

Chapter 5

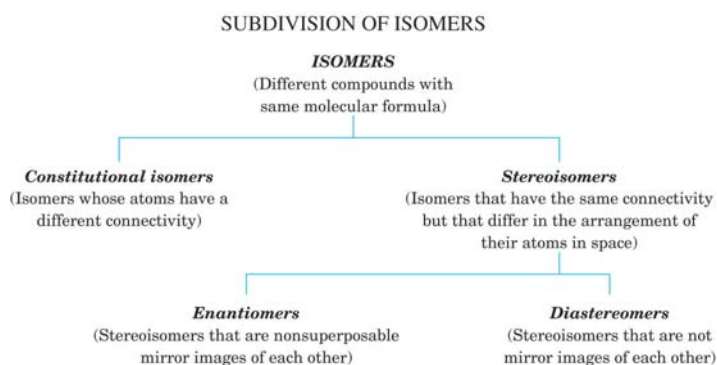
Stereochemistry: Chiral Molecules

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◆ Isomerism: Constitutional Isomers and Stereoisomers

- Stereoisomers are isomers with the same molecular formula and same connectivity of atoms but different arrangement of atoms in space

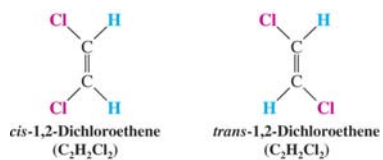


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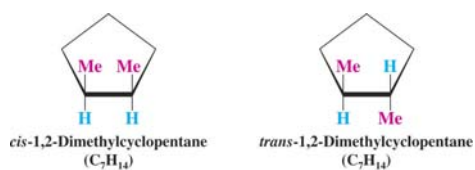
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- **Enantiomers:** stereoisomers whose molecules are nonsuperposable mirror images
- **Diastereomers:** stereoisomers whose molecules are not mirror images of each other

→ Example: cis and trans double bond isomers



→ Example: cis and trans cycloalkane isomers



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◆ Enantiomers and Chiral Molecules

→ Chiral molecule

- ⌘ Not superposable on its mirror image
- ⌘ Can exist as a pair of enantiomers

→ Pair of enantiomers

- ⌘ A chiral molecule and its mirror image

→ Achiral molecule

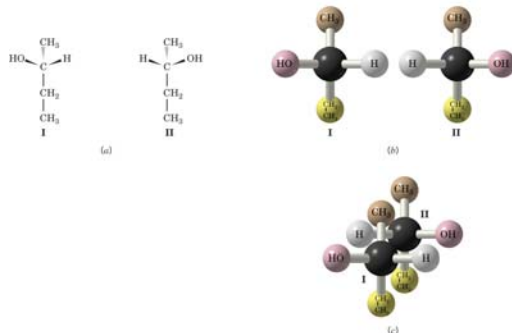
- ⌘ Superposable on its mirror image

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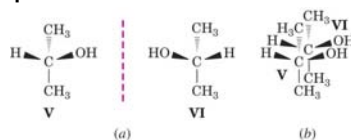
→ Example: 2-butanol

- ⌘ I and II are mirror images of each other (figures a and b)
- ⌘ I and II are not superposable and so are enantiomers (figure c)
- ⌘ 2-butanol is a chiral molecule



→ Example: 2-propanol

- ⌘ Not chiral



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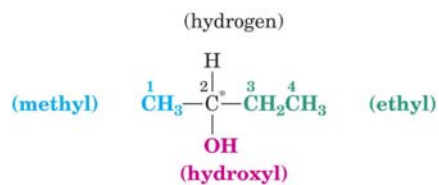
→ Chiral molecule

- ⌘ A molecule with a single tetrahedral carbon bonded to four different groups will always be chiral
- ⌘ A molecule with more than one tetrahedral carbon bonded to four different groups is not always chiral
- ⌘ Switching two groups at the tetrahedral center leads to the enantiomeric molecule in a molecule with one tetrahedral carbon

→ Stereogenic center

- ⌘ An atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer
- ⌘ Carbons at a tetrahedral stereogenic center are designated with an asterisk (*)

→ Example: 2-butanol

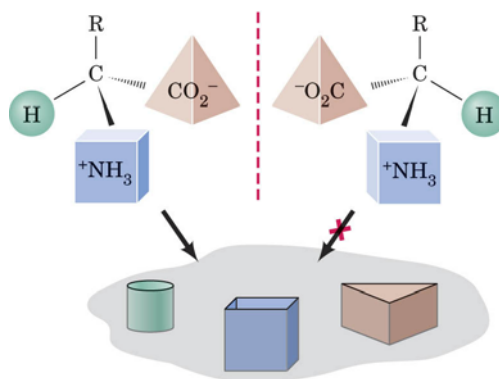


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◆ The Biological Importance of Chirality

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



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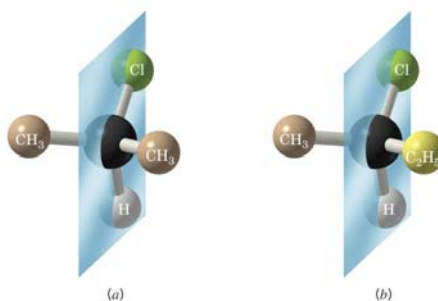
◆ Tests for Chirality: Planes of Symmetry

→ Plane of symmetry

- ⌘ 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

→ Example

- ⌘ 2-Chloropropane (a) has a plane of symmetry but 2-chlorobutane (b) does not



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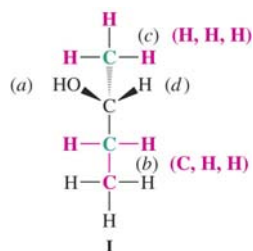
◆ Nomenclature of Enantiomers: The *R,S* System

- Also called the Cahn-Ingold-Prelog system
- The four groups attached to the stereogenic carbon are assigned priorities from highest (a) to lowest (d)
- Priorities are assigned as follows

- Atoms directly attached to the stereogenic center are compared
- Atoms with higher atomic number are given higher priority

→ If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined

→ Example



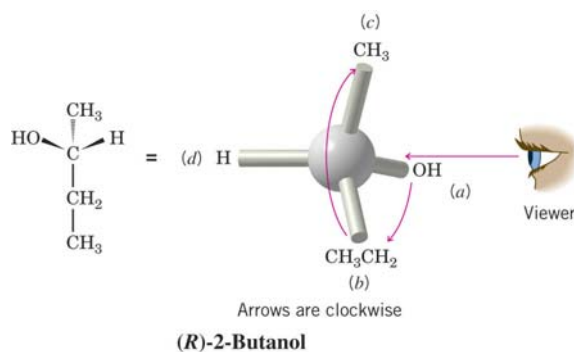
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- The molecule is rotated to put the lowest priority group back

→ If the groups descend in priority (a,b then c) in clockwise direction the enantiomer is *R*

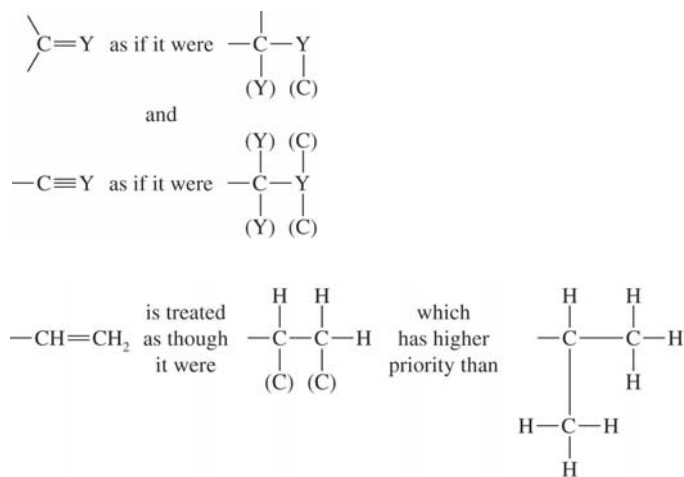
→ If the groups descend in priority in counterclockwise direction the enantiomer is *S*



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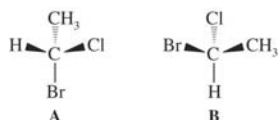
- Groups with double or triple bonds are assigned priorities as if their atoms were duplicated or triplicated



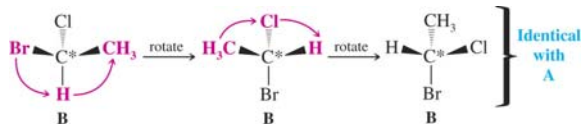
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- Problem: Are A and B identical or enantiomers?

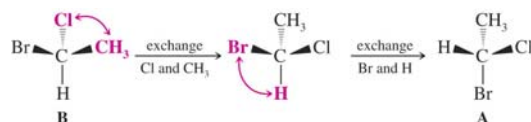


→ Manipulate B to see if it will become superposable with A



→ Exchange 2 groups 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

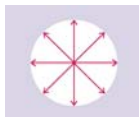


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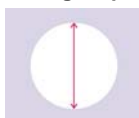
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◆ **Properties of Enantiomers: Optical Activity**

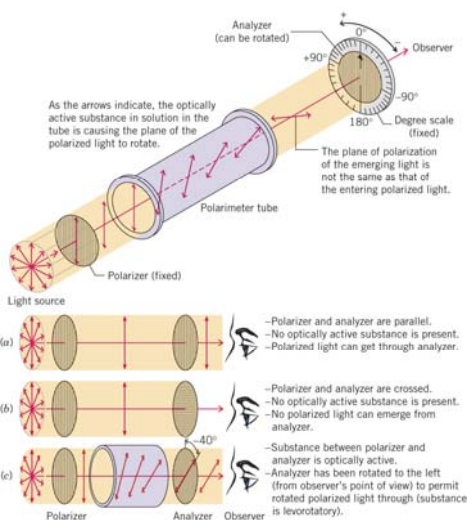
- Enantiomers have almost all identical physical properties (melting point, boiling point, density)
- However enantiomers rotate the plane of plane-polarized light in equal but opposite directions
- Plane polarized light
 - Oscillation of the electric field of ordinary light occurs in all possible planes perpendicular to the direction of propagation



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



● **The Polarimeter**



- **Specific Rotation**

- An empty sample tube or one containing an achiral molecule will not rotate the plane-polarized light

- An optically active substance (e.g. one pure enantiomer) will rotate the plane-polarized light

- ⌘ The amount the analyzer needs to be turned to permit light through is called the observed rotation α

- ⌘ The standard value specific rotation $[\alpha]$ can be calculated

- ⌘ If the analyzer is rotated clockwise the rotation is (+) and the molecule is dextrorotatory

- ⌘ If the analyzer is rotated counterclockwise the rotation is (-) and the molecule is levorotatory

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

where $[\alpha]$ = the specific rotation

α = the observed rotation

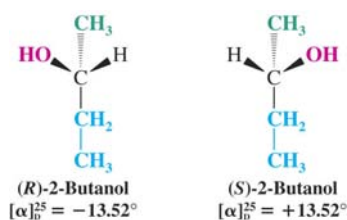
c = the concentration of the solution in grams per milliliter of solution (or density in g mL^{-1} for neat liquids)

l = the length of the tube in decimeters (1 dm = 10 cm)

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- The specific rotation of the two pure enantiomers of 2-butanol are equal but opposite



- There is no straightforward correlation between the R,S designation of an enantiomer and the direction [(+) or (-)] in which it rotates plane polarized light

- **Racemic mixture**

- A 1:1 mixture of enantiomers

- No net optical rotation

- Often designated as (\pm)



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◆ Racemic Forms and Enantiomeric Excess

- Often a mixture of enantiomers will be enriched in one enantiomer

→ One can measure the enantiomeric excess (ee)

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

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

- Example : The optical rotation of a sample of 2-butanol is +6.76°. What is the enantiomeric excess?

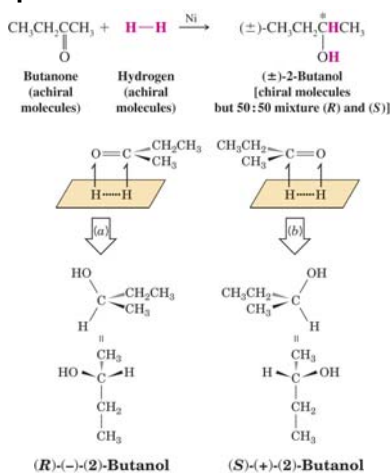
$$\text{Enantiomeric excess} = \frac{+6.76^\circ}{+13.52^\circ} \times 100 = 50\%$$

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◆ The Synthesis of Chiral Molecules

- Most chemical reactions which produce chiral molecules produce them in racemic form

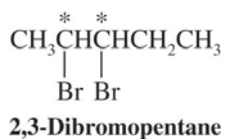


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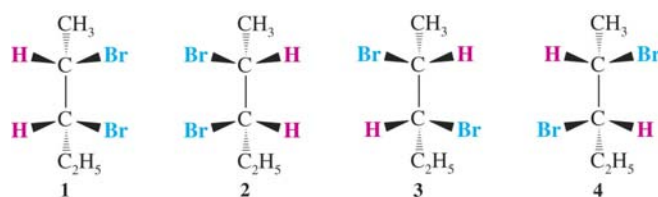
◆ **Molecules with More than One Stereogenic Center**

- The maximum number of stereoisomers available will not exceed 2^n , where n is equal to the number of tetrahedral stereogenic centers



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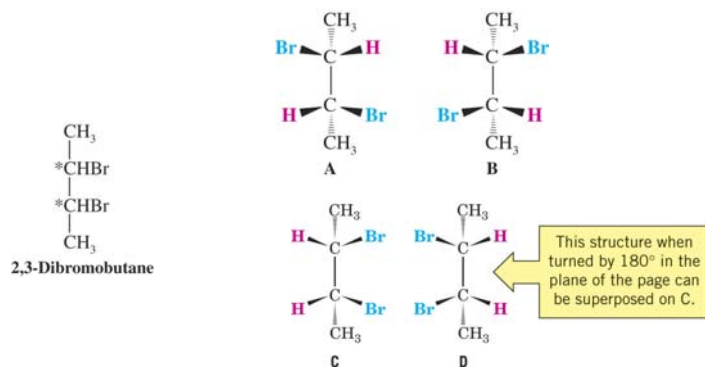
- There are two pairs of enantiomers (1, 2) and (3,4)
 - Enantiomers are not easily separable so 1 and 2 cannot be separated from each other
- Diastereomers: stereoisomers which are not mirror images of each other
 - For instance 1 and 3 or 1 and 4
 - Have different physical properties and can be separated

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◆ Meso Compounds

- Sometimes molecules with 2 or more stereogenic centers will have less than the maximum amount of stereoisomers

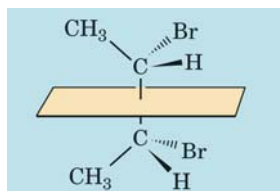


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- Meso compound: achiral despite the presence of stereogenic centers

- Not optically active
- Superposable on its mirror image
- Has a plane of symmetry



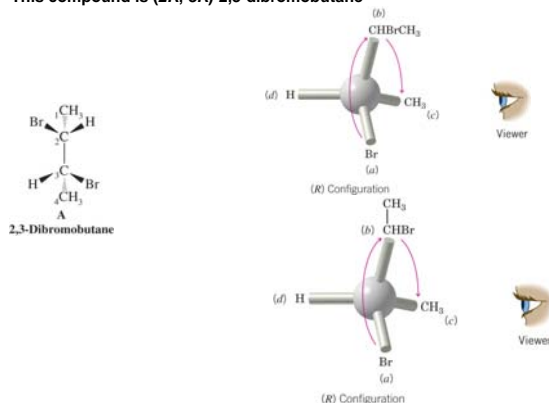
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◆ Naming Compounds with More than One Stereogenic Center

- The molecule is manipulated to allow assignment of each stereogenic center separately

¶ This compound is (2*R*, 3*R*)-2,3-dibromobutane

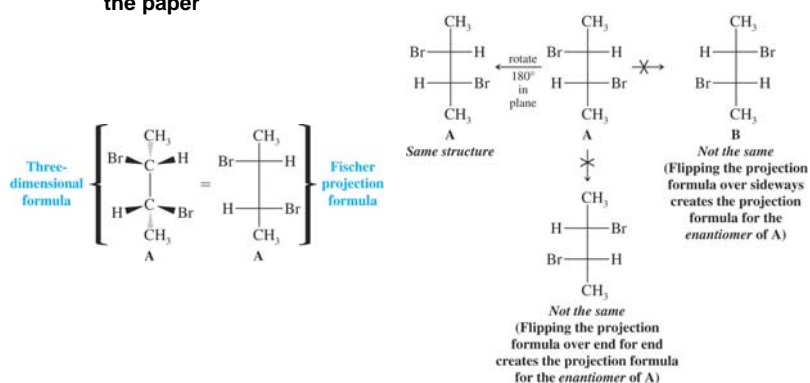


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◆ Fischer Projection Formulas

- A 2-dimensional representation of chiral molecules
 - Vertical lines represent bonds that project behind the plane of the paper
 - Horizontal lines represent bonds that project out of the plane of the paper



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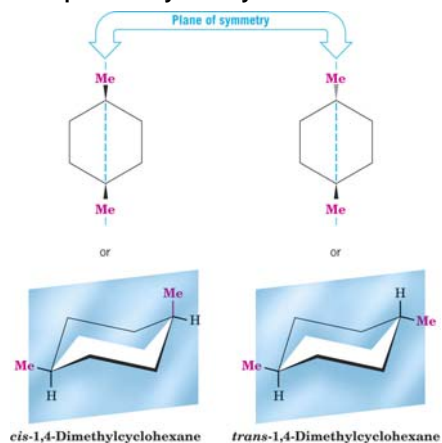
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◆ Stereoisomerism of Cyclic Compounds

● 1,4-dimethylcyclohexane

→ Neither the cis nor trans isomer is optically active

→ Each has a plane of symmetry



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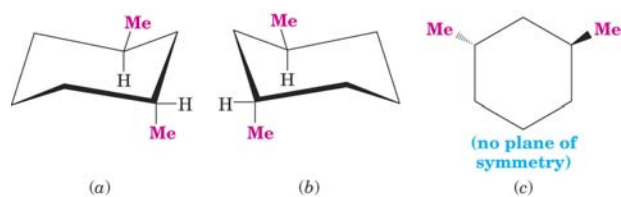
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● 1,3-dimethylcyclohexane

→ 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

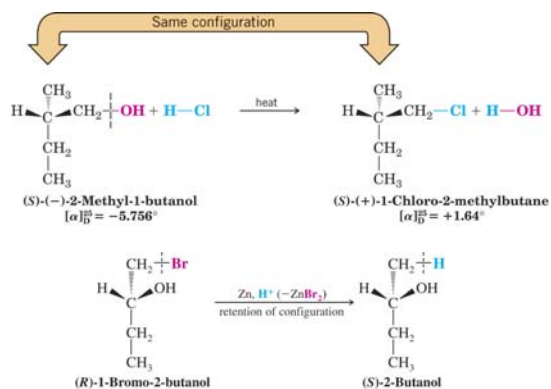


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◆ **Relating Configurations through Reactions in which No Bonds to the Stereogenic Carbon are Broken**

→ A reaction which takes place in a way that no bonds to the stereogenic carbon are broken is said to proceed with *retention of configuration*



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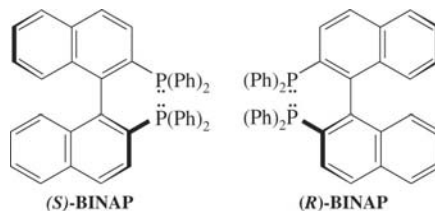
- **Relative configuration: the relationship between comparable stereogenic centers in two different molecules**
 - (*R*)-1-Bromo-2-butanol and (*S*)-2-butanol have the same relative configuration
- **Absolute configuration: the actual 3-dimensional orientation of the atoms in a chiral molecule**
 - Can be determined by x-ray crystallography

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◆ **Chiral Molecules that Do Not Possess a Tetrahedral Atom with Four Different Groups**

- **Atropisomer: conformational isomers that are stable**



- **Allenes: contain two consecutive double bonds**

