

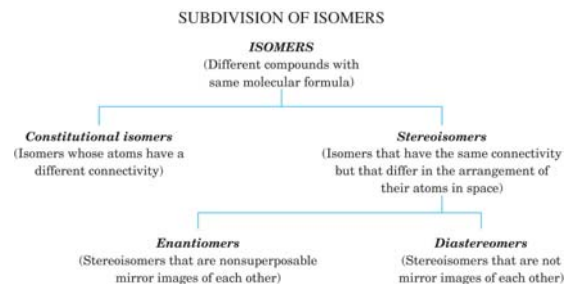
Chapter 5

Stereochemistry: Chiral Molecules

Isomerism: Constitutional Isomers and Stereoisomers

Constitutional Isomers = same molecular formula, different connectivity

Stereoisomers = same molecular formula, same connectivity of atoms but different arrangement of atoms in space



Constitutional Isomers - Review

Same molecular formula – different bond connectivities

Examples of Constitutional Isomers		
formula	constitutional isomers	
C_3H_8O	$CH_3CH_2CH_2OH$	$CH_3\overset{\text{OH}}{\underset{ }{CH}}CH_3$
C_4H_{10}	$CH_3CH_2CH_2CH_3$	$CH_3\overset{\text{CH}_3}{\underset{ }{CH}}CH_2CH_3$

Always different properties

Very different properties if different functional groups

Stereochemistry

Chiral and Achiral Molecules

- Although everything has a mirror image, mirror images may or may not be superimposable.
- Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or **superimposable**.



♦ A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

Stereochemistry

Chiral and Achiral Molecules

- Other molecules are like socks. Two socks from a pair are mirror images that are superimposable. A sock and its mirror image are identical.
- A molecule or object that is superimposable on its mirror image is said to be **achiral**.

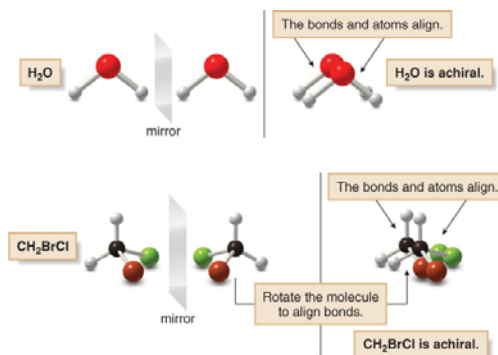


♦ A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

Stereochemistry

Chiral and Achiral Molecules

- We can now consider several molecules to determine whether or not they are **chiral**.



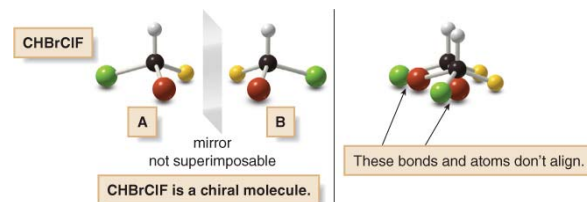
Mirror image = converts right hand into left



Stereochemistry

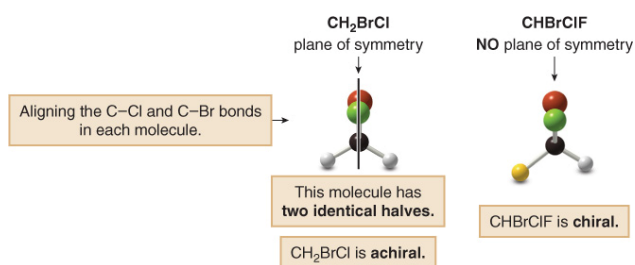
Chiral and Achiral Molecules

- The molecule labeled A and its mirror image labeled B are not superimposable. No matter how you rotate A and B, all the atoms never align. Thus, CHBrClF is a chiral molecule, and A and B are different compounds.
- A and B are stereoisomers—specifically, they are enantiomers.
- A carbon atom with four different groups is a **tetrahedral stereogenic center**.



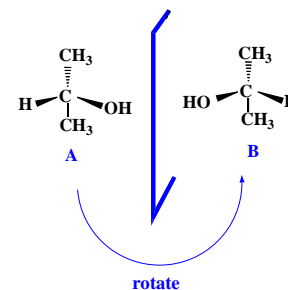
Stereochemistry

Chiral and Achiral Molecules



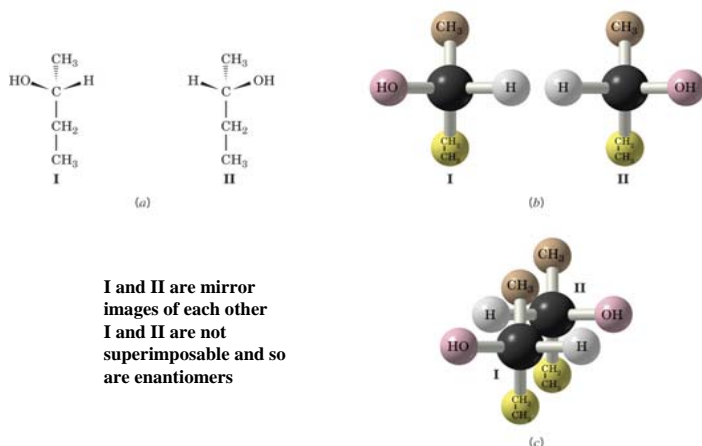
2-propanol is not chiral

B is mirror image of A, but is superimposable by 180° rotation



Everything has a mirror image, the question is whether it is superimposable

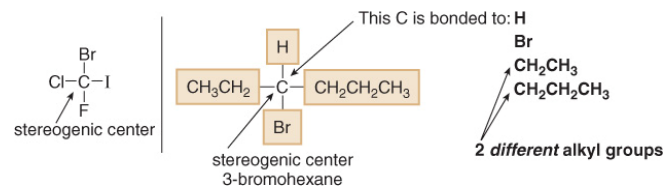
A chiral molecule: 2-butanol



Stereochemistry

Stereogenic Centers

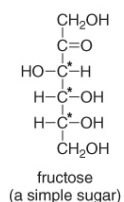
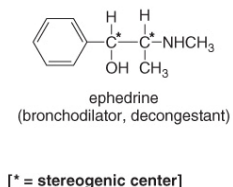
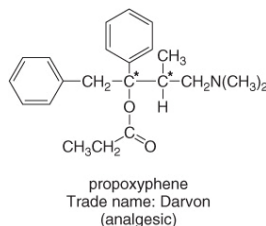
- To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and **look at the four groups—not the four atoms—bonded to it**.
- Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include
 - CH2 and CH3 groups
 - Any sp or sp^2 hybridized C



Stereochemistry

Stereogenic Centers

- Larger organic molecules can have two, three or even hundreds of stereogenic centers.

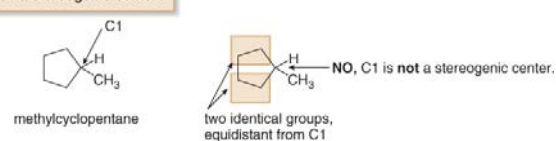


Stereochemistry

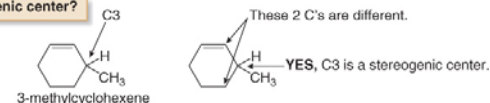
Stereogenic Centers

- Stereogenic centers may also occur at carbon atoms that are part of a ring.
- To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.

Is C1 a stereogenic center?



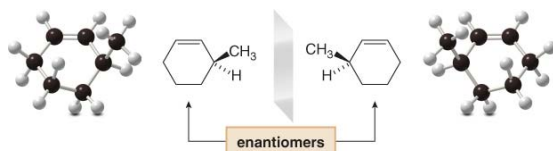
Is C3 a stereogenic center?



Stereochemistry

Stereogenic Centers

- In 3-methylcyclohexene, the CH_3 and H substituents that are above and below the plane of the ring are drawn with wedges and dashes as usual.

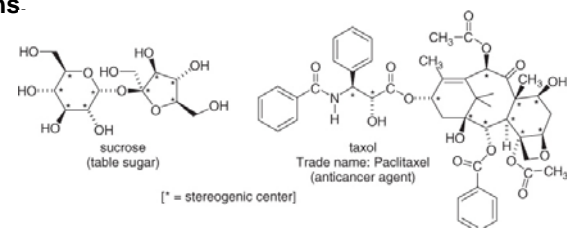
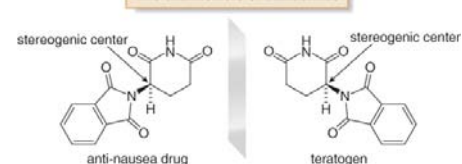


Stereochemistry

Stereogenic Centers

- Many biologically active molecules contain stereogenic centers on ring carbons.

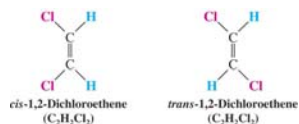
Two enantiomers of thalidomide



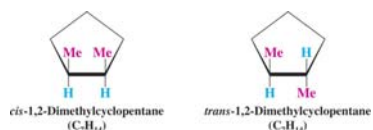
Two types of stereoisomers

1. **Enantiomers:** stereoisomers whose molecules are nonsuperposable mirror images
2. **Diastereomers:** stereoisomers whose molecules are not mirror images of each other

→ Example: cis and trans double bond isomers



→ Example: cis and trans cycloalkane isomers



Enantiomers and Chiral Molecules

- ♦ **Chiral molecule** - has the property of handedness
 - Not superimposable on its mirror image
 - Can exist as a pair of enantiomers
- ♦ **Pair of enantiomers**
 - A chiral molecule and its mirror image
- ♦ **Achiral molecule**
 - Superimposable on its mirror image

Chiral molecules and stereogenic centers

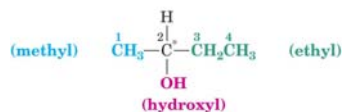
1. A molecule with a single tetrahedral carbon bonded to **four different groups** will always be chiral
2. Switching two groups at the tetrahedral center leads to the enantiomeric molecule
3. A molecule with more than one tetrahedral carbon bonded to four different groups is not always chiral]- **LATER**

Stereogenic Center (also called a “stereocenter”)

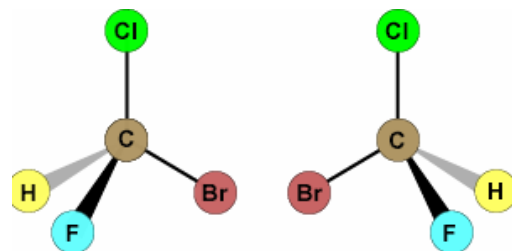
→ In general it is “an atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer”

→ sp^3 carbon is the most common example of a tetrahedral stereogenic center. They are usually designated with an asterisk (*)

- Example: 2-butanol



Mirror images not superimposable = enantiomers



Tests for achirality

1. Draw mirror image. Is it superimposable?



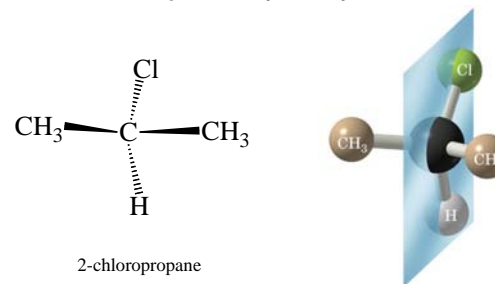
2. Does the species have a bisecting plane of symmetry?



Plane of Symmetry = achiral

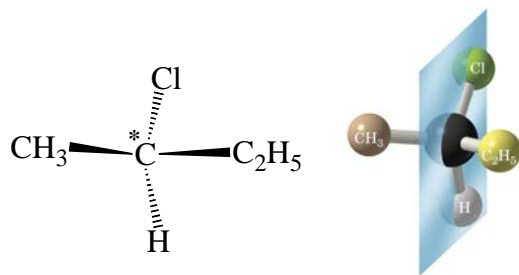
An imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other

A molecule with a plane of symmetry cannot be chiral



If any two groups on a C are identical, achiral

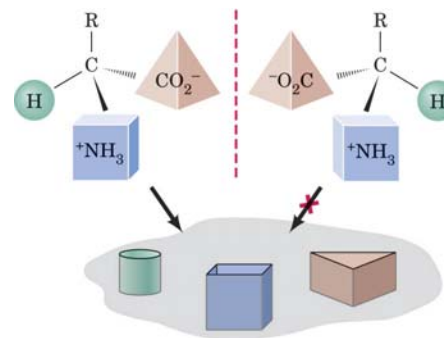
2-chlorobutane: no plane of Symmetry



Compounds with 4 different groups attached to one Carbon must be chiral
unless a meso compound (discussed later)

Many biological processes depend on chirality

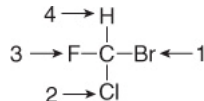
♦ The binding specificity of a chiral receptor site for a chiral molecule is usually only favorable in one way



Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

- Since enantiomers are two different compounds, they need to be distinguished by name. This is done by adding the prefix *R* or *S* to the IUPAC name of the enantiomer.
- Naming enantiomers with the prefixes *R* or *S* is called the **Cahn-Ingold-Prelog** system.
- To designate enantiomers as *R* or *S*, priorities must be assigned to each group bonded to the stereogenic center, in order of decreasing atomic number. **The atom of highest atomic number gets the highest priority (1).**

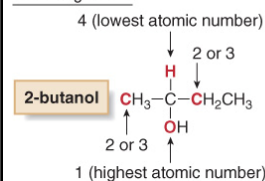


Stereochemistry

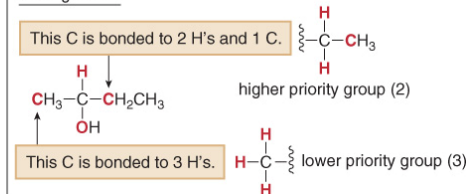
Labeling Stereogenic Centers with *R* or *S*

- If two atoms on a stereogenic center are the same, assign priority based on the atomic number of the atoms bonded to these atoms. One atom of higher priority determines the higher priority.

Following rule 1:



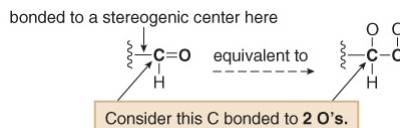
Adding rule 2:



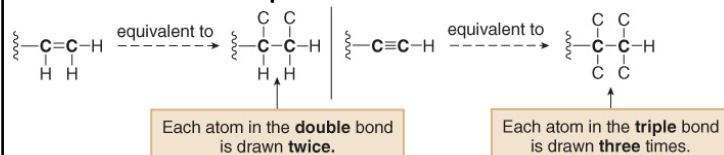
Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

- To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms. For example, the C of a C=O is considered to be bonded to two O atoms.



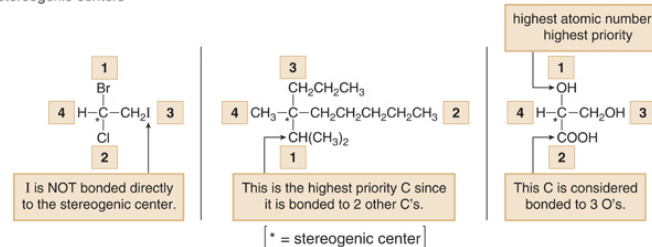
- Other common multiple bonds are drawn below:



Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

Figure 5.6 Examples of assigning priorities to stereogenic centers

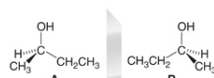


Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

How To Assign *R* or *S* to a Stereogenic Center

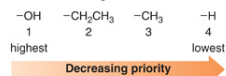
Example Label each enantiomer as *R* or *S*.



two enantiomers of 2-butanol

Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

- The priorities for the four groups around the stereogenic center in 2-butanol were given in rule 2, on page 167.

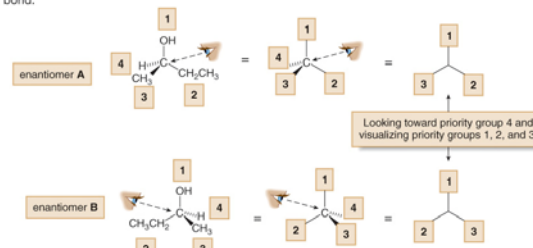


Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

Step [2] Orient the molecule with the lowest priority group (4) back (on a dash), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C–H bond.

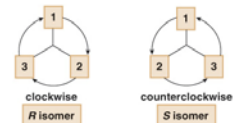


Stereochemistry

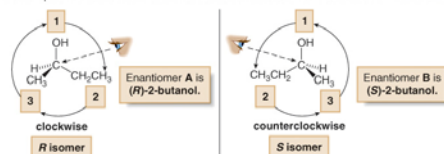
Labeling Stereogenic Centers with *R* or *S*

Step [3] Trace a circle from priority group 1 → 2 → 3.

- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named *R*.
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named *S*.



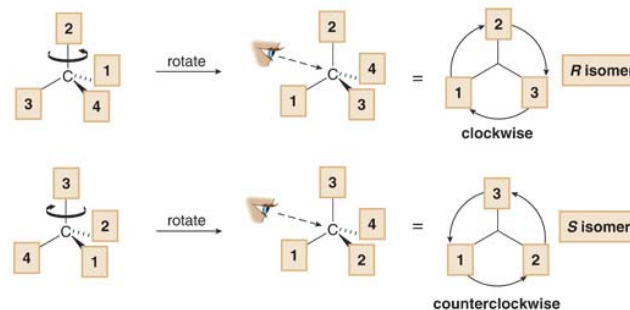
- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



Stereochemistry

Labeling Stereogenic Centers with *R* or *S*

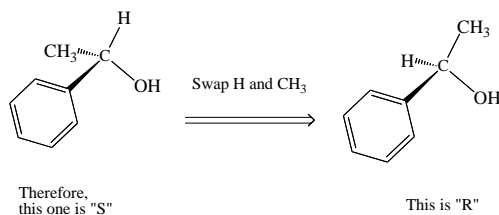
Figure 5.7 Examples:
Orienting the lowest priority group in back



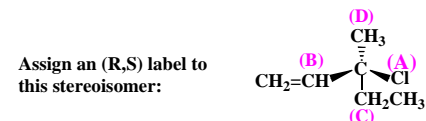
A TRICK: if lowest priority group is not in back

1. Swap any two groups and then assign the opposite of the new priority

- This works because interchanging two groups automatically generates the enantiomer of the original

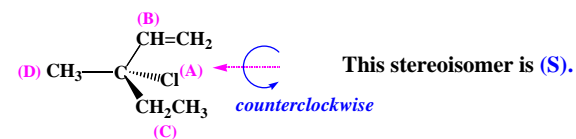


Name this enantiomer of 3-chloro-3-methyl-1-pentene



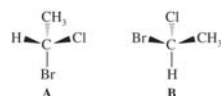
Step 1: Assign Priorities

Step 2: Visualize along the axis with the lowest priority group away from the viewer.

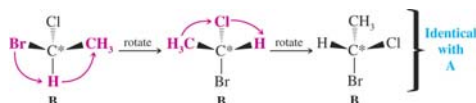


Step 3: Trace out the sequence A→B→C.

Comparing molecules: are A and B identical or enantiomers?

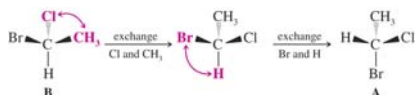


Method 1: Rotate B to see if it will become superimposable with A



Method 2: Exchange 2 groups in order to try to convert B into A

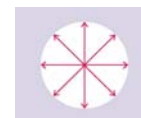
- One exchange of groups leads to the enantiomer of B
- Two exchanges of groups leads back to B



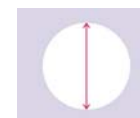
Properties of Enantiomers: Optical Activity

- Enantiomers rotate the plane of plane-polarized light in equal but opposite directions

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



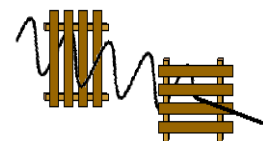
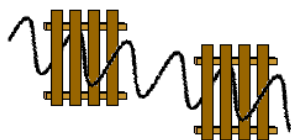
If the light is passed through a polarizer only one plane emerges



Plane polarized light

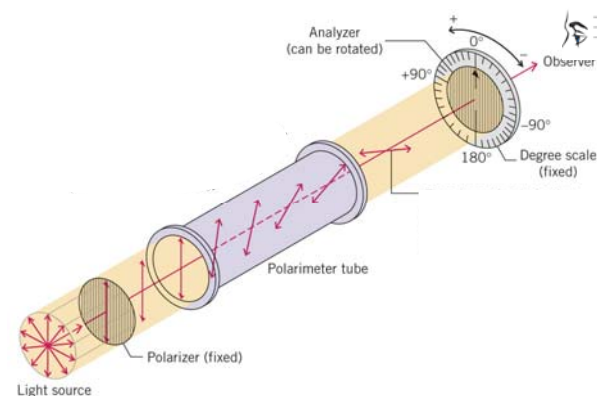
Plane polarized light oscillates in a single plane

Like a rope
through a picket
fence



The plane-polarized light cannot get through
Two filters that are 90° to one another.

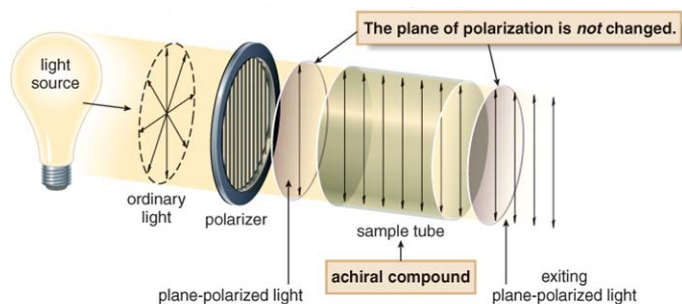
Schematic of a Polarimeter



Stereochemistry

Physical Properties of Stereoisomers

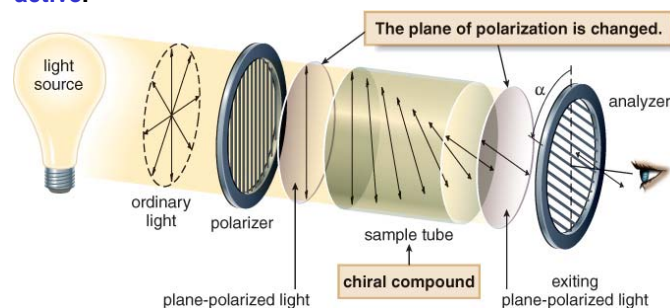
- With achiral compounds, the light that exits the sample tube remains unchanged. A compound that does not change the plane of polarized light is said to be **optically inactive**.



Stereochemistry

Physical Properties of Stereoisomers

- With chiral compounds, the plane of the polarized light is rotated through an angle α . The angle α is measured in degrees ($^\circ$), and is called the **observed rotation**. A compound that rotates polarized light is said to be **optically active**.



Stereochemistry

Physical Properties of Stereoisomers

- The rotation of polarized light can be **clockwise or anticlockwise**.
- If the rotation is clockwise (to the right of the noon position), the compound is called **dextrorotatory**. The rotation is labeled **d** or **(+)**.
- If the rotation is counterclockwise, (to the left of noon), the compound is called **levorotatory**. The rotation is labeled **l** or **(-)**.
- Two enantiomers rotate plane-polarized light to an equal extent but in opposite directions**. Thus, if enantiomer A rotates polarized light $+5^\circ$, the same concentration of enantiomer B rotates it -5° .
- No relationship** exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.

Stereochemistry

Physical Properties of Stereoisomers

- An equal amount of two enantiomers is called a **racemic mixture** or a **racemate**. A racemic mixture is optically inactive. Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.

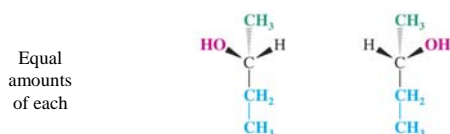
TABLE 5.1 The Physical Properties of Enantiomers A and B Compared

Property	A alone	B alone	Racemic A + B
Melting point	identical to B	identical to A	may be different from A and B
Boiling point	identical to B	identical to A	may be different from A and B
Optical rotation	equal in magnitude but opposite in sign to B	equal in magnitude but opposite in sign to A	0°

Racemic Mixture = A 1:1 mixture of enantiomers

- No net optical rotation
- Often designated as (\pm)
- Racemic mixture = racemate

(\pm) -2-butanol or as (\pm) -CH₃CH₂CHOHCH₃



Stereochemistry

Physical Properties of Stereoisomers

- Specific rotation** is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light. Specific rotation is denoted by the symbol $[\alpha]$ and defined using a specific sample tube length (l , in dm), concentration (c in g/mL), temperature (25°C) and wavelength (589 nm).

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation ($^\circ$)
 l = length of sample tube (dm)
 c = concentration (g/mL)

[dm = decimeter
 1 dm = 10 cm]

An example of specific rotation

A sample of a compound **A** in chloroform (0.500 g/mL) at 25.0°C shows a rotation of +2.5° in a 1.0 decimeter cell. What is the specific rotation?

$$[\alpha]_l^{\text{temp}} = \frac{\alpha}{L \times C} = \frac{+2.5^\circ}{1.0 \text{ dm} \times 0.5 (\text{g/mL})} = +5.0^\circ \text{ dm}^{-1} (\text{g/mL})^{-1}$$

Stereochemistry

Physical Properties of Stereoisomers

- Enantiomeric excess (optical purity)** is a measurement of how much one enantiomer is present in excess of the racemic mixture. It is denoted by the symbol **ee**.

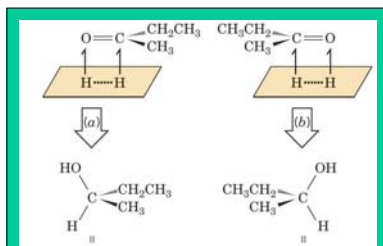
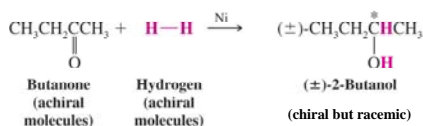
ee = % of one enantiomer - % of the other enantiomer.

- Consider the following example—If a mixture contains 75% of one enantiomer and 25% of the other, the enantiomeric excess is 75% - 25% = 50%. Thus, there is a 50% excess of one enantiomer over the racemic mixture.
- The enantiomeric excess can also be calculated if the specific rotation $[\alpha]$ of a mixture and the specific rotation $[\alpha]$ of a pure enantiomer are known.

$$\text{ee} = ([\alpha]_{\text{mixture}} / [\alpha]_{\text{pure enantiomer}}) \times 100.$$

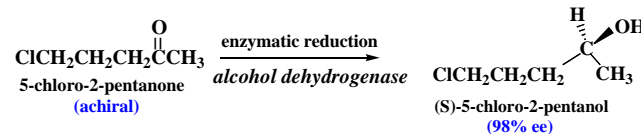
The Synthesis of Chiral Molecules

Most chemical reactions which produce chiral molecules generate the racemic mixture (50%R, 50% S)



Enantioselective Synthesis

However, if one of the reagents is chiral, as is common in biological systems, then the products may be chiral

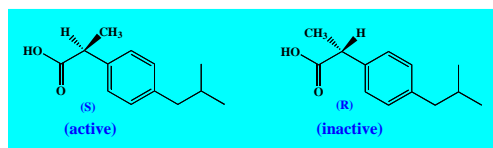


(In this case, the *alcohol dehydrogenase* is the chiral reagent)

THIS OCCURS BECAUSE the top and bottom faces of the ketone appear to be different to the chiral reagent (the enzyme)

Chiral Drugs and Pharmaceutical Companies

Typically only one enantiomer of a drug is biologically active

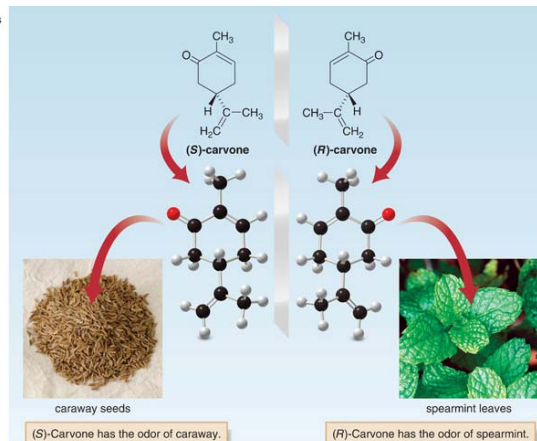


Ibuprofen

Stereochemistry

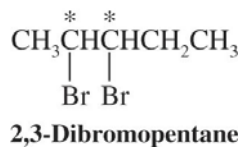
Chemical Properties of Enantiomers

Figure 5.13 Two enantiomers can have different odors



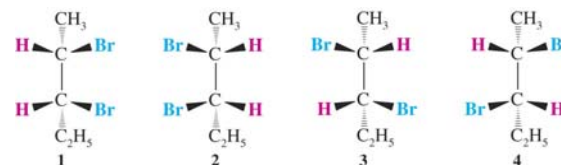
Molecules with More than One Stereogenic Center

Each new stereogenic center may generate a potential pair of stereoisomers, so the theoretical number of possible stereoisomers is 2^n



How many stereoisomers?

Four stereoisomers of 2,3-dibromopentane



Relationship of 1 and 2 = **enantiomers**

Relationship of 3 and 4 = **enantiomers**

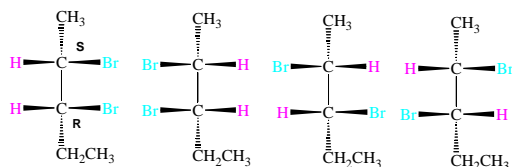
(Enantiomers = same properties, cannot be separated)

Relationship of (1 and 3), (2 and 3), or (1 and 4) = **diastereomers**

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

They have **different physical properties** and can be separated

Four stereoisomers of 2,3-dibromopentane



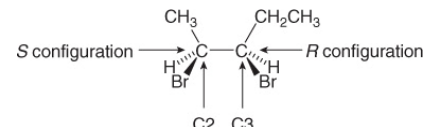
Let's figure out the configurations of all 4 stereoisomers

Use the same rules, and assign each stereogenic center separately

Stereochemistry

R and S Assignments in Compounds with Two or More Stereogenic Centers.

- When a compound has more than one stereogenic center, the *R* and *S* configuration must be assigned to each of them.

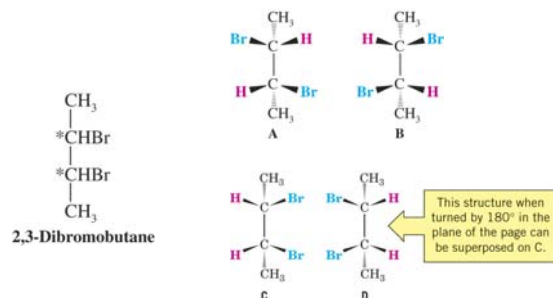


One stereoisomer of 2,3-dibromopentane
The complete name is (2*S*,3*R*)-2,3-dibromopentane

- Identical compounds have the *same* *R,S* designations at every tetrahedral stereogenic center.
- Enantiomers have exactly *opposite* *R,S* designations.
- Diastereomers have the *same* *R,S* designation for at least one stereogenic center and the *opposite* for at least one of the other stereogenic centers.

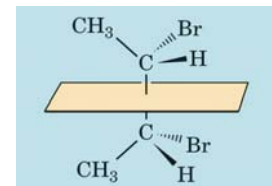
Meso compounds

Sometimes molecules with 2 or more stereogenic centers will have **fewer than 2^n stereoisomers**



Meso compound are achiral

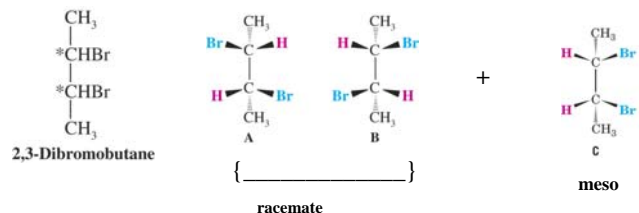
- Because superposable on its mirror image
- Despite the presence of stereogenic centers
- Not optically active
- Has a plane of symmetry



Definition: a meso compound is a compound that is achiral despite having stereogenic centers

Meso Compounds

There are **only three stereoisomers of 2,3-dibromobutane**, not four.

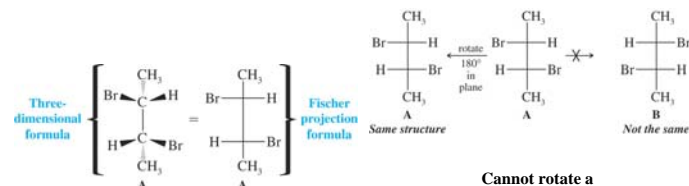


CONCLUSION: there can be fewer than 2^n stereoisomers if the compound can possess a **plane of symmetry**.

Fischer Projections

A 2-dimensional representation of chiral molecules

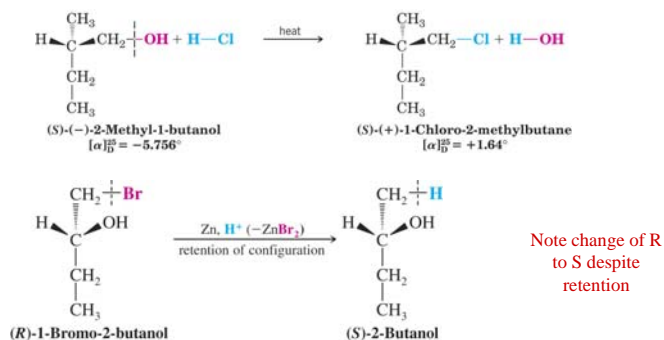
- Vertical lines represent bonds projecting behind the plane of the paper
- Horizontal lines represent bonds projecting out of the plane of the paper



Confusing but widely used because they are easy to draw.

Relating Configurations of Stereogenic Centers

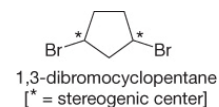
If no bonds to the stereogenic carbon are broken, the reaction is said to proceed with **retention of configuration**



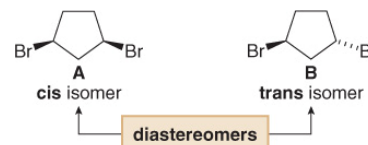
Stereochemistry

Disubstituted Cycloalkanes

- Consider 1,3-dibromocyclopentane. Since it has two stereogenic centers, it has a maximum of four stereoisomers.



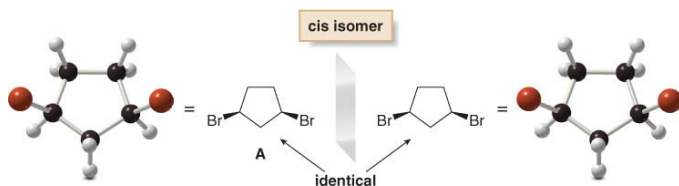
- Recall that a disubstituted cycloalkane can have two substituents on the same side of the ring (**cis isomer, A**) or on opposite sides of the ring (**trans isomer, B**). These compounds are stereoisomers but not mirror images.



Stereochemistry

Disubstituted Cycloalkanes

- To draw the other two stereoisomers if they exist, draw mirror images of each compound and determine whether the compound and its mirror image are superimposable.

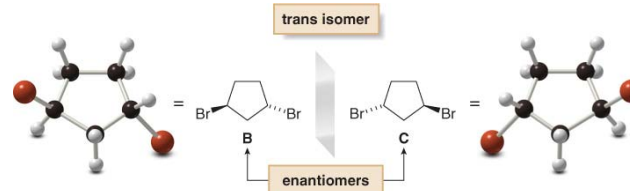


- The *cis* isomer is superimposable on its mirror image, making the images identical. Thus, A is an achiral meso compound.

Stereochemistry

Disubstituted Cycloalkanes

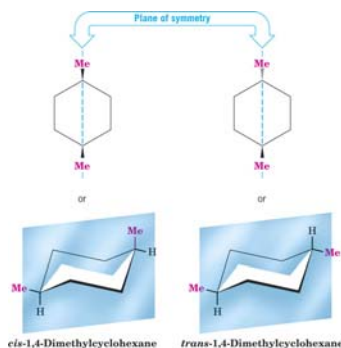
- The *trans* isomer is not superimposable on its mirror image, labeled C, making B and C different compounds. B and C are enantiomers.



- Because one stereoisomer of 1,3-dibromocyclopentane is superimposable on its mirror image, there are only three stereoisomers, not four.

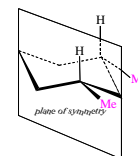
Stereoisomerism of Cyclic Compounds

- 1,4-dimethylcyclohexane
 - Neither the *cis* nor *trans* isomers is optically active
 - Each has a plane of symmetry

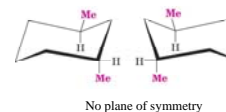


♦ 1,3-dimethylcyclohexane

- The *trans* and *cis* compounds each have two stereogenic centers
- The *cis* compound has a plane of symmetry and is *meso*



- The *trans* compound exists as a pair of enantiomers

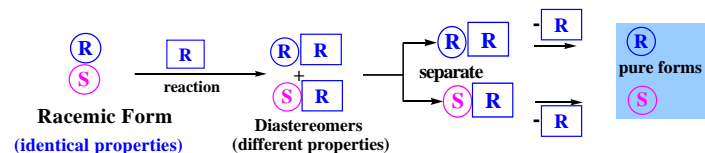


Ring flip of (a) produces another (a), not the mirror image (b)

Separation of enantiomers = resolution

Cannot be separated directly Why not?

Can be separated by a chiral reagent which creates diastereomeric relationship



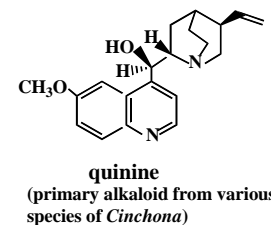
R is a **resolving agent**. It is a single enantiomer of a chiral compound that can react with both enantiomers of the racemic mixture to form a pair of diastereomers.

General Approach to Resolution

Often used are organic acids or bases which are found optically pure in nature

They form acid-base salts which, as diastereomers, have different solubilities in water and can be separated by selective crystallization

One can then easily regenerate starting acid or base



Resolution of a Carboxylic Acid

