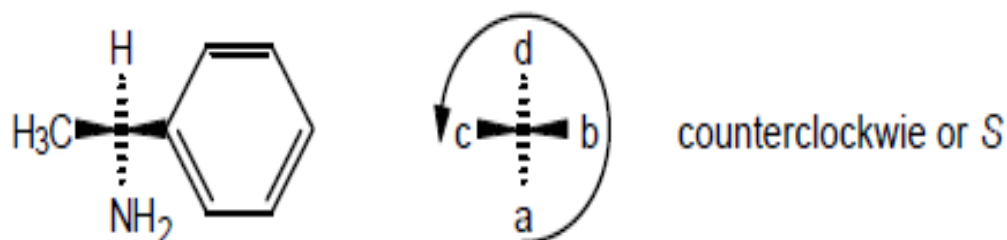
What is absolute configuration for each of the stereogenic center shown in the following compounds?



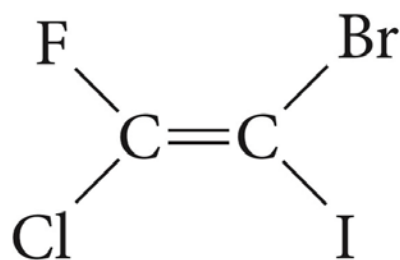
- a. Priority order:  $\text{OH} > \text{CH}=\text{O} > \text{CH}_3 > \text{H}$ . Configuration is *R*.



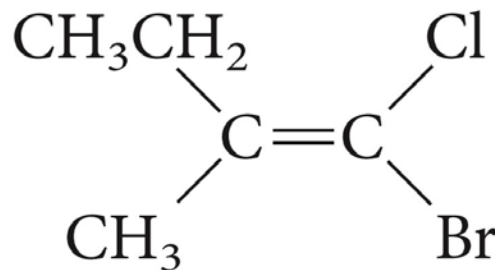
- b. Priority order:  $\text{NH}_2 > -\text{C}_6\text{H}_5 > \text{CH}_3 > \text{H}$ . The configuration is *S*.



## 5.4 The *E-Z* convention for *Cis-Trans* Isomers



*cis or trans?*

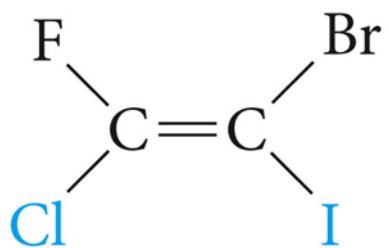


*cis or trans?*

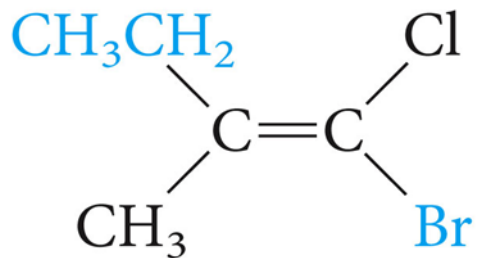
Assign the priorities of the two groups attached to each carbon of the double bond:

If the two higher-priority groups are on **opposite** sides of the double bond, the prefix **E** (from the German *entgegen*, opposite) is used.

If the two higher-priority groups are on the **same** side of the double bond, the prefix is **Z** (from the German *zusammen*, together).

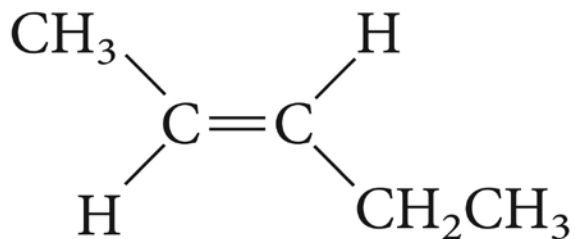


(*Z*)-1-bromo-2-chloro-2-fluoro-1-iodoethene

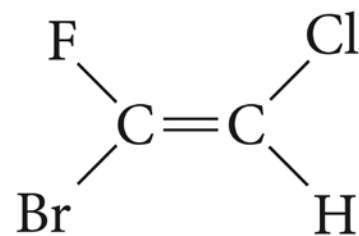


(*E*)-1-bromo-1-chloro-2-methyl-1-butene

Name each compound by the *E-Z* system



(*E*)-2-pentene

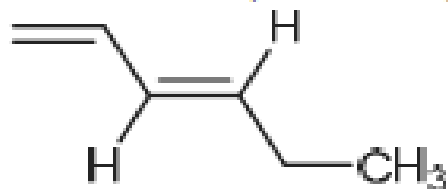


(*E*)-1-bromo-2-chloro-1-fluoroethene

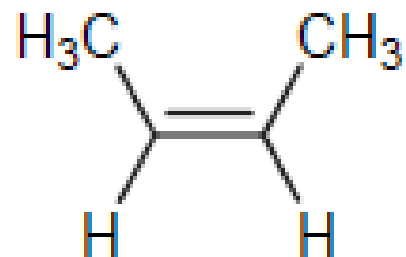
Write the structure for

a. (*E*)-1,3-hexadiene

b. (*Z*)-2-butene



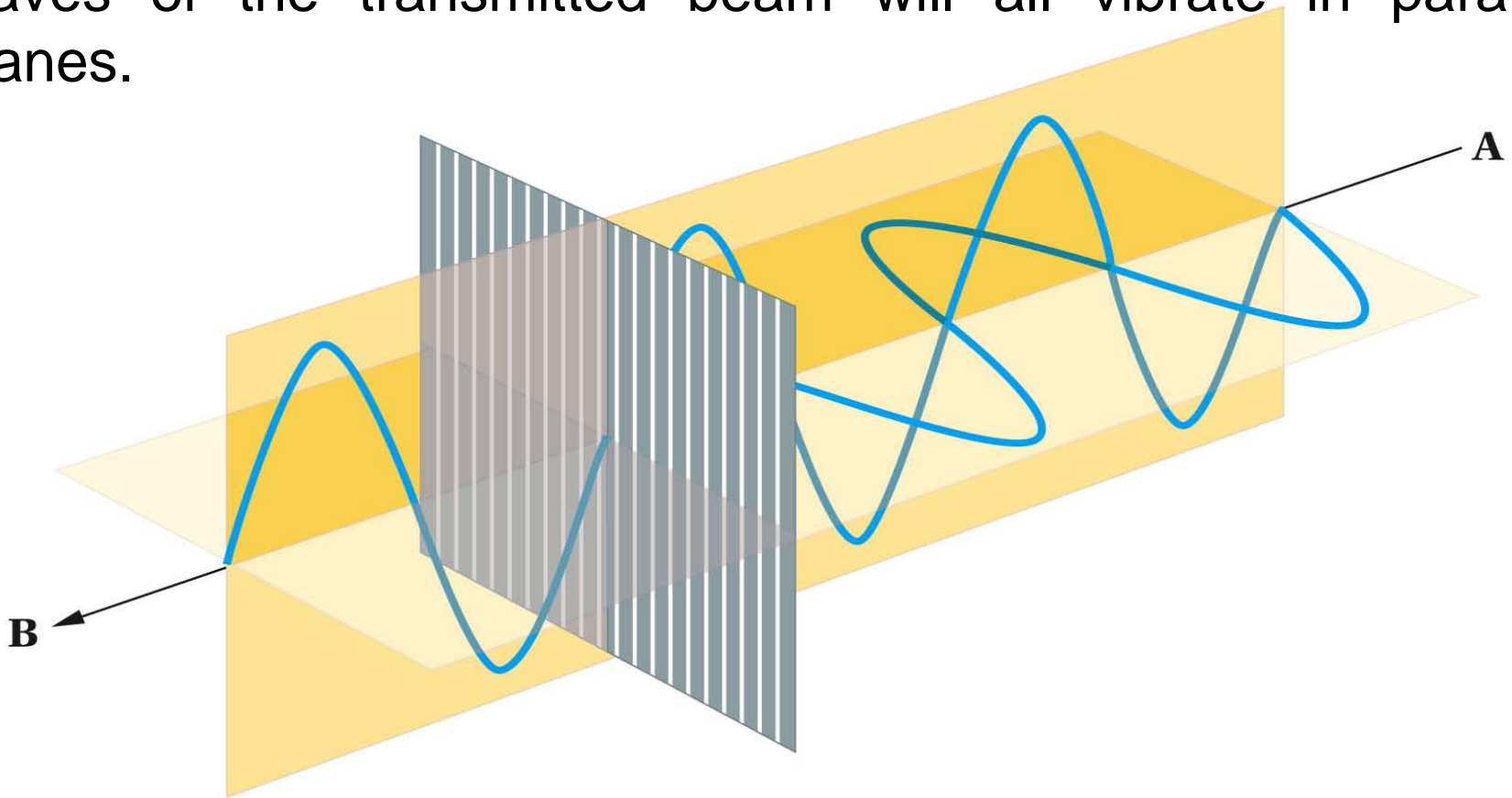
(*E*)-1,3-hexadiene

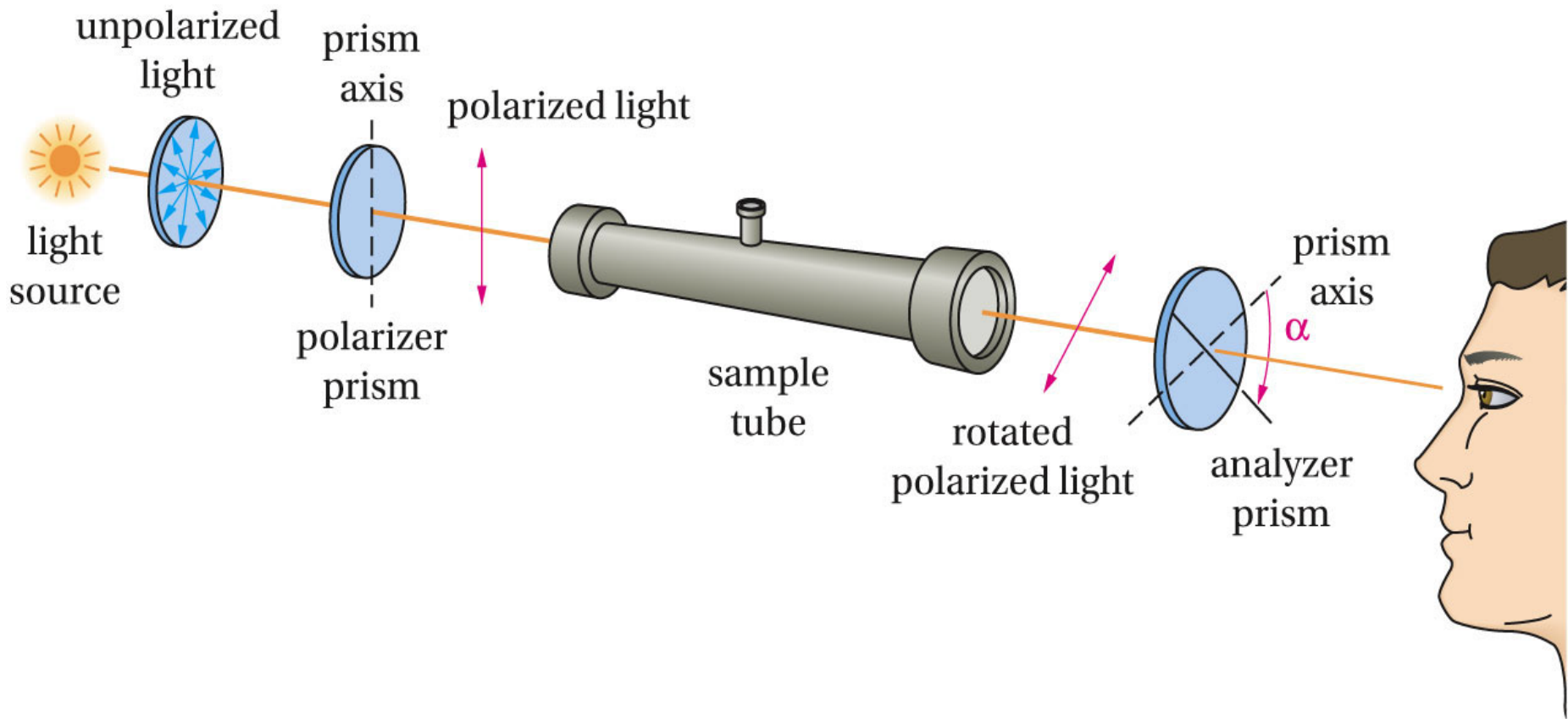


(*Z*)-2-butene

## 5.5 Polarized Light and Optical Activity

An ordinary light beam consists of waves that vibrate in all possible planes perpendicular to its path. However, if this light beam is passed through certain types of substances, the waves of the transmitted beam will all vibrate in parallel planes.





A **polarimeter** is an instrument used to detect optical activity. An **optically active** substance rotates plane-polarized light, whereas an **optically inactive** substance does not.

- The angle through which the analyzer prism must be rotated in this experiment is called  $\alpha$ , the **observed rotation**. It is equal to the number of degrees that the
- optically active substance rotated the beam of plane-polarized light. If the analyzer must be rotated to the *right* (clockwise), the optically active substance is said to be **dextrorotatory (+)**; if rotated to the *left* (counterclockwise), the substance is **levorotatory (-)**



## Specific Rotation

$$[\alpha]_{D}^{25} = \frac{\alpha}{C \times \ell}$$

temperature  $\rightarrow$  25

wavelength of light (e.g. D-line of Na lamp,  $\lambda=589.6$  nm)  $\rightarrow$  D

observed rotation  $\rightarrow$   $\alpha$

concentration of sample solution in g/mL  $\rightarrow$  C

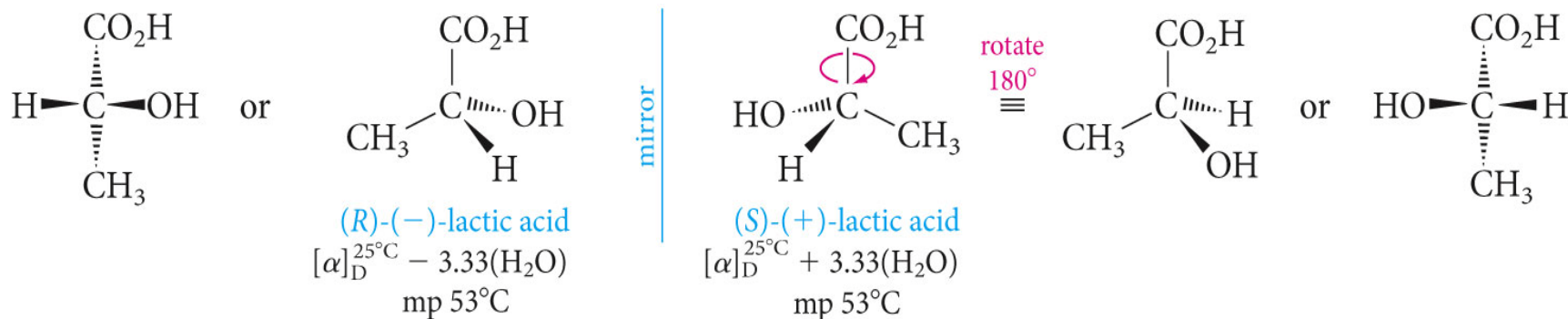
length of cell in dm (1 dm = 10 cm)  $\rightarrow$   $\ell$

### Example

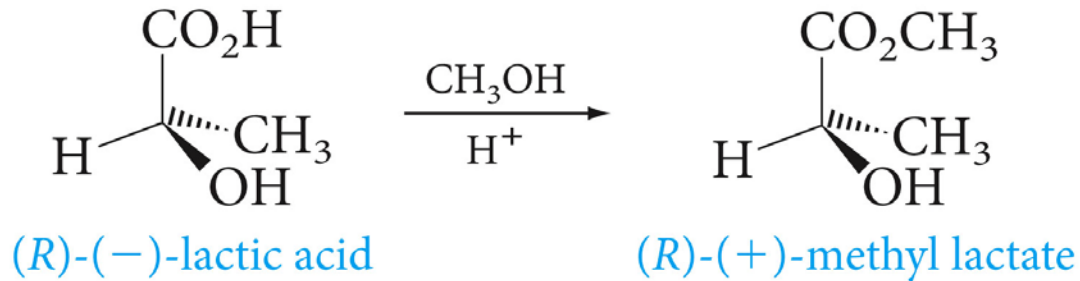
Camphor is optically active. A camphor sample (1.5g) dissolved in ethanol (optically inactive) to a total volume of 50 mL, placed in a 5-cm polarimeter sample tube, gives an observed rotation of  $+0.66^{\circ}$  at  $20^{\circ}\text{C}$  (using the sodium D-line). Calculate and express the specific rotation of camphor.

## 5.6 Properties of Enantiomers

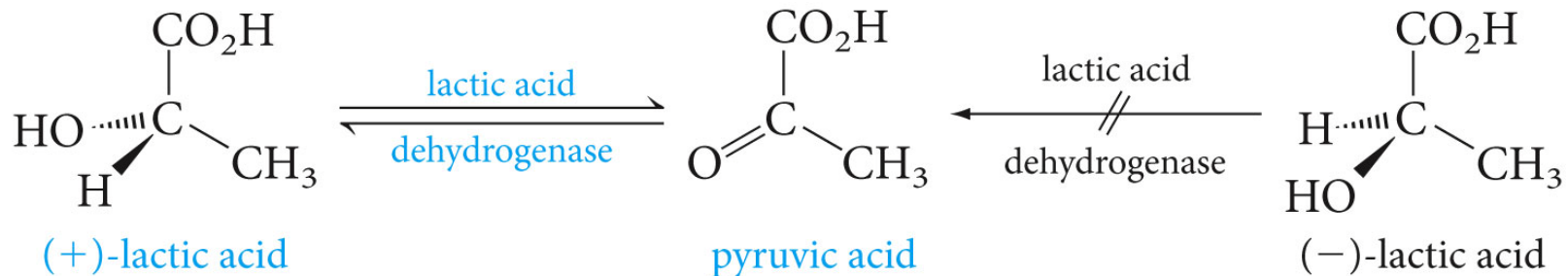
*Enantiomers have identical achiral properties*, such as melting point, boiling point, density, and various types of spectra. Their solubilities in an ordinary, achiral solvent are also identical. However, *enantiomers have different chiral properties*, one of which is the *direction* in which they rotate plane-polarized light (clockwise or counterclockwise).



There is no obvious relationship between configuration (*R* or *S*) and sign of rotation.

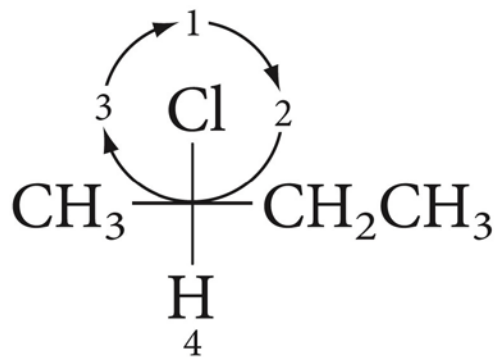
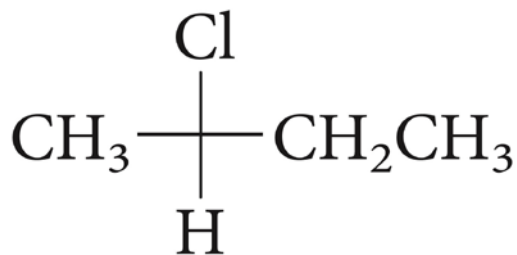


Enantiomers often behave differently in a biological setting because these properties usually involve a reaction with another chiral molecule. For example, the enzyme *lactic acid dehydrogenase* will oxidize (+)-lactic acid to pyruvic acid, but it will *not* oxidize (-)-lactic acid

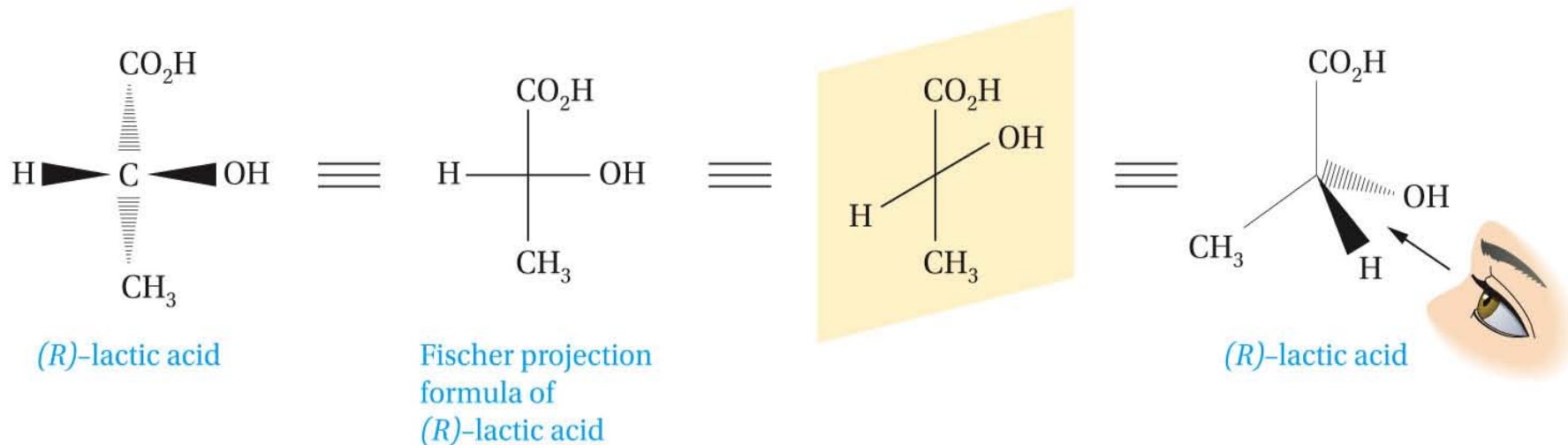


## 5.7 Fischer Projection Formulas

A **Fischer projection** is a type of two-dimensional formula of a molecule used to represent the three-dimensional configurations of stereogenic centers.



clockwise = *R*

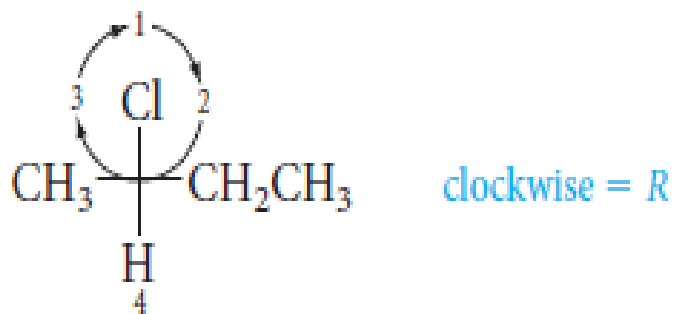
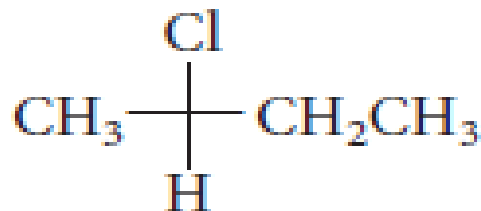


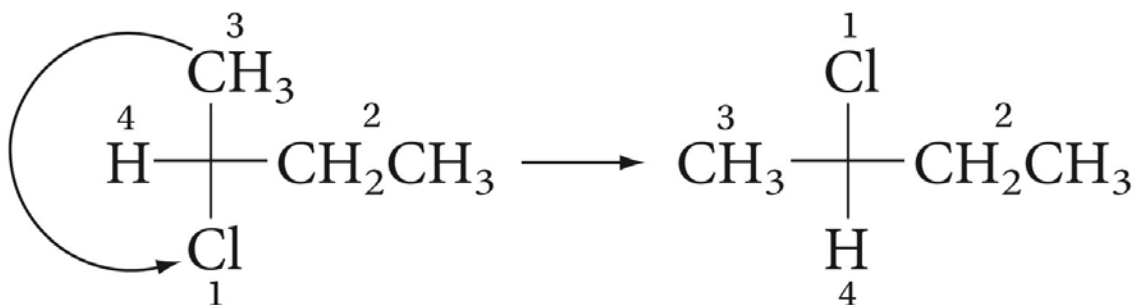
There are two important things to notice about Fischer projection formulas.

First, the C for the stereogenic carbon atom is omitted and is represented simply as the crossing point of the horizontal and vertical lines.

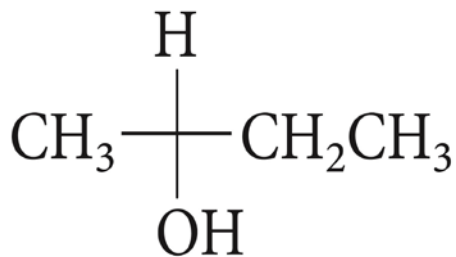
Second, horizontal lines connect the stereogenic center to groups that project *above* the plane of the page, *toward* the viewer; vertical lines lead to groups that project *below* the plane of the page, *away* from the viewer.

Determine the absolute (*R* or *S*) configuration of the stereoisomer of 2-chlorobutane shown in the following Fischer projection

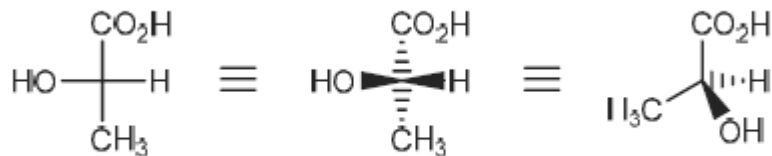




Determine the absolute configuration of the following enantiomer of 2-butanol from its Fischer projection



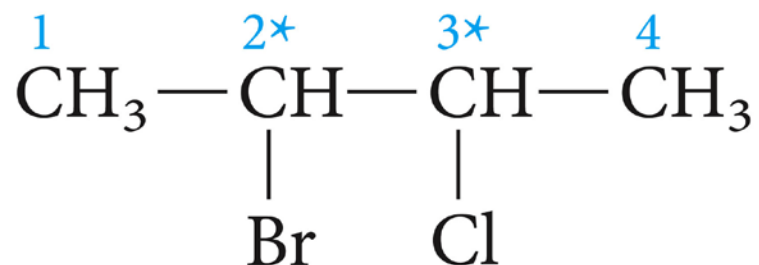
5.15



(S)-lactic acid

## 5.8 Compounds with More Than One Stereogenic Center; Diastereomers.

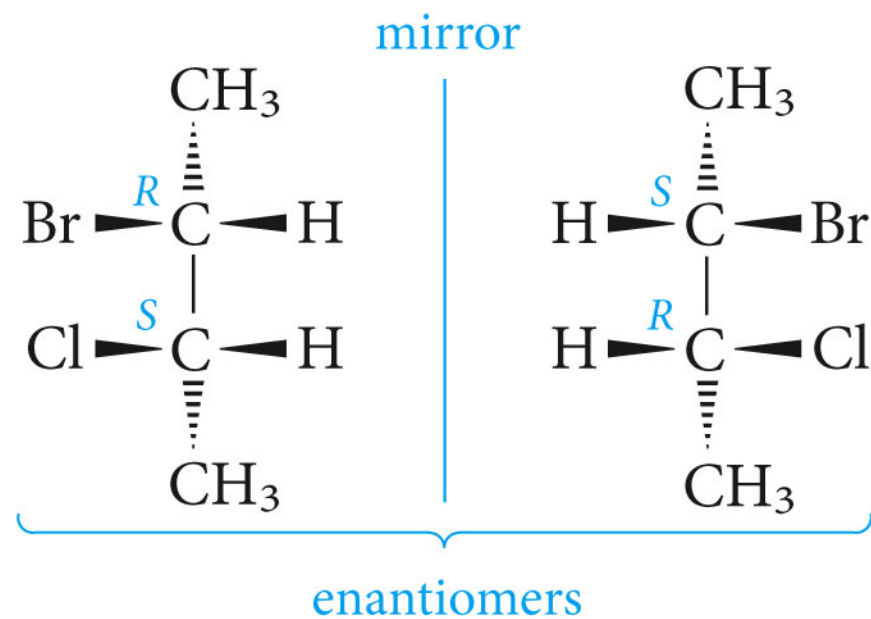
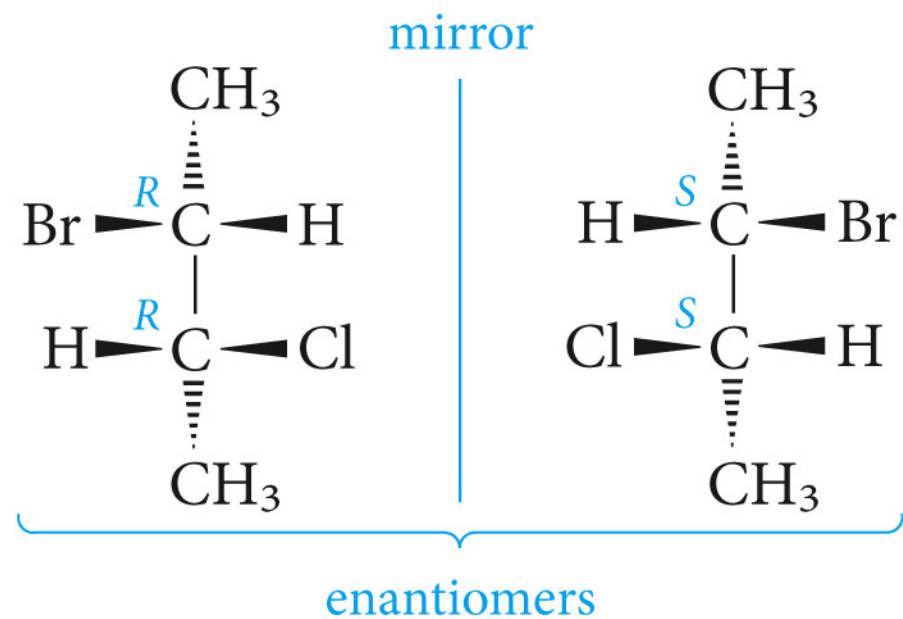
It is important to be able to determine how many isomers exist and how they are related to one another.



2-bromo-3-chlorobutane

***n** chiral centers give rise to  $2^n$  possible stereoisomers.*





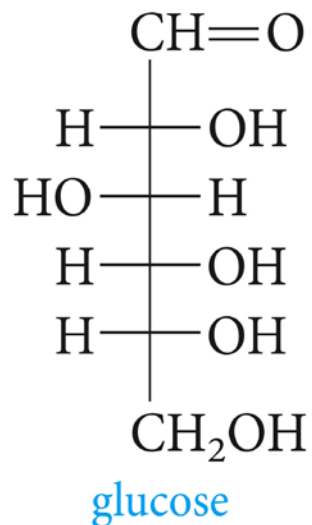
The four stereoisomers of 2-bromo-3-chlorobutane a compound with two stereogenic centers

Consider the relationship between, for example, the  $(2R,3R)$  and  $(2R,3S)$  forms of the isomers. These forms are *not* mirror images because they have the *same* configuration at carbon-2, though they have opposite configurations at carbon-3.

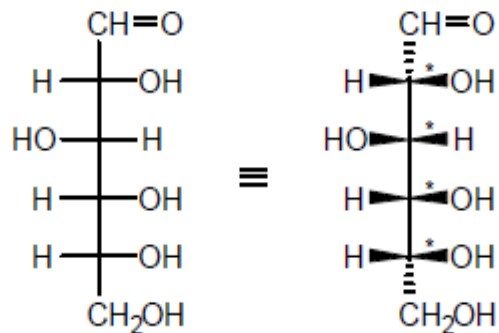
They are certainly stereoisomers, but they are not enantiomers. For such pairs of stereoisomers, we use the term **diastereomers**.

**Diastereomers** are stereoisomers that are not mirror images of each other.

Given is the Fischer projection of glucose (blood sugar), how many stereoisomers of this sugar are possible?

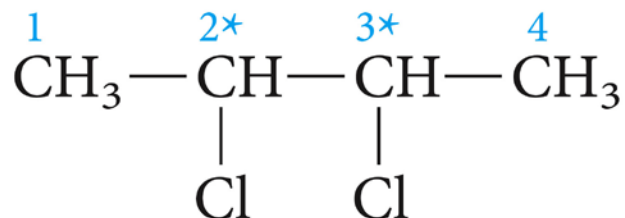


There are *four* different stereogenic centers, marked below with asterisks. There are, therefore,  $2^4 = 16$  possible stereoisomers.

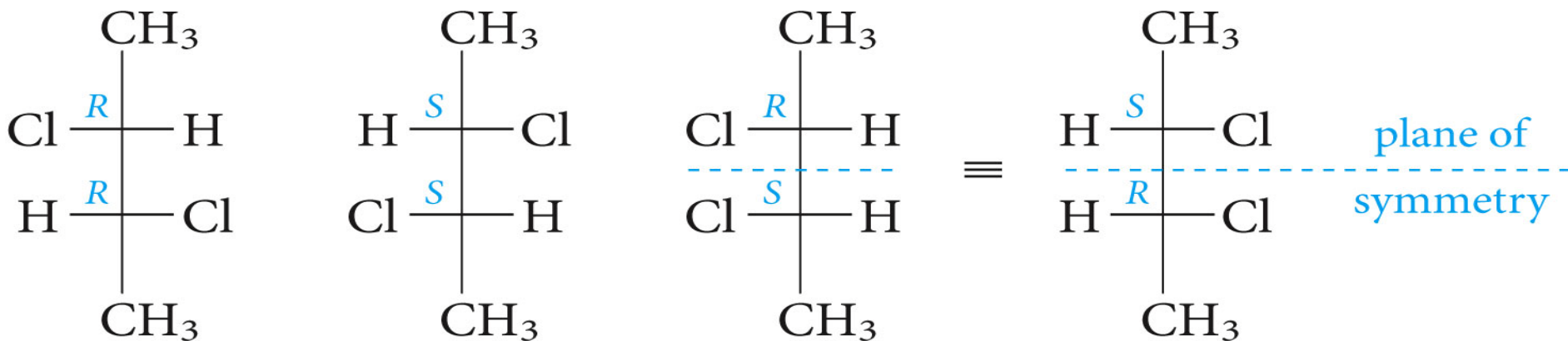


## 5.9 Meso Compounds; the Stereoisomers of Tartaric Acid

Consider the stereoisomers of 2,3-dichlorobutane



2,3-dichlorobutane

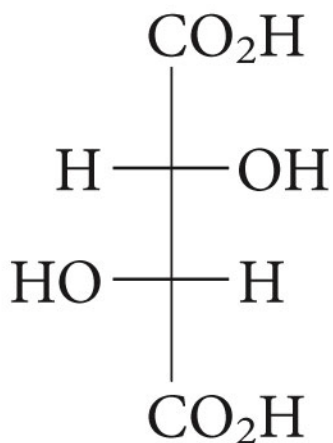
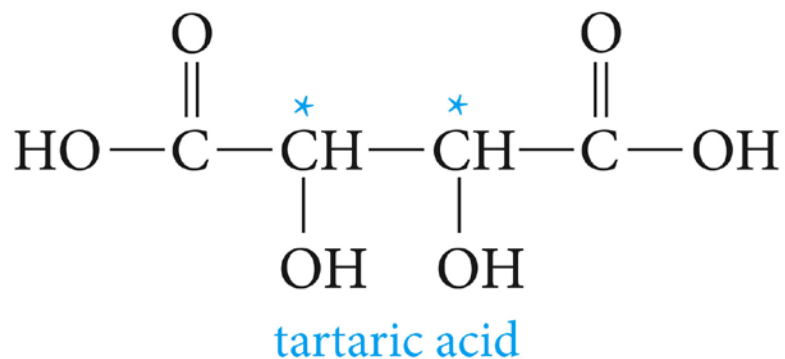


enantiomers, chiral

identical, achiral  
a *meso* form

The "two" structures, (R,S) and (S,R), in fact, now represent a single compound

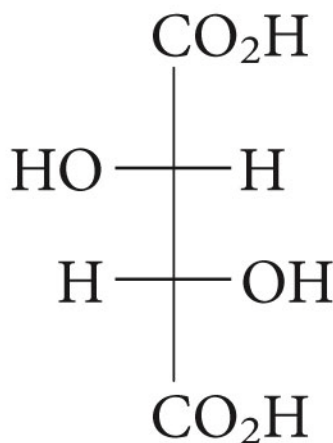
A **meso compound** is an achiral diastereomer of a compound with stereogenic centers



*(R,R)*

+12

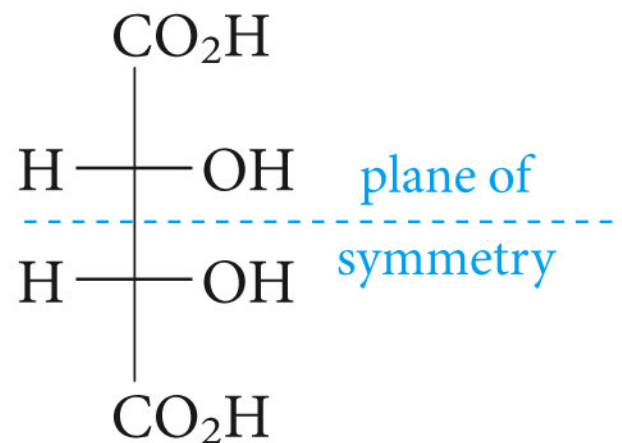
170



*(S,S)*

-12

170



*meso (R,S)*

0

140

Configuration

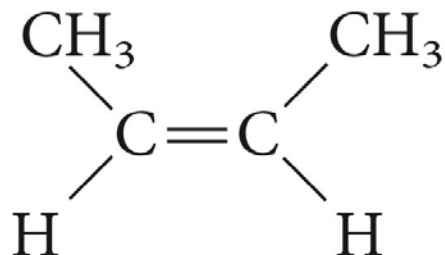
$[\alpha]_D^{20}$  (H<sub>2</sub>O)

Melting point, °C

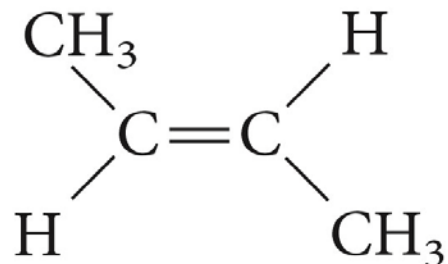
## 5.10 Stereochemistry A Recap of Definitions

A	{	<i>Conformers:</i>	interconvertible by rotation about single bonds
		<i>Configurational Isomers:</i>	not interconvertible by rotation, only by breaking and making bonds
B	{	<i>Chiral:</i>	mirror image not superimposable on itself
		<i>Achiral:</i>	molecule and mirror image are identical
C	{	<i>Enantiomers:</i>	mirror images; have opposite configurations at all stereogenic centers
		<i>Diastereomers:</i>	stereoisomers but not mirror images; have same configuration at one or more centers, but differ at the remaining stereogenic centers

# 1. *Cis-trans* 2-butene (*Z* and *E* notation)



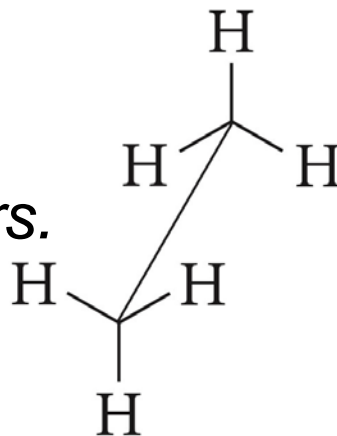
and



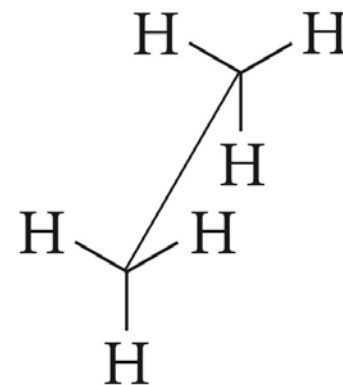
These isomers are *configurational*, *achiral*, and *diastereomers*

## 2. Staggered and eclipsed ethane.

These are *achiral conformers*.  
They are *diastereomeric conformers*.

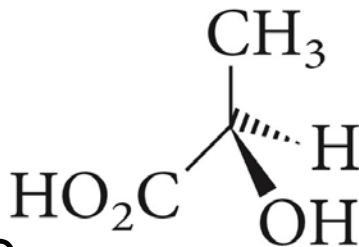


and

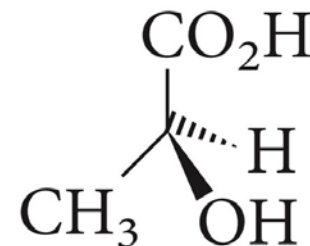


## 3. (*R*)- and (*S*)-lactic acid.

These isomers are *configurational*, each is *chiral*, and they constitute a pair of *enantiomers*.

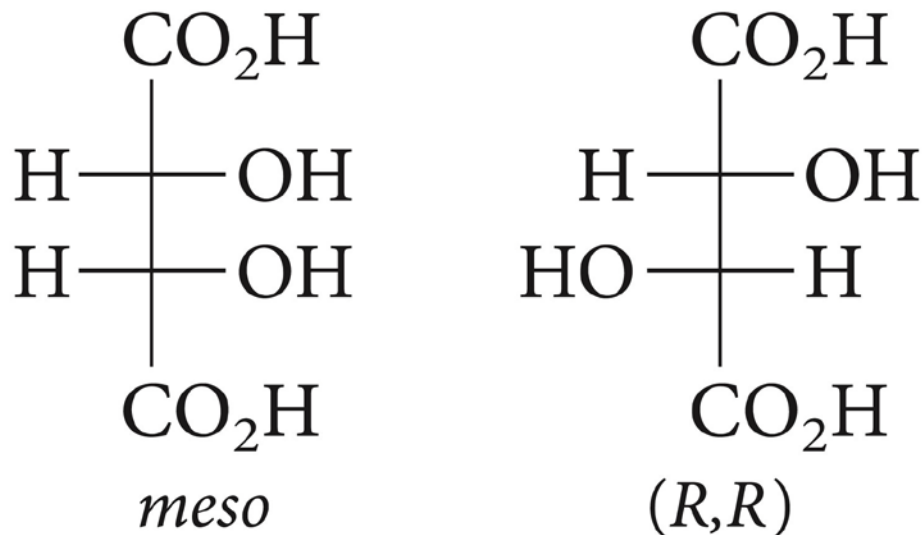


and

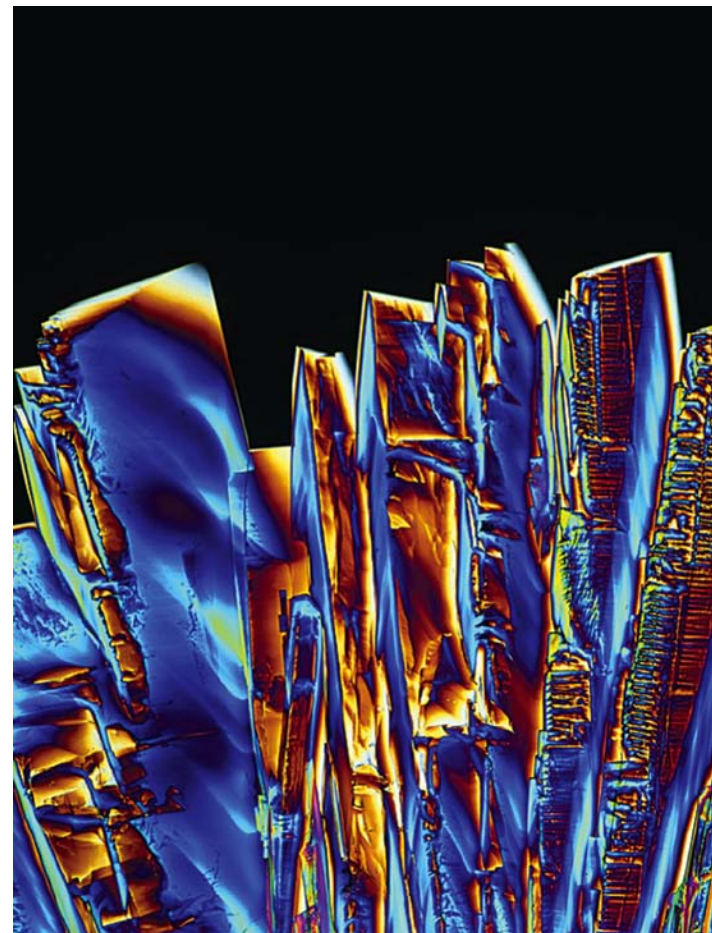




## 4-Meso- and (R,R)-tartaric acids



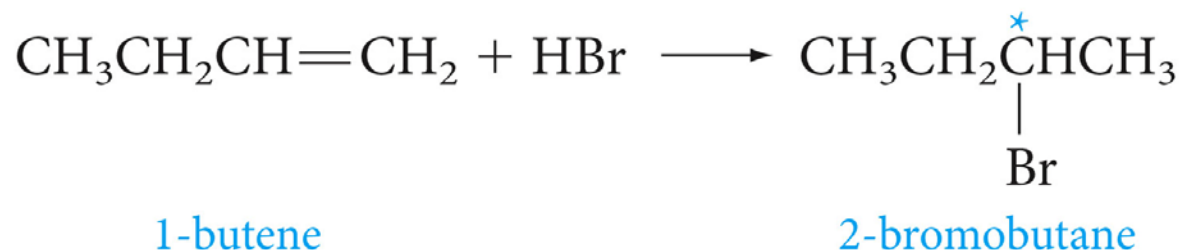
These isomers are *configurational* and *diastereomers*. One is *achiral*, and the other is *chiral*.



Tartaric acid crystals under polarized light

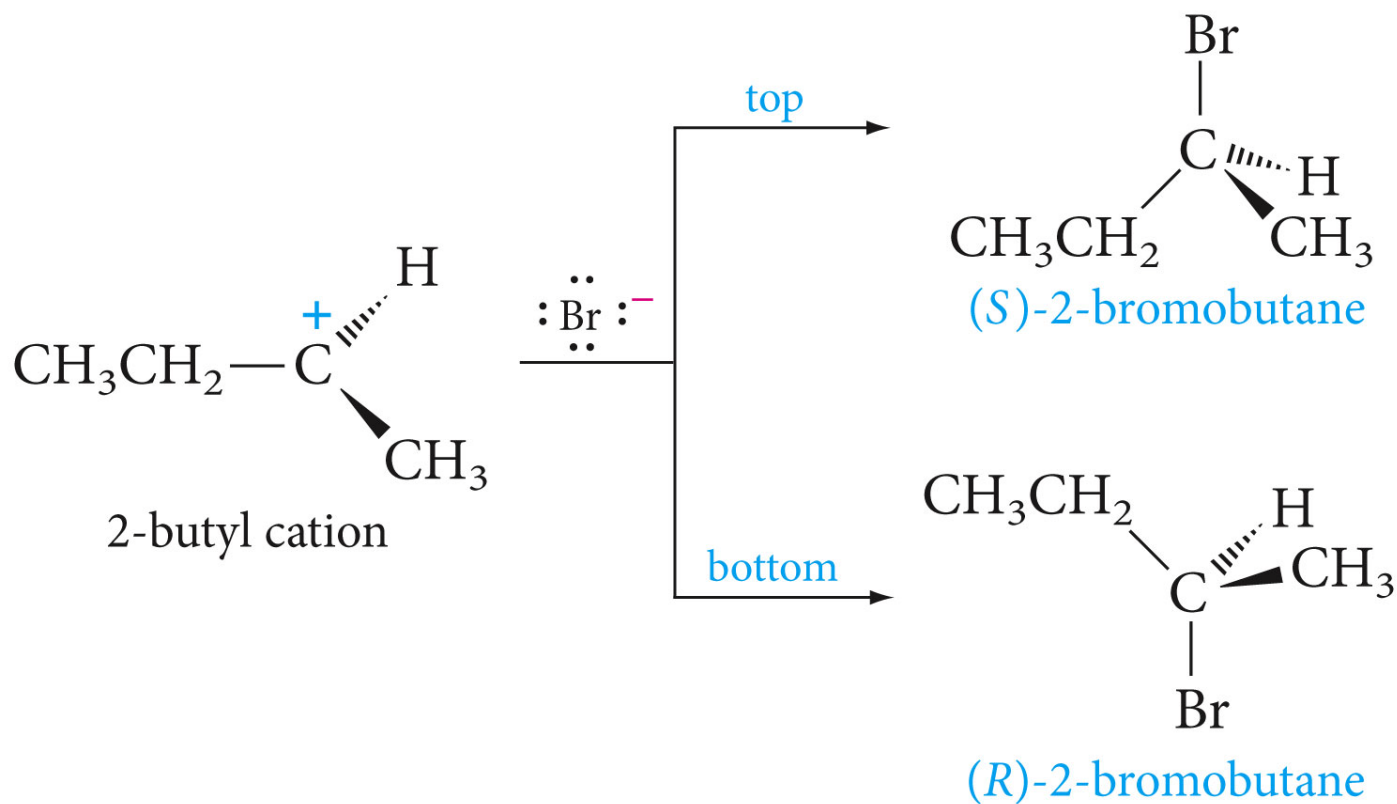
## 5.11 Stereochemistry and Chemical Reactions

How important is stereochemistry in chemical reactions?



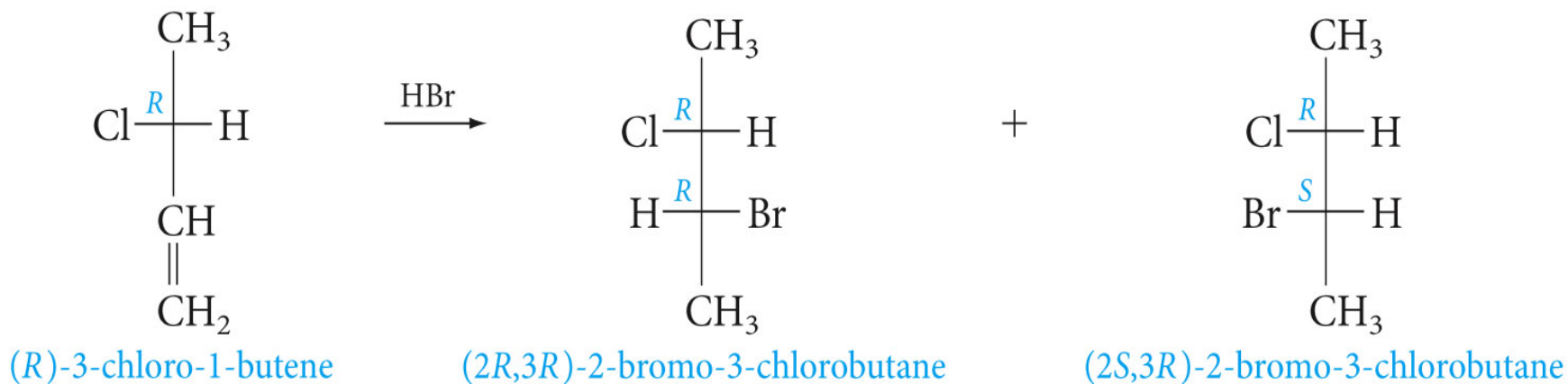
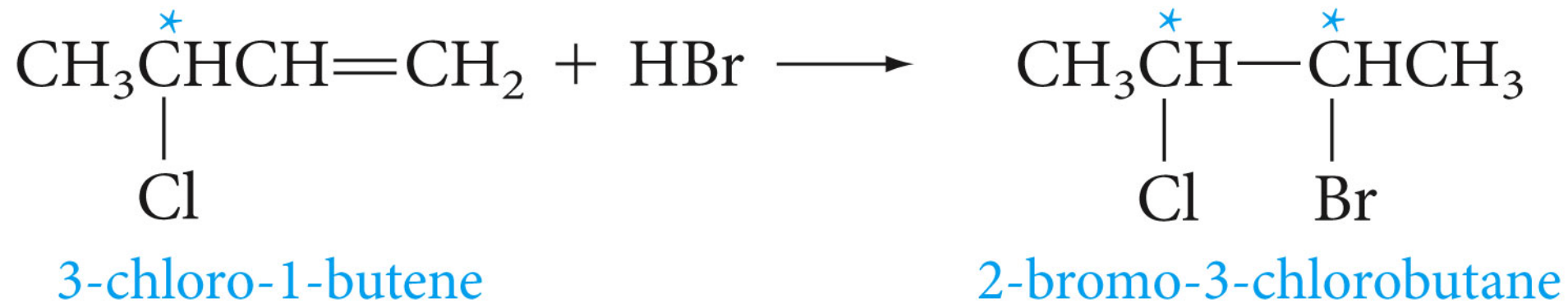
The product has one stereogenic center, marked with an asterisk, but both enantiomers are formed in exactly equal amounts. The product is a **racemic mixture**. Why? Let us consider the generally accepted mechanism.





When chiral products are obtained from achiral reactants, both enantiomers are formed at the same rates, in equal amounts.

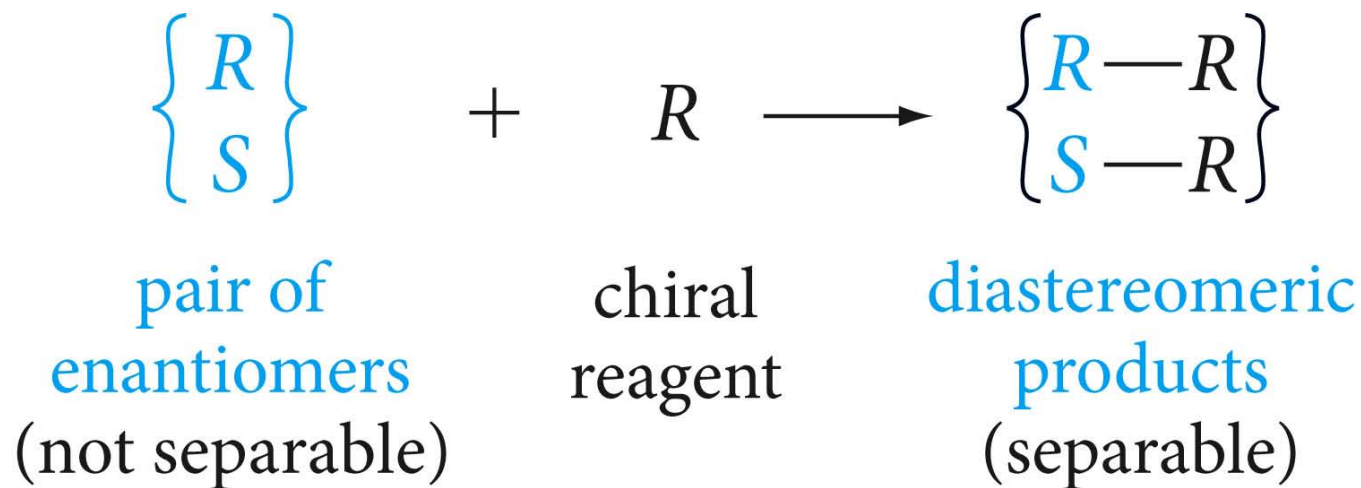
A **racemic mixture** is a 50:50 mixture of a pair of enantiomers.



Reaction of a **chiral** reagent with an **achiral reagent** when it creates a new stereogenic center, leads to **diastereomeric** products at different rates and in unequal amounts.

## 5.12 Resolution of a Racemic Mixture

To separate a racemic mixture, we first react with a chiral reagent. The product will be a pair of diastereomers. These, differ in all types of physical properties and can therefore be separated by ordinary methods.

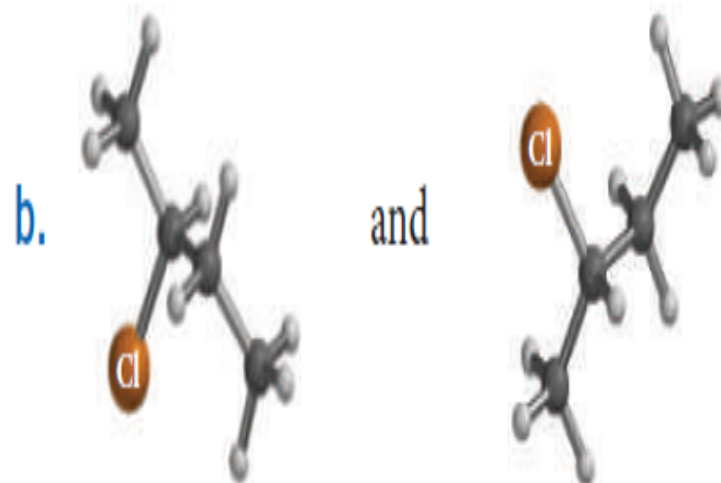
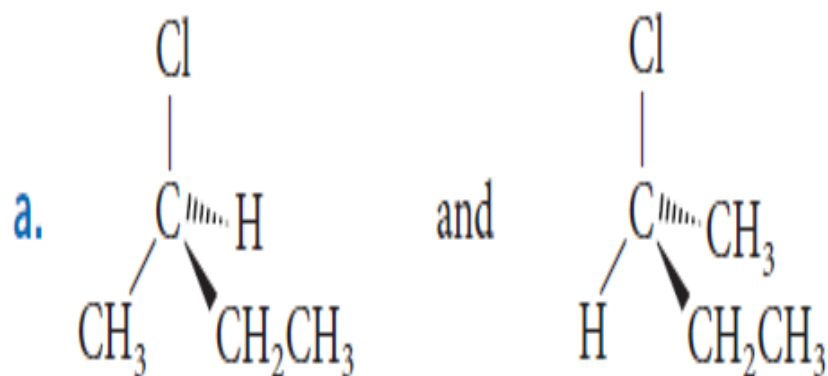


# **Chapter 5**

## **Homework**

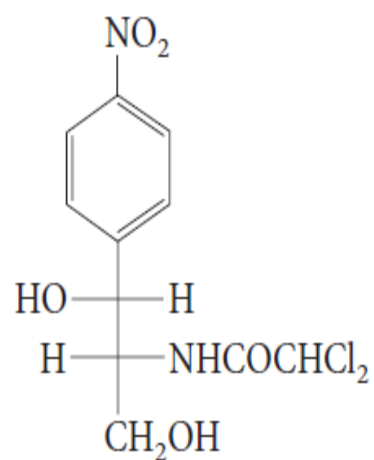
**27 30 31 33 34 36 39 42 43 44**

5.31 Tell whether the following structures are identical or enantiomers:





5.49 Chloramphenicol is an antibiotic that is particularly effective against typhoid fever. Its structure is



What is the configuration (*R,S*) at each stereogenic center?