Organic Chemistry

Stereochemistry

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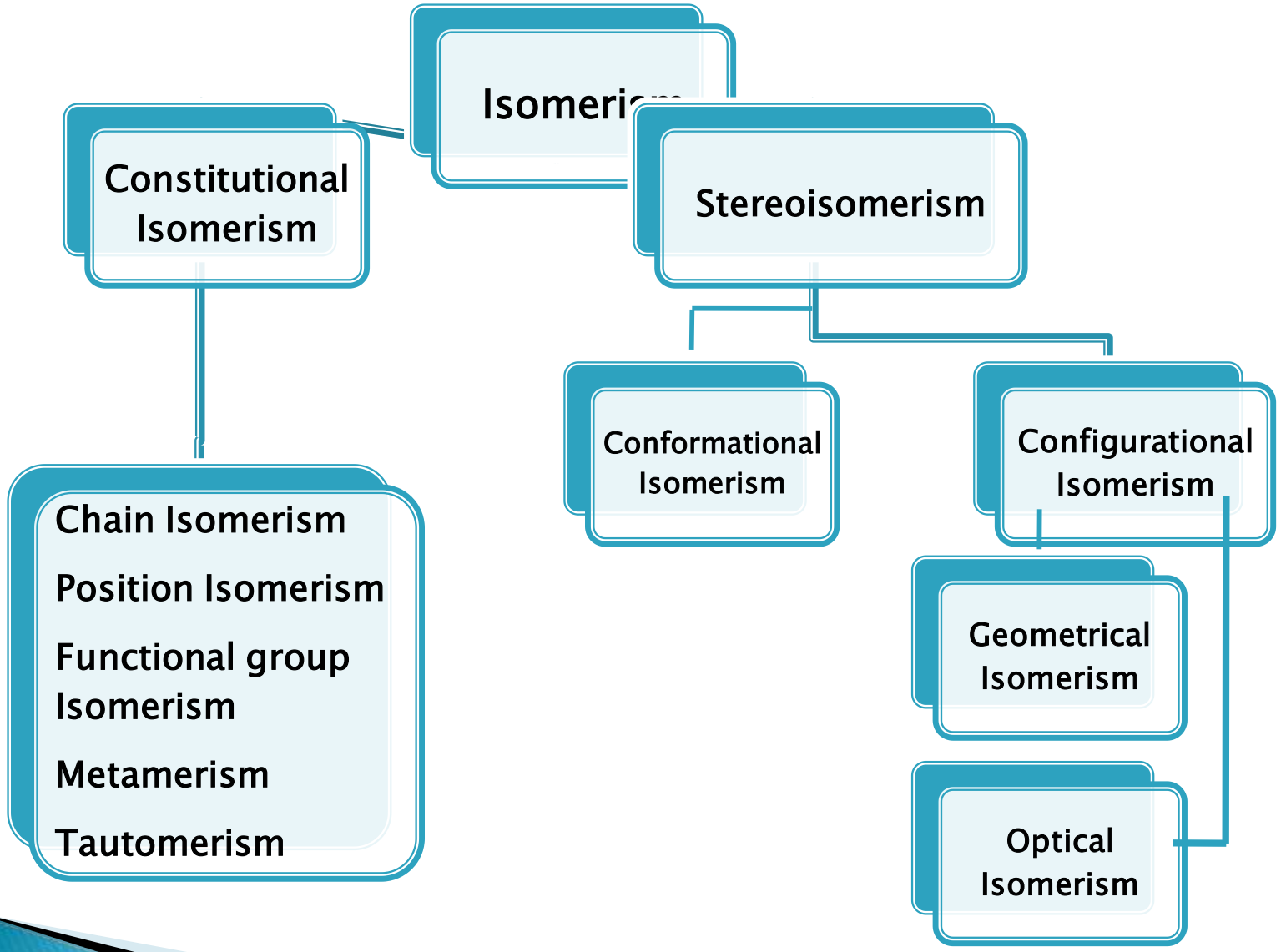
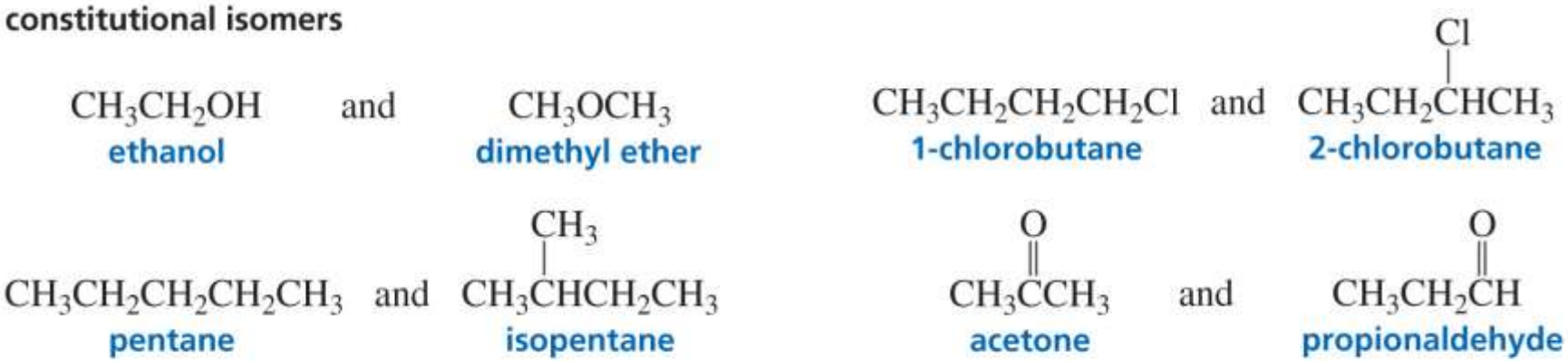
Isomers; Compounds with the same molecular formula but structures



Constitutional Isomers

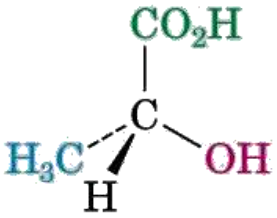
(conective isomers)

Constitutional isomers differ in the way their atoms are *connected*

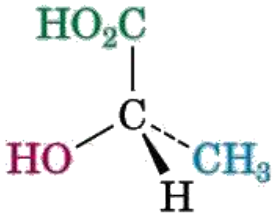


Stereo Isomers; The isomers that have the same molecular formula and have the same connectivity, but differ in the way their atoms are arranged in space. Stereo-isomers are compounds with different properties (separatable) but do not readily interconvert (require breaking of a bond)

Enantiomers
(nonsuperimposable mirror-image stereoisomers)



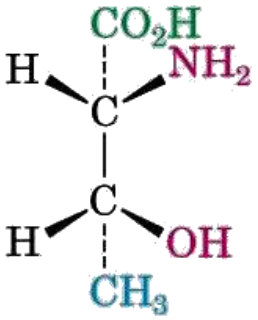
(*R*)-Lactic acid



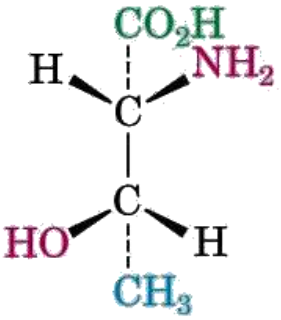
(*S*)-Lactic acid

Diastereomers
(nonsuperimposable, non–mirror-image stereoisomers)

Configurational diastereomers



2*R*,3*R*-2-Amino-3-hydroxybutanoic acid



2*R*,3*S*-2-Amino-3-hydroxybutanoic acid

Enantiomers; Enantiomers are non super imposable mirror images of a compound that differ in the direction in which they rotate plane polarized light. Their physical properties are the same

Diastereomers; (all other stereo-isomers Includes cis, trans and configurational) have a complete set of different common physical properties.

Table Some properties of isomers of tartaric acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$ (degrees)	Density (g/cm^3)	Solubility at 20°C ($g/100\ mL\ H_2O$)
(+)	168–170	+12	1.7598	139.0
(−)	168–170	−12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

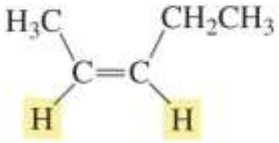
Geometrical Isomers

Geometric isomers; These isomers result from restriction of rotation along double bonds. Also known as Cis-Trans isomers.

Cis isomer; Isomers in which hydrogens or alkyl groups are on the same side of the double bond or ring.

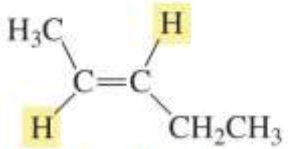
Trans isomer; Hydrogens or alkyl groups are on the opposite side of the double bond or ring.

cis-2-pentene

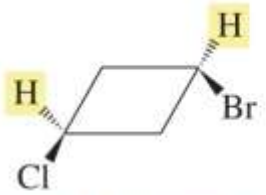


cis-2-pentene

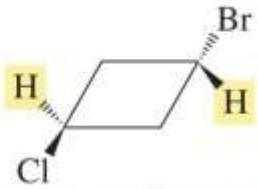
trans-2-pentene



trans-2-pentene



cis-1-bromo-3-chlorocyclobutane



trans-1-bromo-3-chlorocyclobutane

cis-1,4-dimethylcyclohexane

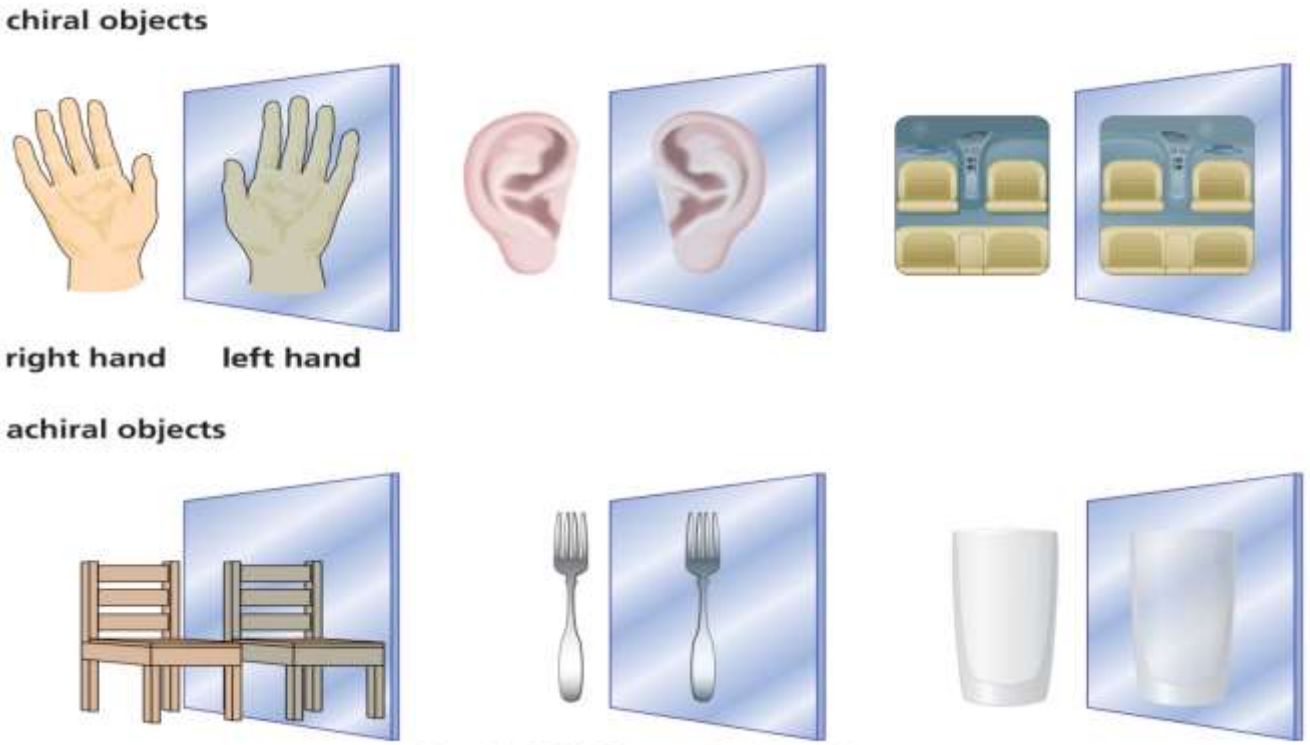
trans-1,4-dimethylcyclohexane

Chiral Compounds

- Molecules that are not superimposable with their mirror images are **chiral**.
- A **plane of symmetry** divides an entire molecule into two pieces that are exact mirror images.
- A molecule with a plane of symmetry is the same as its mirror image and is said to be **achiral.**
- The lack of a plane of symmetry is called “handedness”, **chirality.**
- Hands, gloves are prime examples of chiral object They have a “left” and a “right” version

Nonsuperimposable Mirror Images

“Handedness”; hands (gloves) and feet (shoes) have right- and left-handed forms

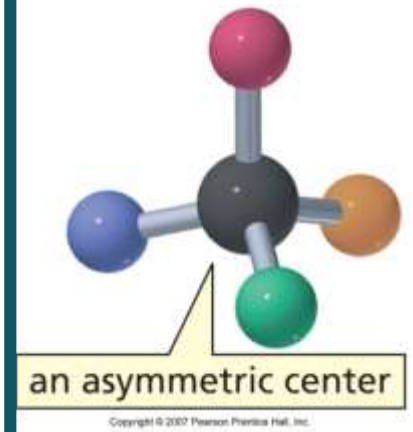


RULE - look for symmetry in a molecule - symmetry breaks chirality

Asymmetric Centers

Chiral molecules - generally molecules containing an asymmetric center

Asymmetric (chiral) center - tetrahedral atom bonded to four different groups - indicated with an *asterisk (*)*

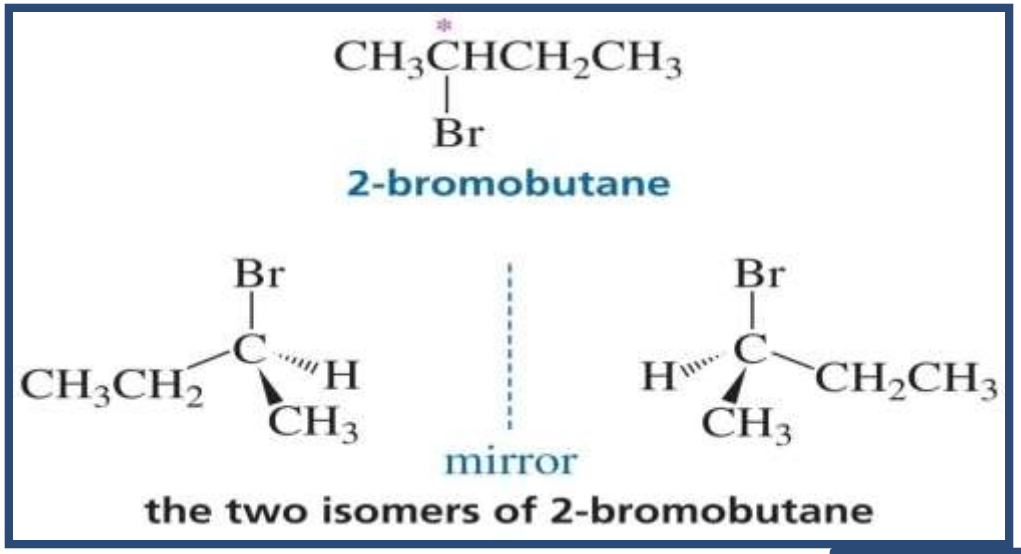


RULE - only sp^3 hybridized atoms can be chiral.

NOTE - molecules may not appear to be different until you go out several atoms

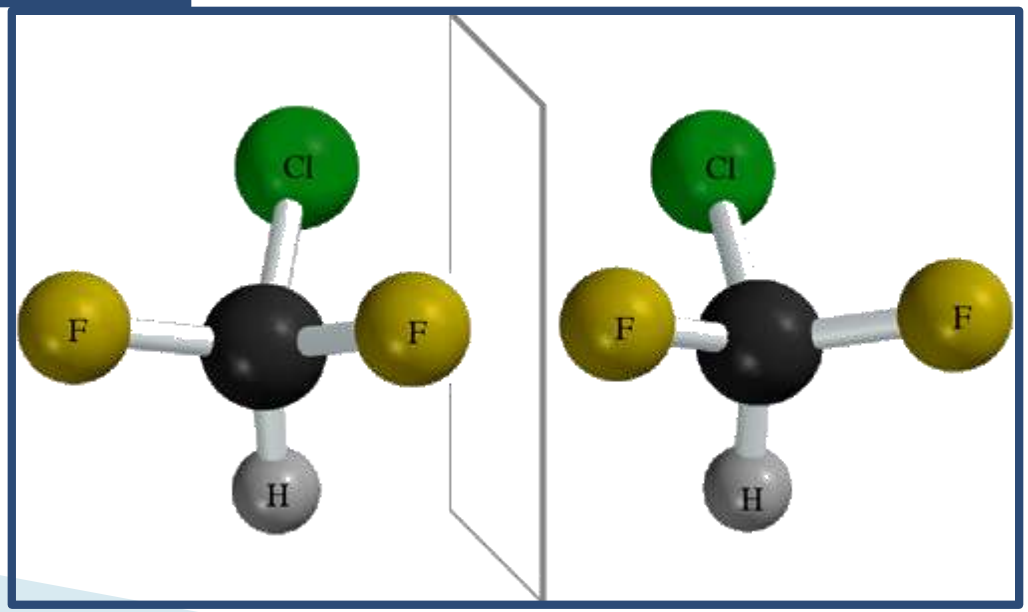
One Asymmetric Center

Molecules with one asymmetric center can exist as 2 stereoisomers.



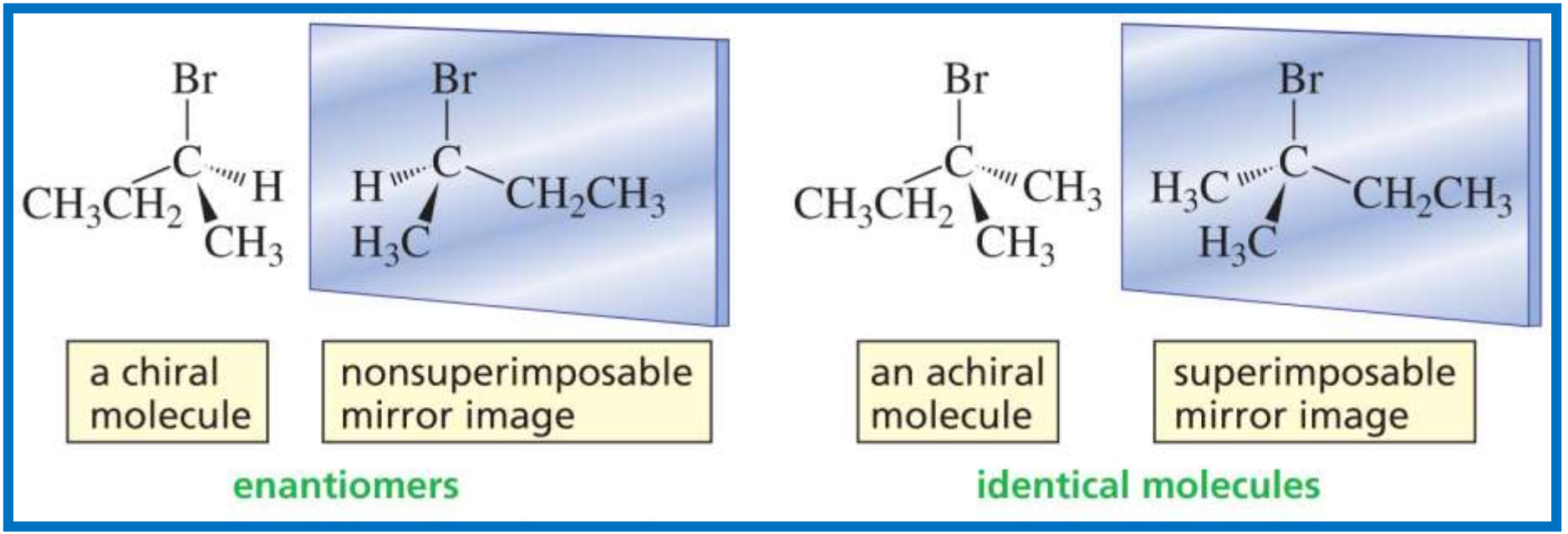
These Two Enantiomers are chiral compounds

Enantiomers of **bromochlorofluoromethane**



Achiral Molecules

Have super imposable mirror images

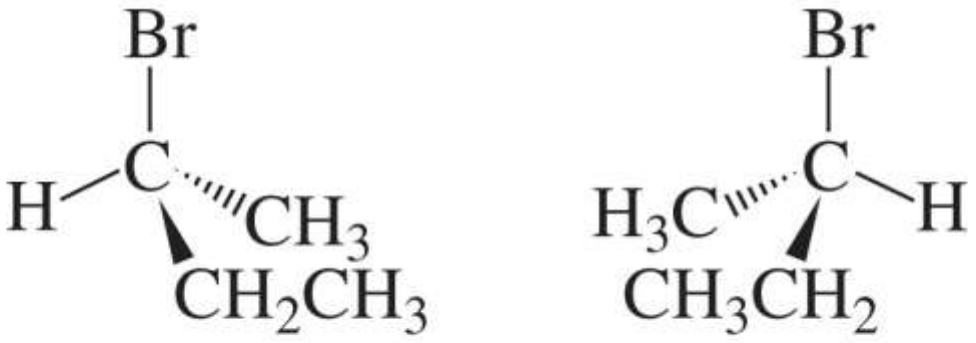


Drawing Enantiomers

Solid lines; bonds in the plane of the paper

Solid Wedge; coming out of the paper toward you

Hatched Wedge; going back into space behind the paper.



perspective formulas of the enantiomers of 2-bromobutane

Enatiomers

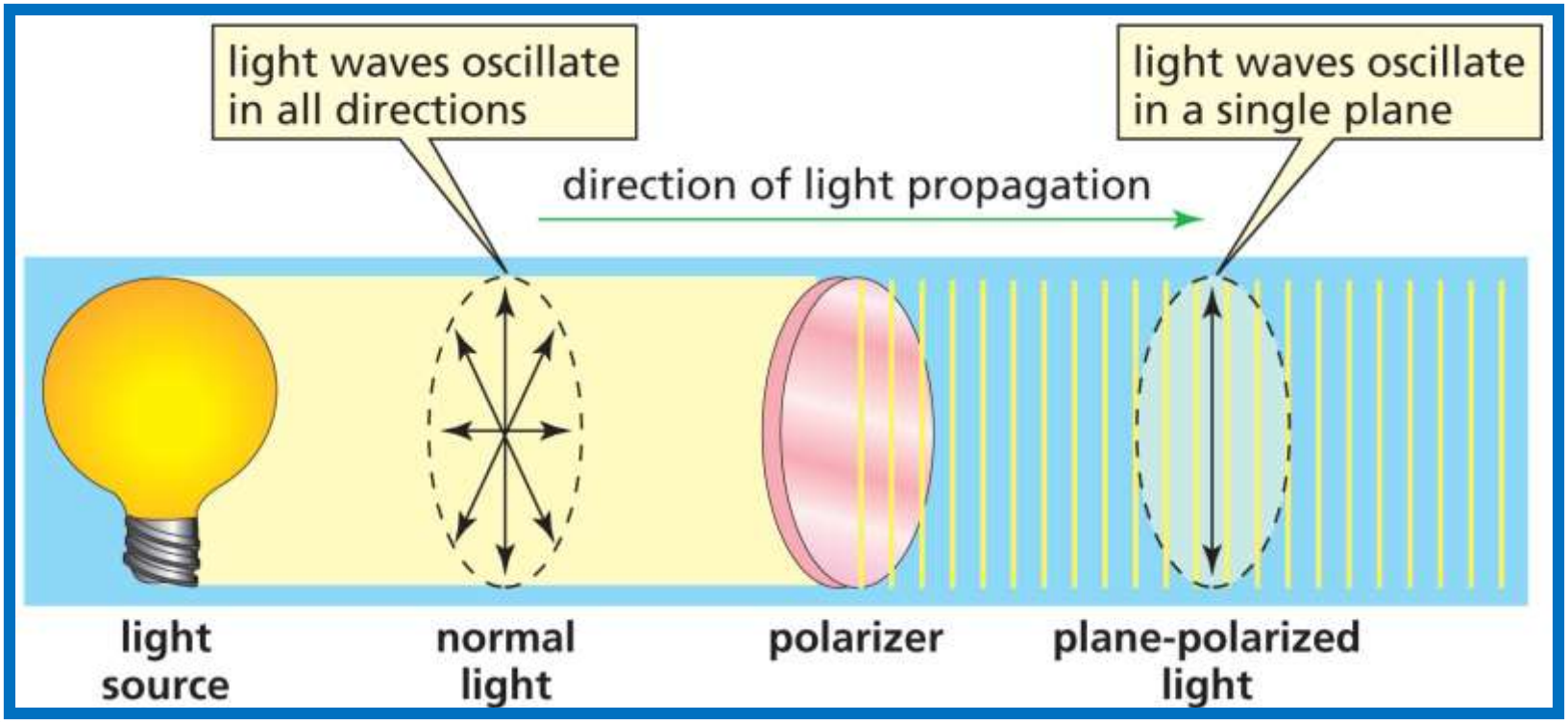
- **Have the same melting points**
- **Have the same boiling points**
- **Have the same solubility**

……So How do you Tell them apart??

Optical Activity

Interaction with plane-polarized light - light where all the rays/waves oscillate in a single plane

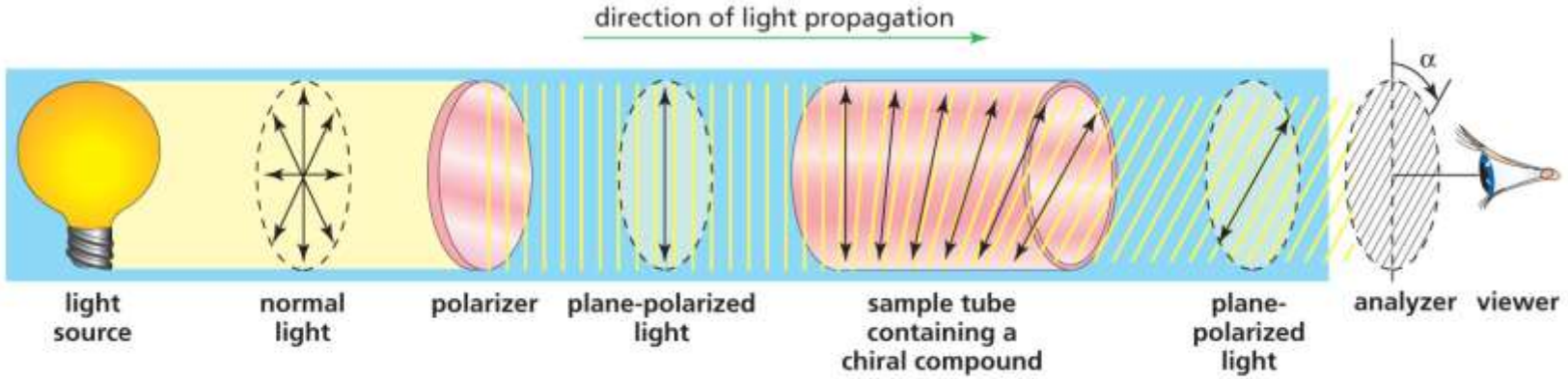
(normal light has ray oscillations in all directions)



Measuring Optical Activity

- Light restricted to pass through a plane is *plane-polarized*
- Plane-polarized light that passes through solutions of achiral compounds remains in that plane.
- Solutions of chiral compounds rotate plane-polarized light and the molecules are said to be *optically active*
- Phenomenon discovered by Biot in the early 19^{th} century
- Light passes through a plane polarizer.
- Plane polarized light is rotated in solutions of optically active compounds
- Measured with polarimeter
- Rotation, in degrees, is [α].Clockwise rotation is called **dextrorotatory,** Anti-clockwise is **levorotatory**

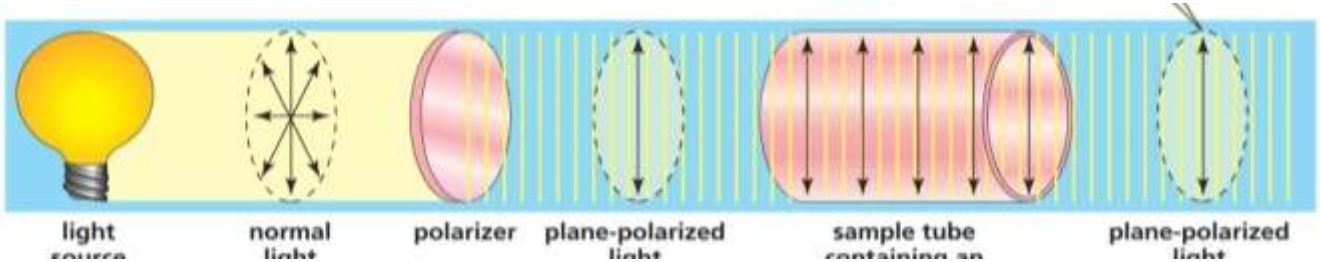
Polarimeter - Monochromatic (single wavelength) light passes through a series of polarizers and a sample



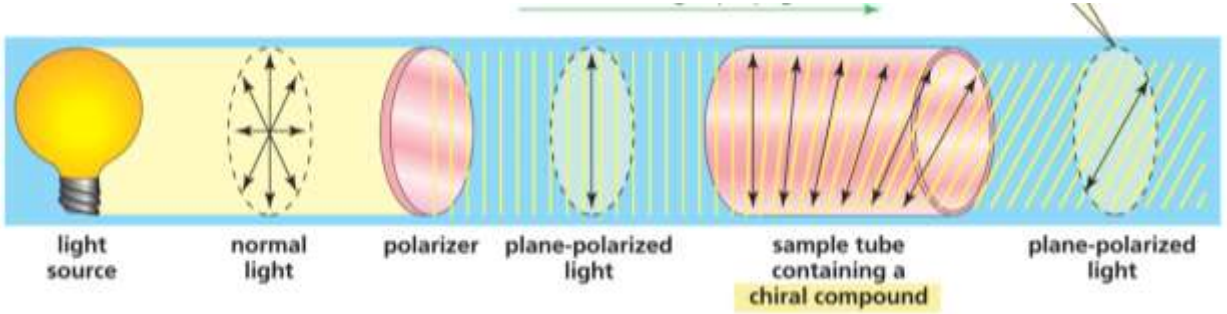
Look At a Polorizer and How it Works

Optical Activity

A solution of *achiral compounds* - light emerges with its plane of polarization unchanged - the solution is *optically inactive*.



A solution of *chiral compounds* - light emerges with its plane of polarization changed - the solution is *optically active* and rotates the plane of polarized light clockwise or counterclockwise.



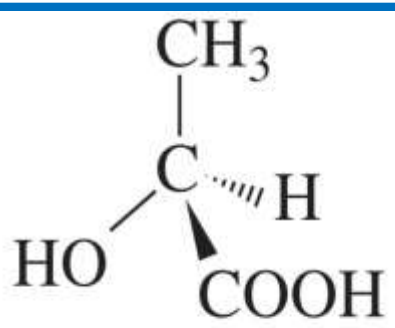
Optical Activity

Dextrorotatory (+) compounds rotate plane polarized light ***clockwise*** Latin - *dextro* - “to the right”(*d*).

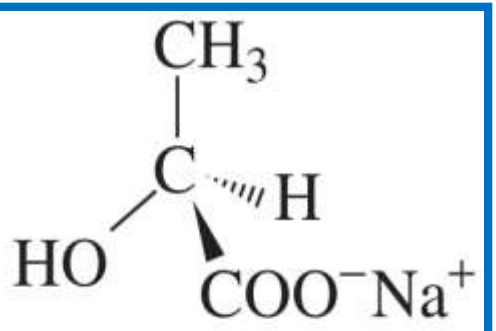
Levorotatory (-) compounds rotate plane polarized light ***counter clockwise*** Latin - *levo* - “to the left”(*l*).

Do not confuse (+) and (-) with *R* and *S* – (+) and (-) refer to the rotation of plane polarized light - *the only way to determine is experimentally.* ***R* and *S* indicate the arrangement of groups around an asymmetric center - *this can be determined by looking at the structure of the compound*.**

Some *S* compounds are (+) dextrorotatory, and some are (-) levorotatory



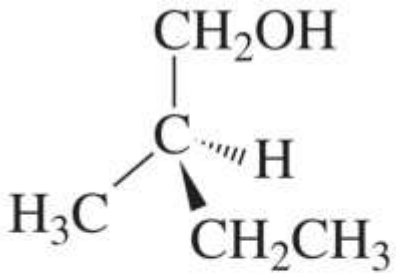
(*S*)-(+)-lactic acid



(*S*)-(–)-sodium lactate

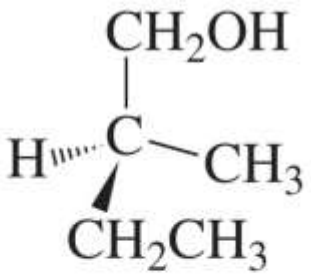
Measuring Optical Activity

Specific rotation - rotation of a 1g/mL sample in 10 cm sample tube



(*R*)-2-methyl-1-butanol

$[\alpha]_D^{20\,°C} = +5.75$



(*S*)-2-methyl-1-butanol

$[\alpha]_D^{20\,°C} = -5.75$

Table 5.1 Specific Rotation of Some Naturally Occurring Compounds

Cholesterol	−31.5
Cocaine	−16
Codeine	−136
Morphine	−132
Penicillin V	+233
Progesterone (female sex hormone)	+172
Sucrose (table sugar)	+66.5
Testosterone (male sex hormone)	+109

RULE; enantiomers have specific rotations of the same magnitude, but different direction (sign)

RULE; equal mixtures of two enantiomers (racemic mixture or racemate) are optically inactive - racemic mixtures are indicated by (±) - *Why?*

Specific rotations are of same magnitude, but different sign.

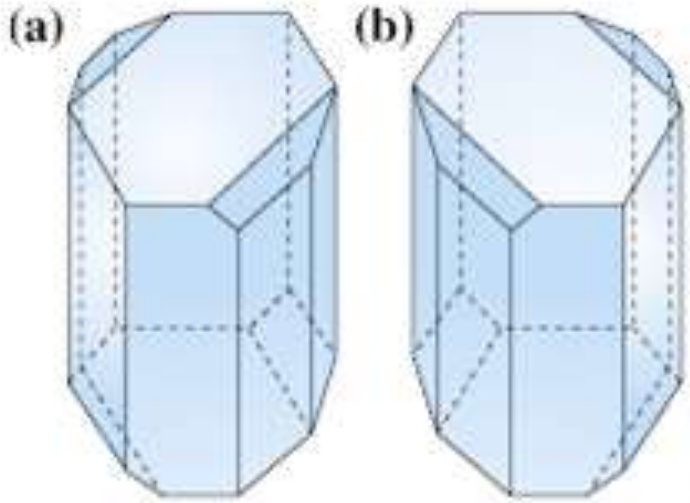
Concentrations of each enantiomer are equal.

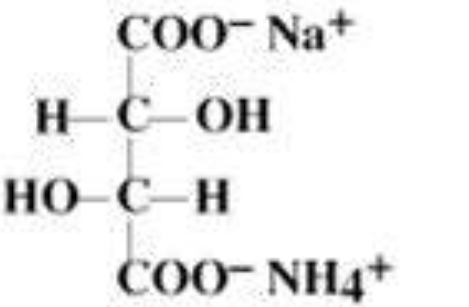
Pasteur's Discovery of Enantiomers (1849)

- Louis Pasteur discovered that sodium ammonium salts of tartaric acid crystallize into right handed and left handed forms.

- The optical rotations of equal concentrations of these forms have opposite optical rotation

- The solutions contain mirror image isomers, called *enantiomers* and they crystallized in distinctly different shapes – <u>such an event is rare</u>





Sodium ammonium tartrate

Enantiomeric Excess

RULE; Racemic mixtures are optically inactive.

What about mixtures of enantiomers that aren't 50:50?

Observed specific rotation - specific rotation measured for a particular sample:

Enantiomerically pure (*S*)-(+)-2-bromobutane - presence of only one enantiomer means observed specific rotation = specific rotation (+23.1)

Racemic mixture of (*S*)-(+)-2-bromobutane - presence of equal mixtures of both enantiomers means observed specific rotation = 0

A mixture of enantiomers, containing more enantiomer of the S configuration than the enantiomer of the R configuration.

enantiomeric excess (ee):

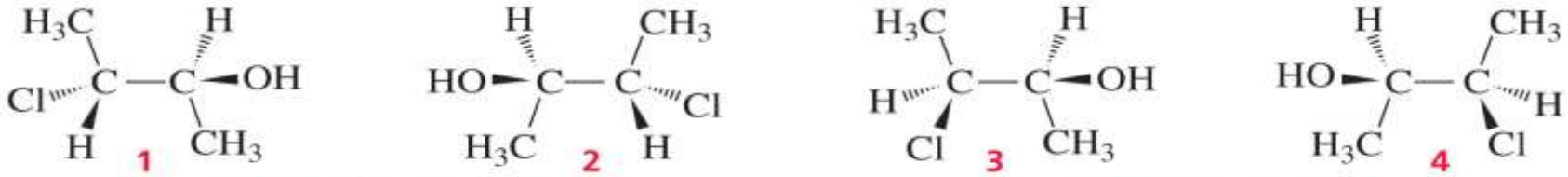
$$\text{enantiomeric excess} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100\%$$

RULE - An ee of 40% means the remaining 60% must be racemic, of which half is the same configuration as that in excess - mixture is 70% of one enantiomer.

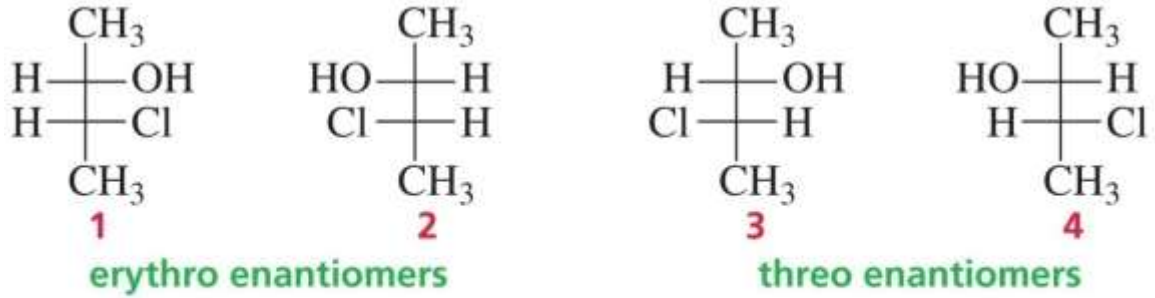
Asymmetric Centers

RULE; A compound can have a *maximum* of 2^n stereoisomers, where *n* = the number of asymmetric centers (not counting cis-trans isomeric centers)

3-chloro-2-butanol; 2 asymmetric centers = 4 stereoisomers:



perspective formulas of the stereoisomers of 3-chloro-2-butanol (staggered)



Fisher projections of the stereoisomers of 3-chloro-2-butanol

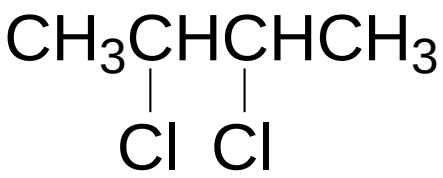
Meso Compounds

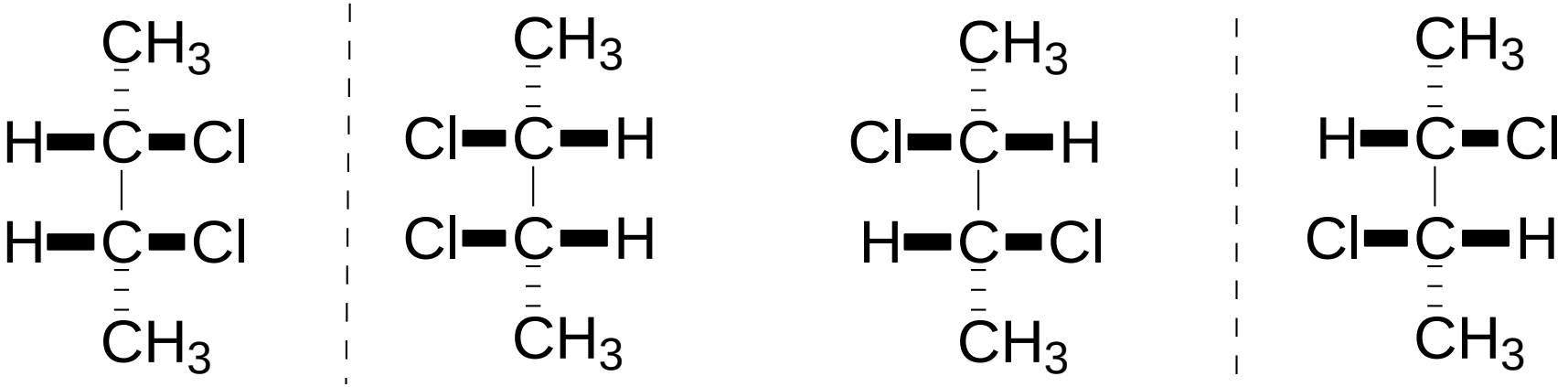
An achiral compound with chiral carbons is called a *meso* compound. A compound with 2 or more asymmetric centers, and a **plane of symmetry** - cuts molecule in half so that one half of the molecule is the mirror image of the other

Symmetry plane not drawn through ***asymmetric centers***

Note this plane of symmetry does not eliminate the presence of stereocenters (you still have sp^3 carbon atoms with four different atoms attached - you just have multiple stereocenters with the same four atoms!)

Stereoisomers of 2,3-Dichlorobutane



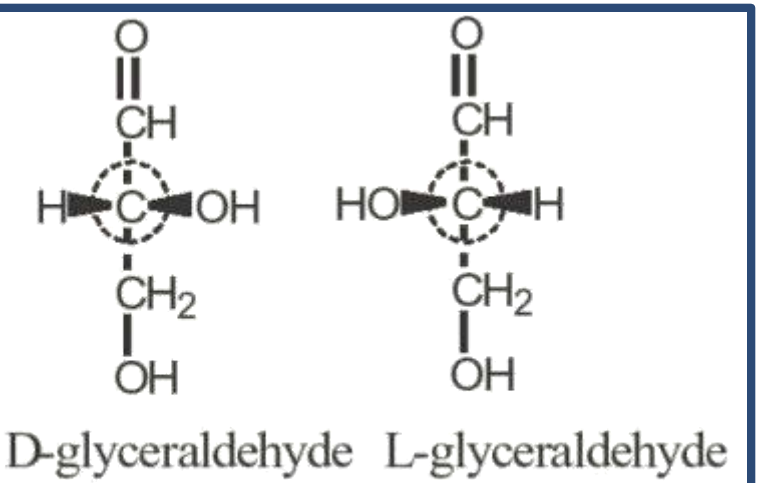


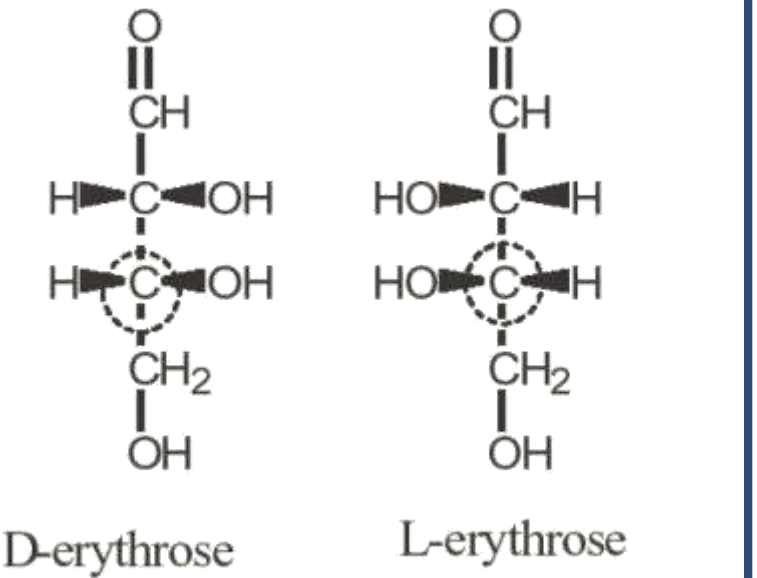
Meso Compound

Enantiomers

Relative 3-Dimensional Structure

D-erythrose is the mirror image of L-erythrose
This does not apply in general
The original method was a correlation system, classifying related molecules into “families” focused on carbohydrates
Correlate to D- and L Glyceraldehyde.

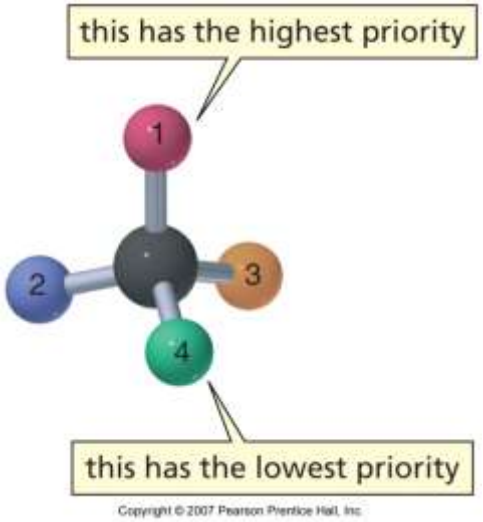


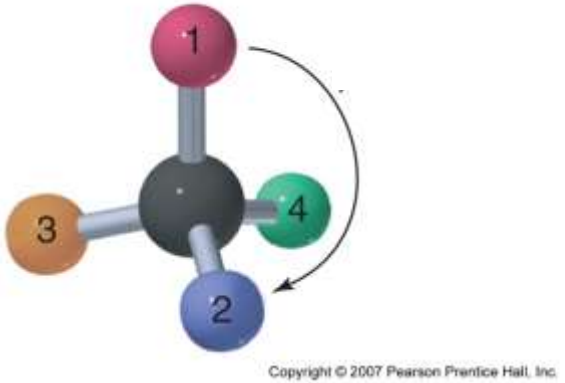


Naming Enantiomers –*R/S* System

For any pair of enantiomers with one asymmetric center, one member has the *R* configuration, another has the *S* configuration.

Step 1; Rank the groups/atoms bonded to the asymmetric center inorder of priority - use the same RULES we learned for priority assignment in alkenes



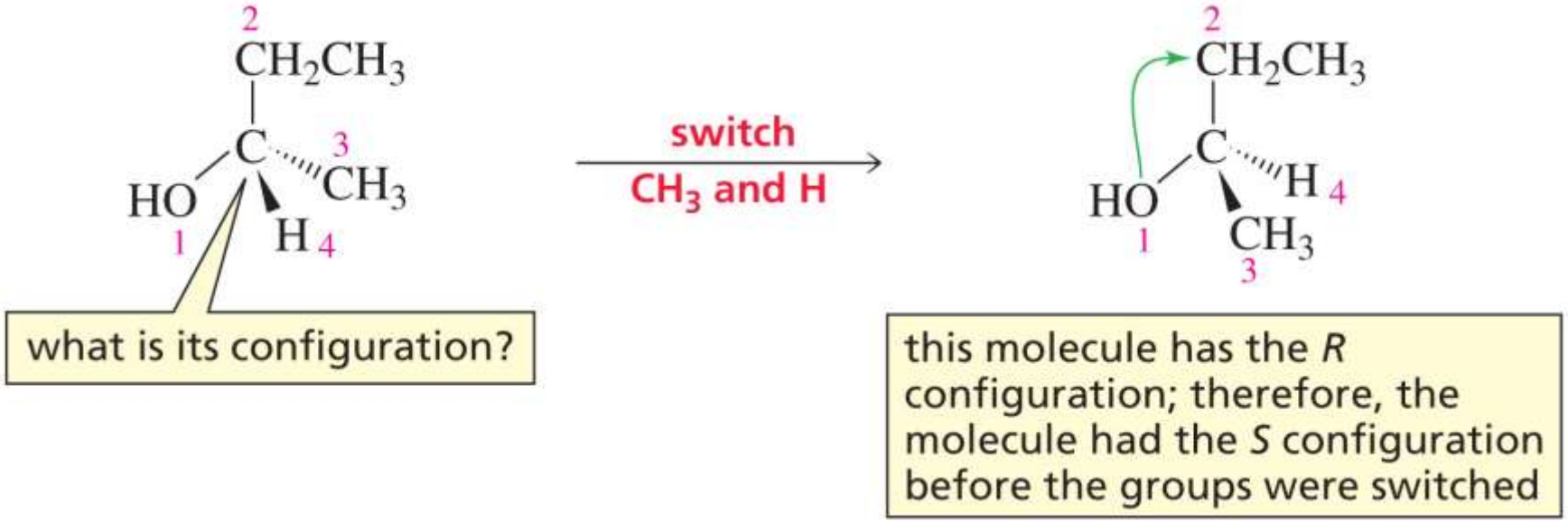


Step 2; Orient the molecule so that the group/atom with the lowest priority (4) is directed away from you - *draw an imaginary arrow from the group/atom of highest priority (1) to the group/atom with the next highest priority (2)*

Naming Enantiomers -*R,S* System

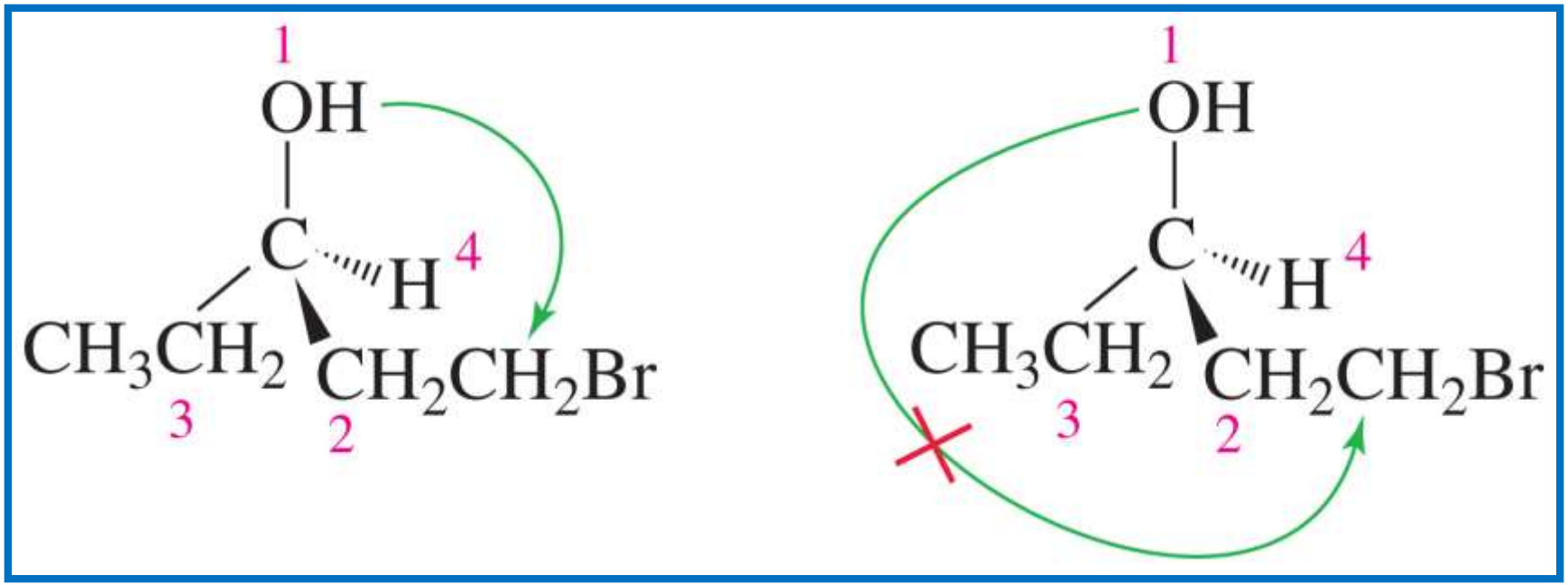
Step 3; if the group/atom with the lowest priority is *NOT* bonded by a hatched wedge, Then visualize yourself holding the group and mentally project your body to the other side of the molecule. Then Make the Determination**.**

Note: the book uses a switch the bond approach……. It's harder for me



Naming Enantiomers -*R,S* System

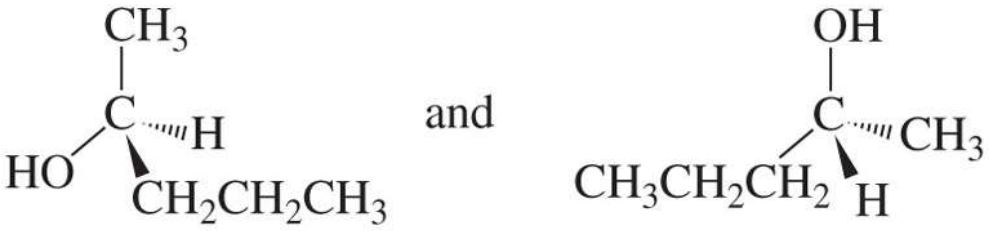
RULE; When drawing the arrow from group 1 to group 2, you can draw past the group with the lowest priority (4), but never past the group with the next-lowest priority (3)



Naming Enantiomers -*R,S* System

Recognizing Pairs of Enantiomers

Do each of the following pairs of structures represent identical molecules or a pair of enantiomers?



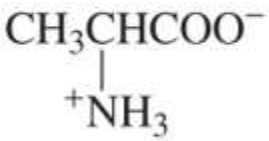
The easiest way to find out whether two molecules are enantiomers or identical molecules is to determine their configurations. If one has the *R* configuration and the other has the *S* configuration, they are enantiomers. If they both have the *R* configuration or both have the *S* configuration, they are identical molecules. Because the structure on the left has the *S* configuration and the structure on the right has the *R* configuration, we know that they represent a pair of enantiomers.

Naming Enantiomers -*R,S* System

PROBLEM-SOLVING STRATEGY

Drawing an Enantiomer with a Desired Configuration

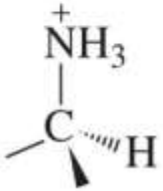
(*S*)-Alanine is a naturally occurring amino acid. Draw its structure using a perspective formula.



alanine

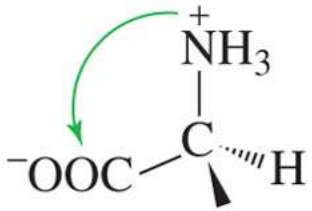
First draw the bonds about the asymmetric center. Remember that the two bonds in the plane of the paper must be adjacent to one another.

Put the group with the lowest priority on the hatched wedge. Put the group with the highest priority on any remaining bond.

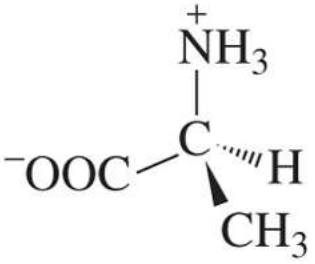


Naming Enantiomers -*R,S* System

Because you have been asked to draw the *S* enantiomer, draw an arrow counterclockwise from the group with the highest priority to the next available bond and put the group with the next highest priority on that bond.



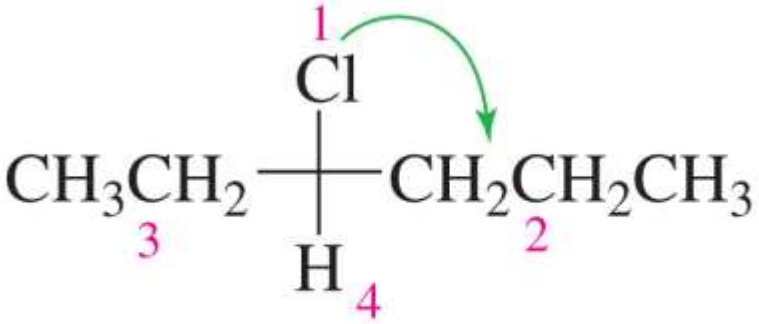
Put the remaining substituent on the last available bond.



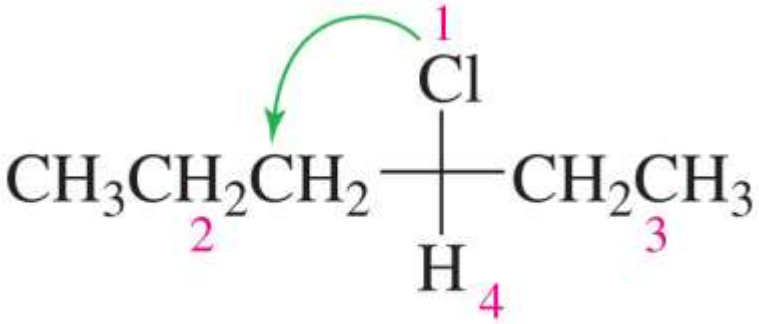
Naming Enantiomers -*R,S* System

Step 1 - using *Fisher Projections*, rank the atoms bonded to an asymmetric center in order of priority

Step 2 - if the group/atom with the *lowest priority is on a vertical bond*, draw an arrow from the group/atom with the highest priority (1) to the group/atom with the second highest priority (2). Clockwise = *R*, counterclockwise = *S*



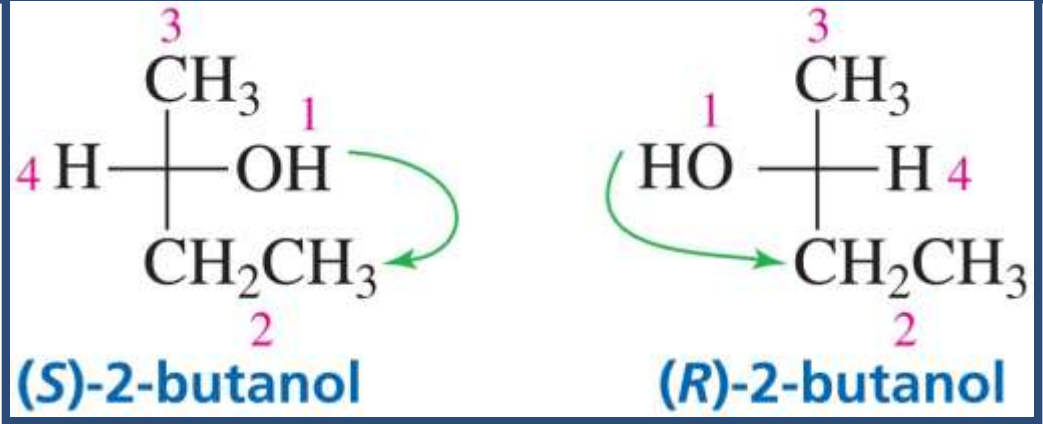
(*R*)-3-chlorohexane



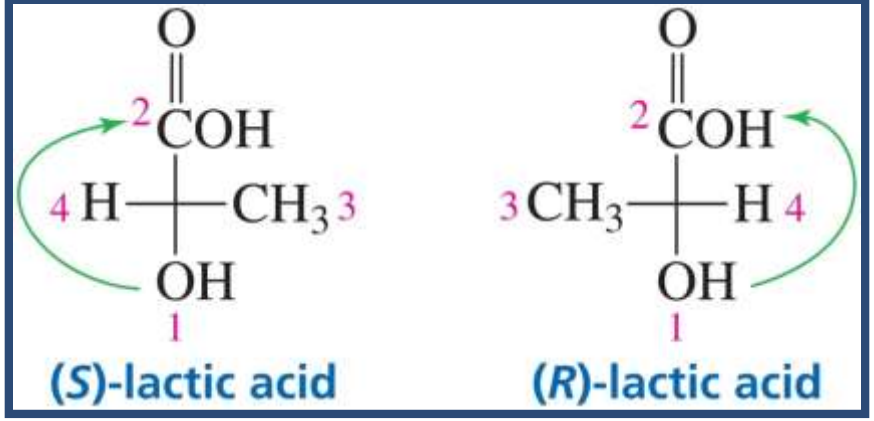
(*S*)-3-chlorohexane

Naming Enantiomers -*R,S* System

Step 3; if the group/atom with the *lowest priority is on a horizontal bond*, *you get the opposite configuration.* Draw an arrow from the group/atom with the highest priority (1) to the group/atom **with the second highest** priority (2). **Clockwise = *S*, counterclockwise = *R***

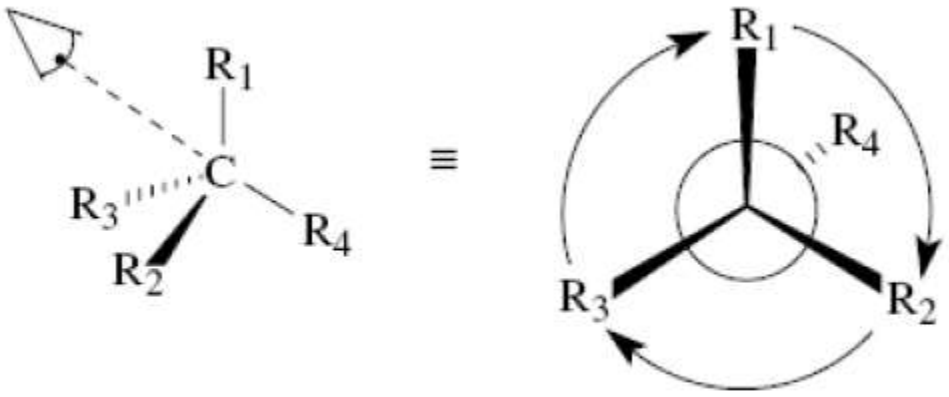


RULE; When drawing the arrow from group 1 to group 2, you can draw past the group with the lowest priority (4), but never past the group with the next-lowest priority (3)

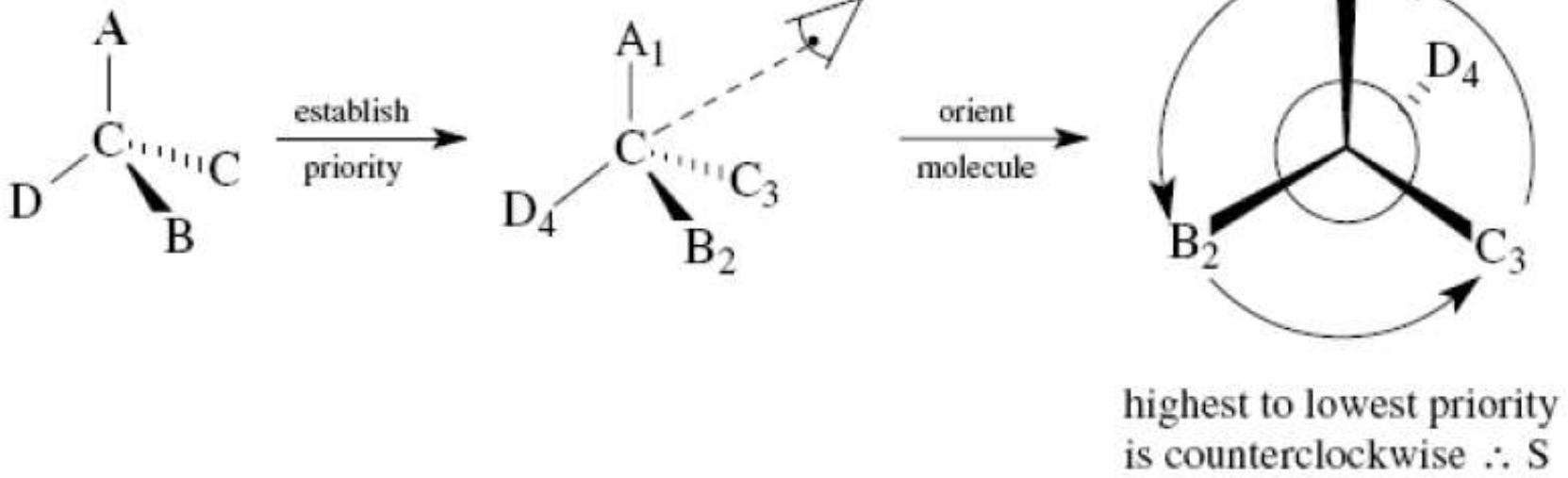


Summary RS Nomenclature

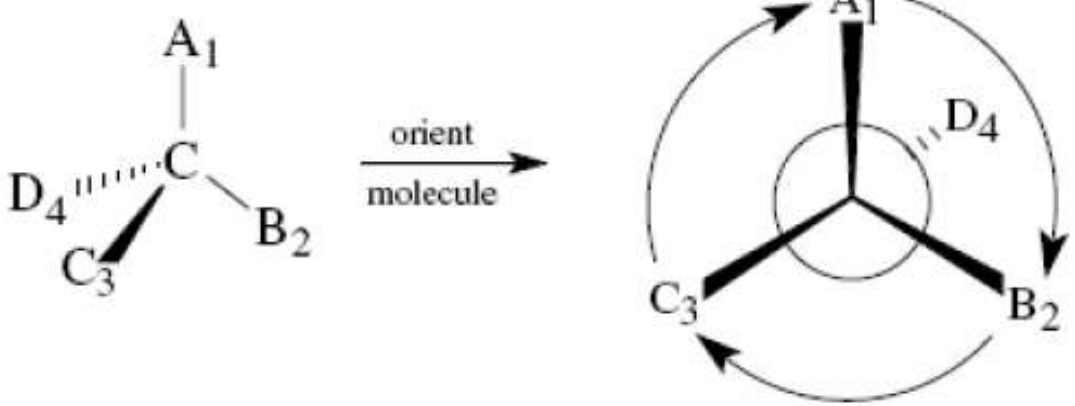
A general method for assigning the configuration to any chiral center.
In summary:
1. Assign priorities to the groups attached to the chiral center.
2. Orient the molecule so the group of lowest priority points directly away from your eye.
3. Follow the direction of the remaining groups from the highest to lowest priority. If the procession is clockwise, the configuration is designated R; if the procession is counterclockwise, the configuration is designated S.



clockwise ∴ R configuration



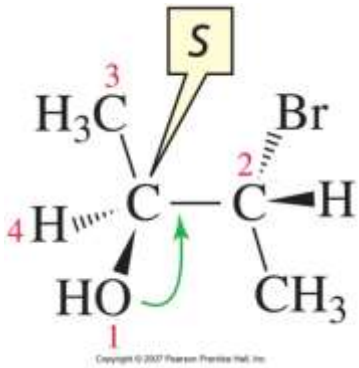
highest to lowest priority
is counterclockwise ∴ S

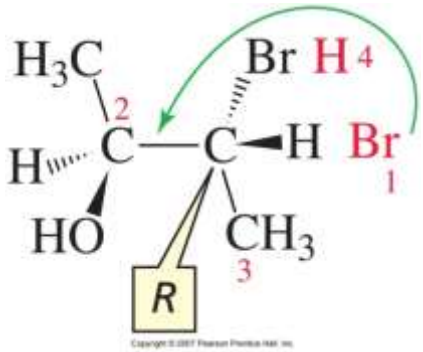


highest to lowest priority
is clockwise ∴ R

Naming with more than1 Stereocenter

R or S configuration assignment must be made to each asymmetric center individually





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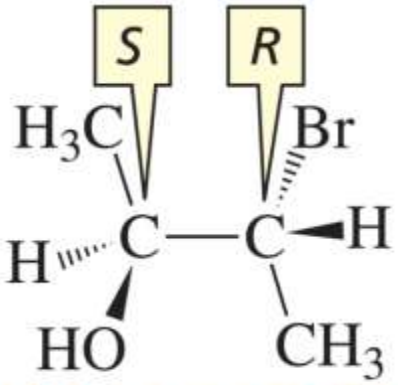
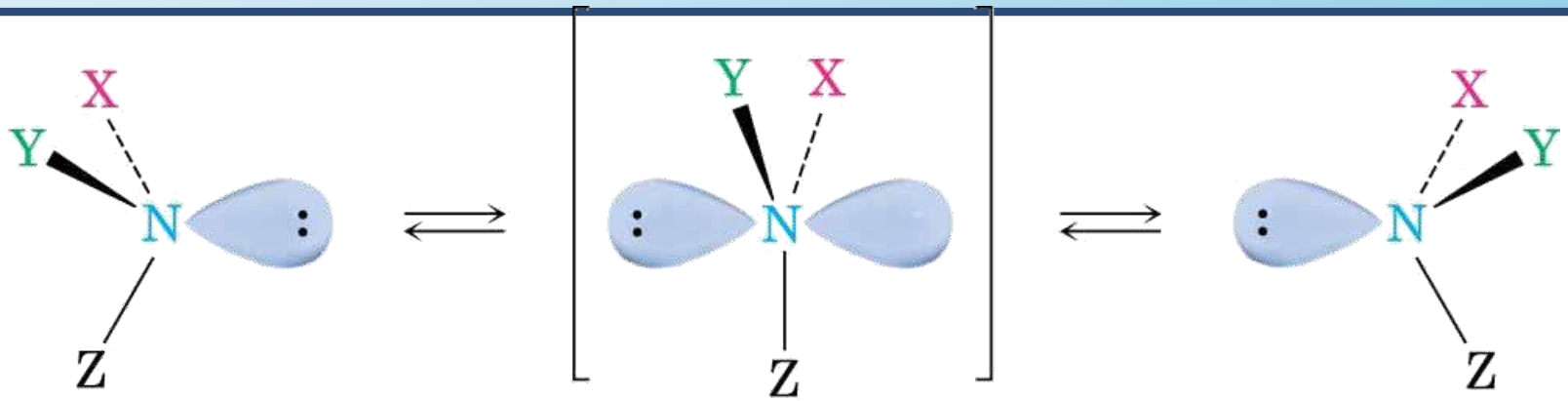


(2*S*,3*R*)-3-bromo-2-butanol

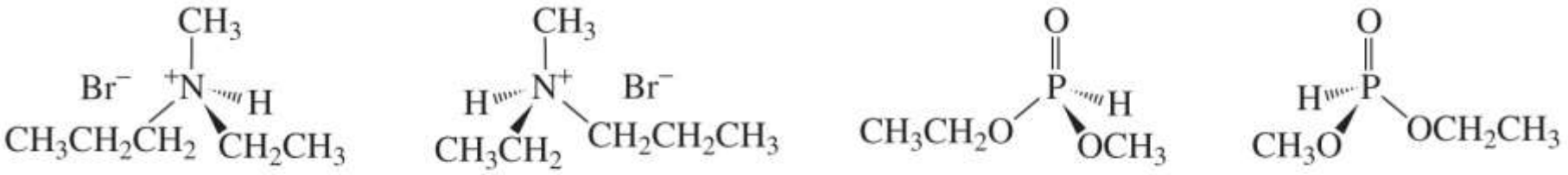
Nitrogen & Phosphorus Centers

Asymmetric center - any atom that has four different groups or atoms attached

- Trivalent nitrogen is tetrahedral
- Does not form a chiral nitrogen since it rapidly flips
- Also applies to phosphorus but it flips more slowly.

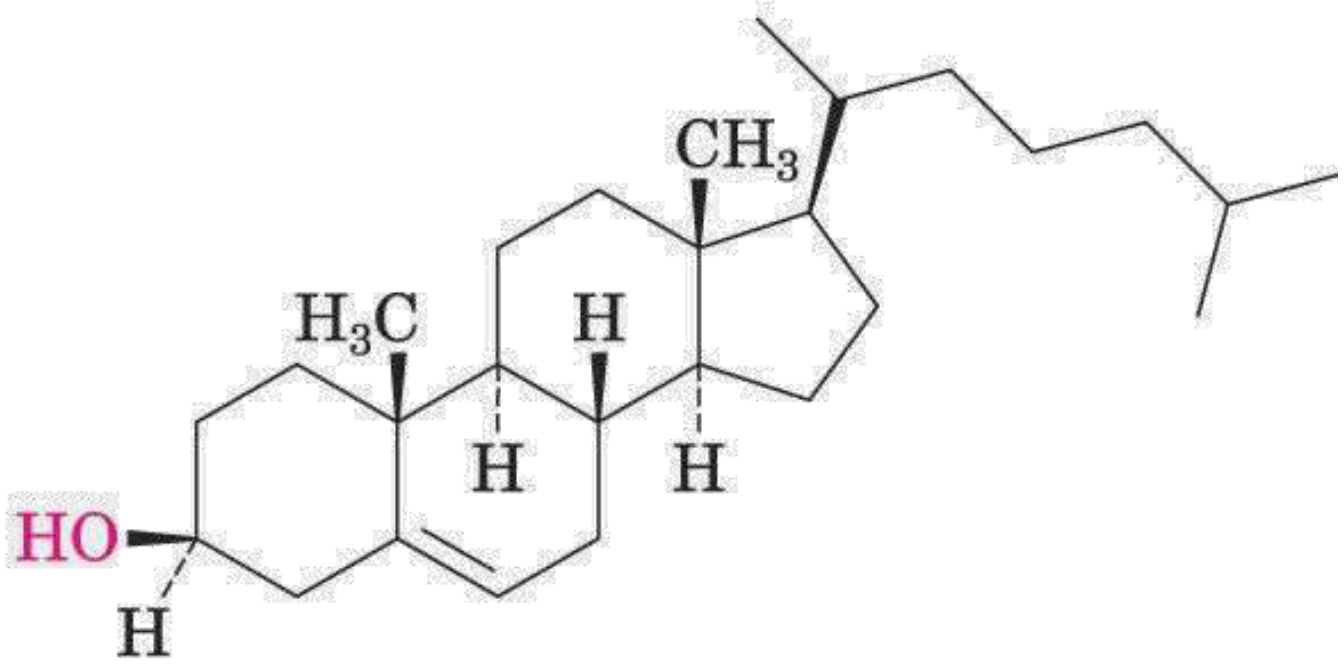


sp^3-hybridized (tetrahedral) **sp^2-hybridized (planar)** **sp^3-hybridized (tetrahedral)**



enantiomers enantiomers

How many chiral carbons cholesterol has?



Cholesterol

Resolution:

Is the process of separating a pair of enantiomers into the pure stereoisomers.

Methods of resolving racemic mixtures:

1. Mechanical separation:

Louis Pasteur first used this method in 1848 to separate the stereoisomers of a crystalline tartaric acid salt.

Separate solutions of the two separate isomers had the same specific rotation, but differed in the sign of rotation. This is a rather special method, which can't be applied to all racemic mixtures.

2.Resolution using Diastereomers.

This method is based on the fact that diastereomers have different physical properties.

The method involves the followings:

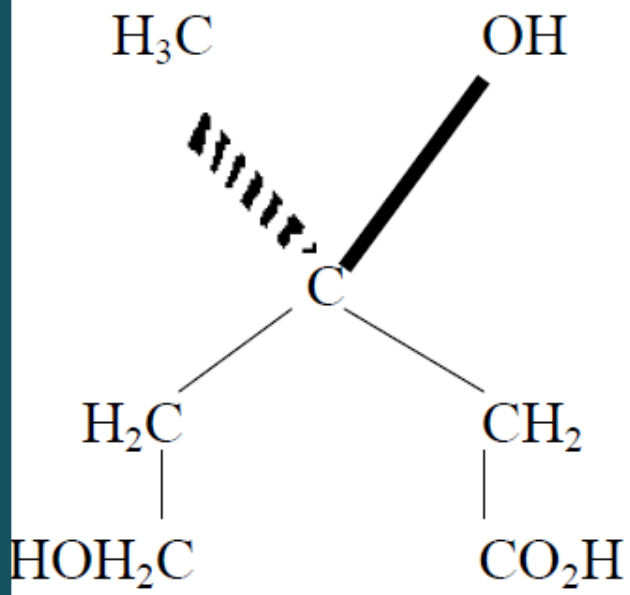
a. the racemic mixture is reacted with an optically active reagent yielding a product which a mixture of two diastereomers.

b. according to a certain physical property (say their solubility in ethanol), the diasterereomers are separated from one another.

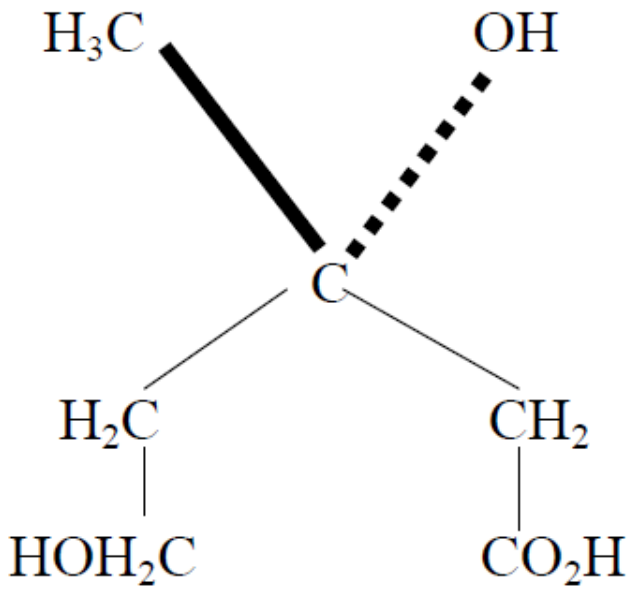
c. the separated diastereomers are each reacted to reconvert them to the optically active reagent and the separated enantiomers.

3.Enzymatic (Biological)resolution.

If a racemic mixture can be fed to a living organism, then it is often found that one enantiomer is preferentially metabolized. If this is so, then the unwanted isomer can sometimes be recovered. When a racemic mixture of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) is fed to rats, one optical isomer is totally absorbed, and almost all the other is excreted in the urine, from which it can be recovered.



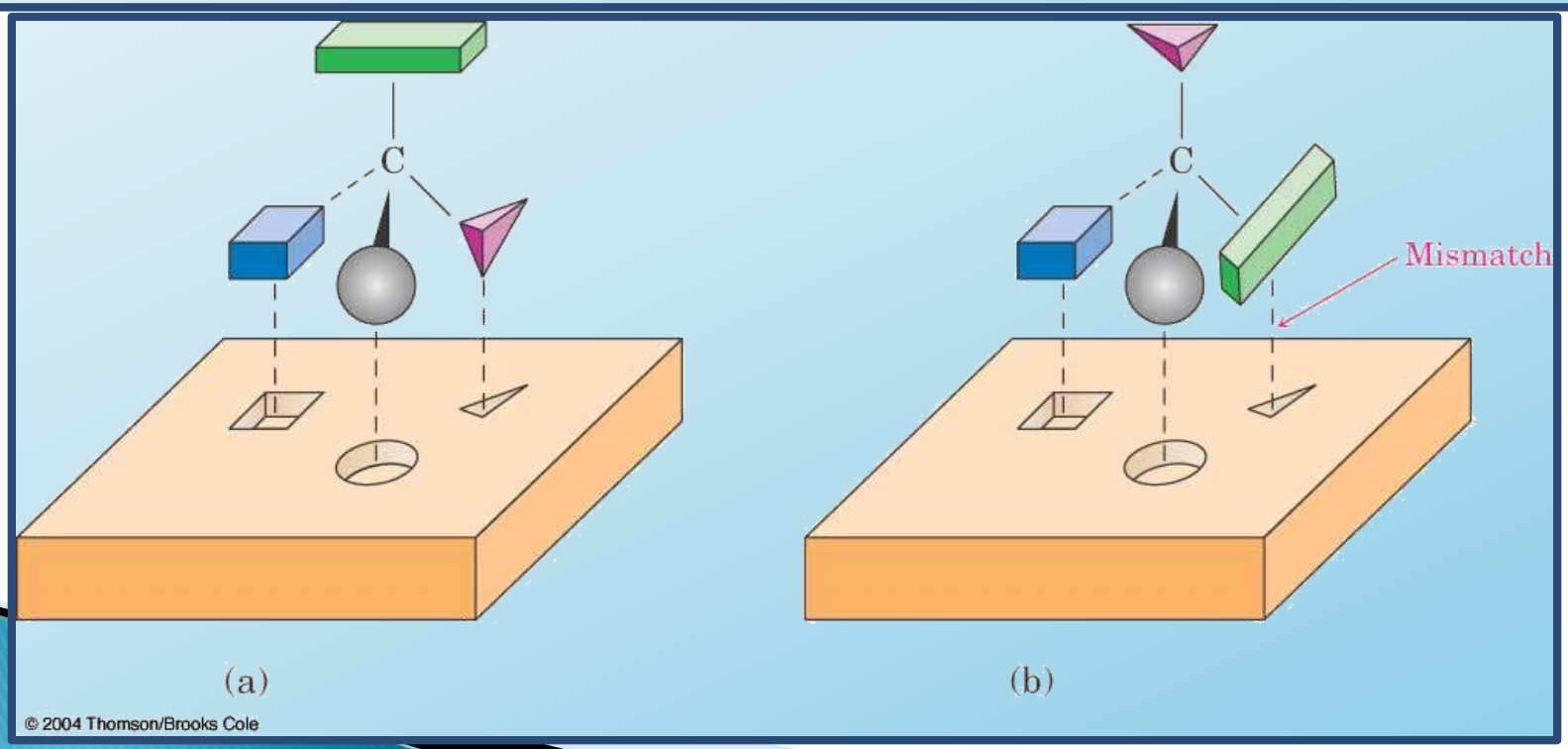
Metabolized



Excreted

Chirality in Nature

- Stereoisomers are readily distinguished by chiral receptors in nature
- Properties of drugs depend on stereochemistry
- Think of biological recognition as equivalent to 3-point interaction



Biological Molecules

RULE - Enzymes are chiral reagents because their binding site is chiral