

UNIT 3

STEREOCHEMISTRY

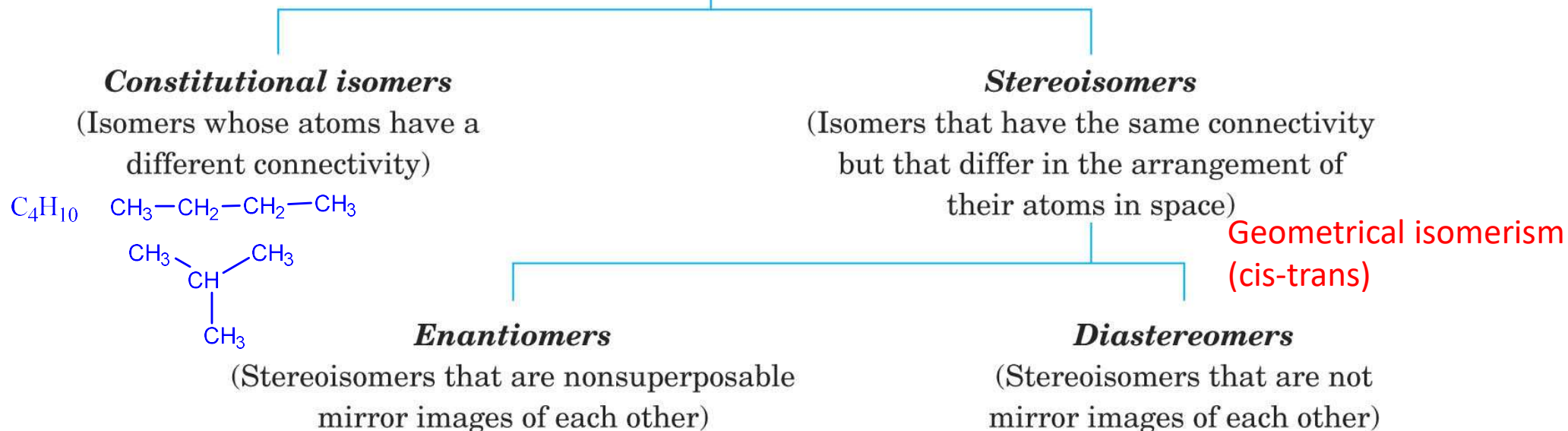
Stereochemistry refers to chemistry in three dimensions.

Stereoisomers have the same order of attachment of atoms, but different arrangement of the atoms in space.

SUBDIVISION OF ISOMERS

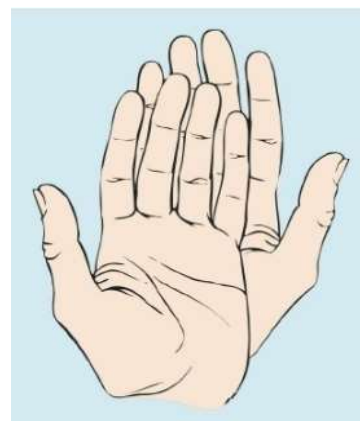
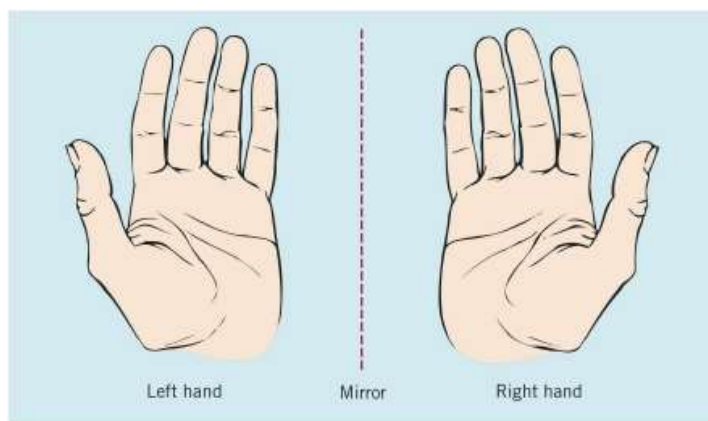
ISOMERS

(Different compounds with same molecular formula)



Enantiomers

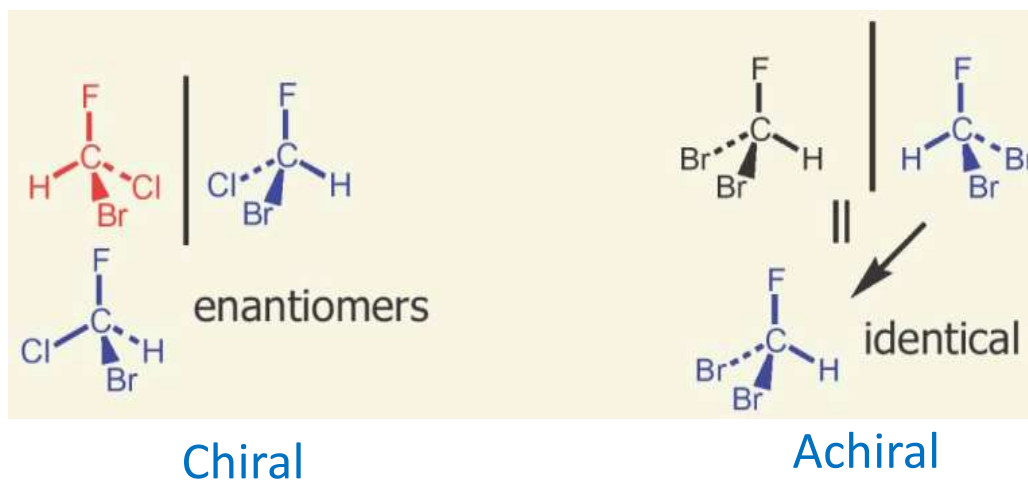
Superposable (superimposable): the ability of every identical atom lies on one another in two different molecules.



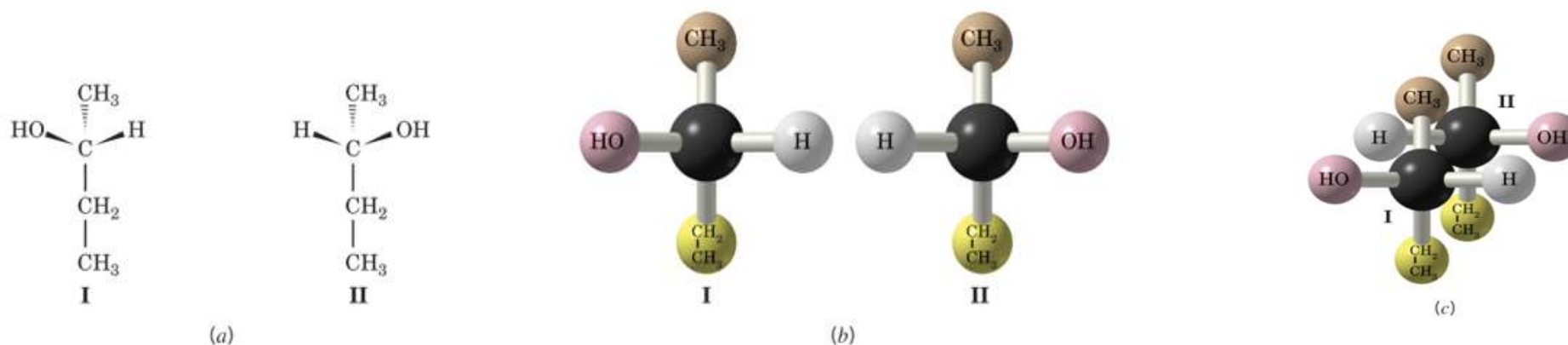
Left and right hand are mirror image of each other but **not superposable**

A molecule is **chiral** if its two mirror-image forms are not superimposable in three dimensions.

Achiral molecule: has superimposable mirror image.



2-butanol

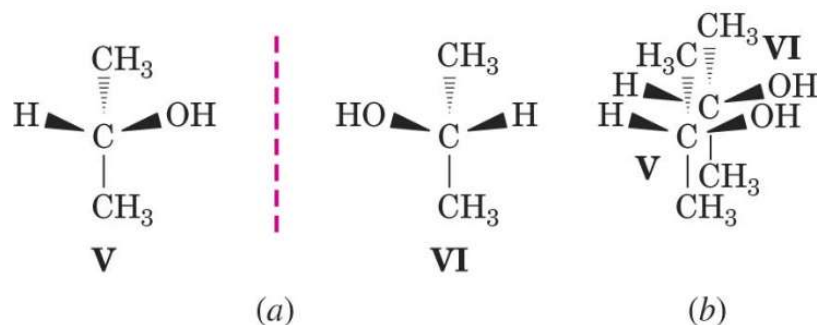


I and II are mirror images of each other (figures a and b)

I and II are not superposable and so are enantiomers (figure c)

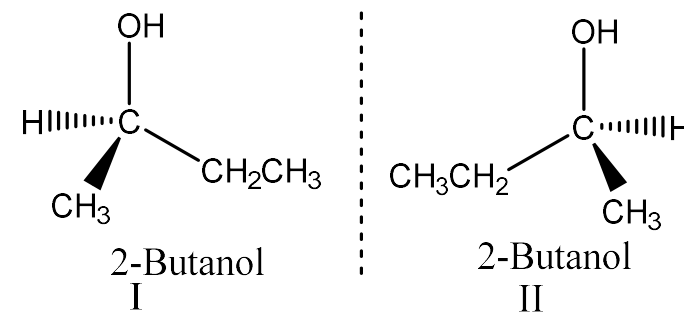
2-butanol is a chiral molecule

2-propanol



2-propanol is not chiral

Enantiomers : Chiral molecule and its mirror molecule

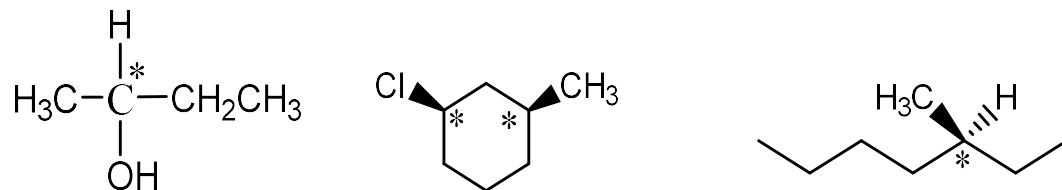


I and II are enantiomers

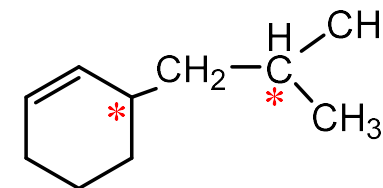
Chirality Center (*)

(chiral center, stereogenic center, stereocenter, asymmetric center, asymmetric carbon)

- A tetrahedral carbon atom that bears four different atoms or groups called a **chiral center**



- a chiral center cannot be sp - or sp^2 -hybridized carbon (must be sp^3).

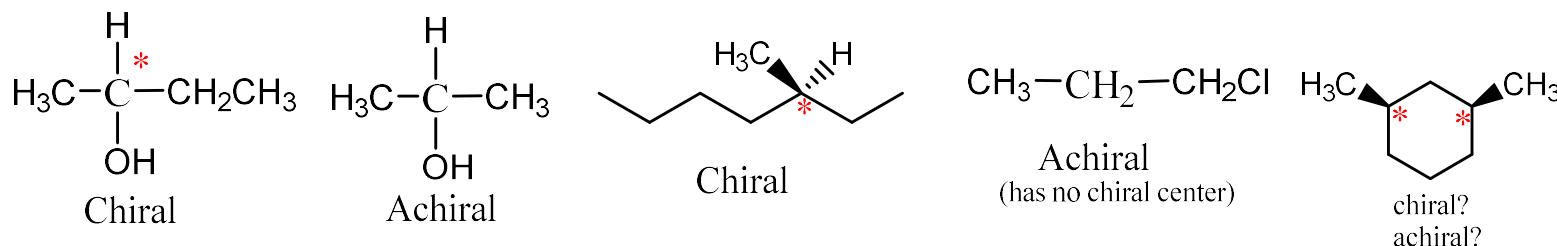


Test for chirality

- a molecule with one chiral center is **chiral**

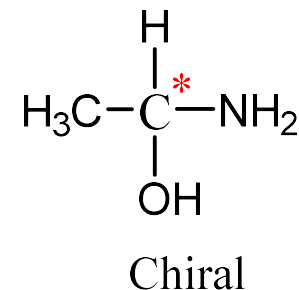
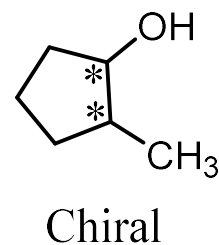
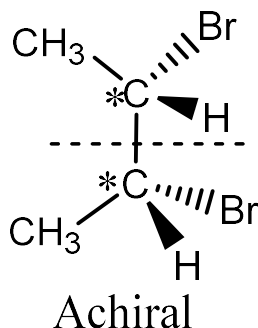
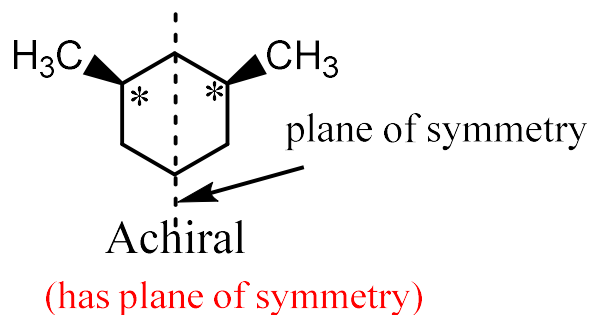
a molecule that has no chiral center is **achiral**

a molecule with more than one chiral center may or may not be chiral. In this case we use the second test for chirality

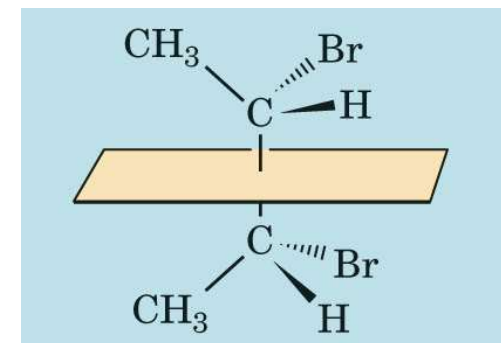
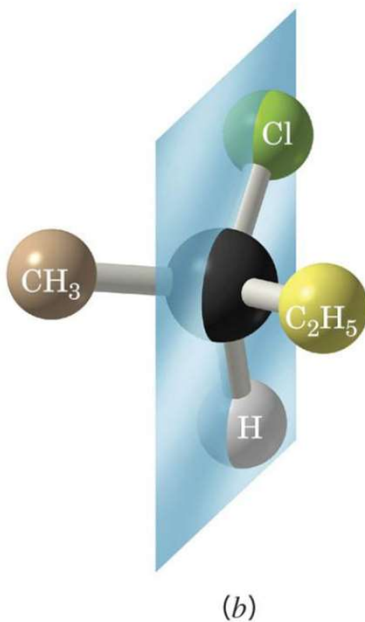
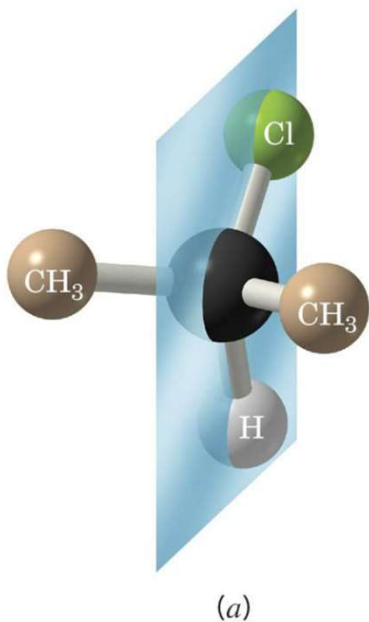


2. All molecules with **planes of symmetry** are **achiral**

(A plane of symmetry divides an entire molecule into two pieces that one half of the molecule is the mirror image of the other half)



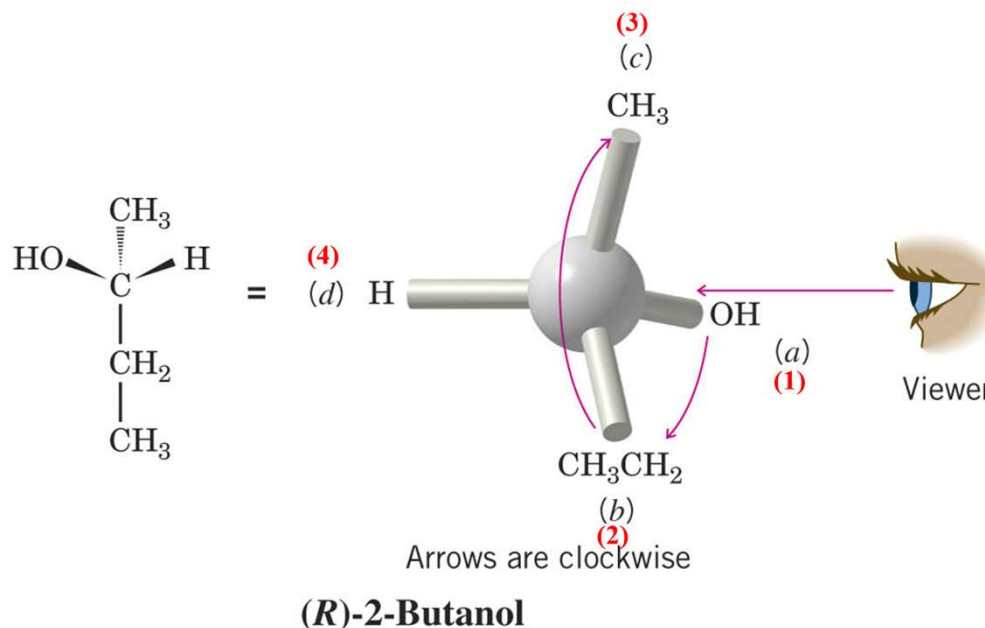
2-chloropropane vs. 2-chlorobutane

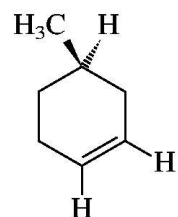
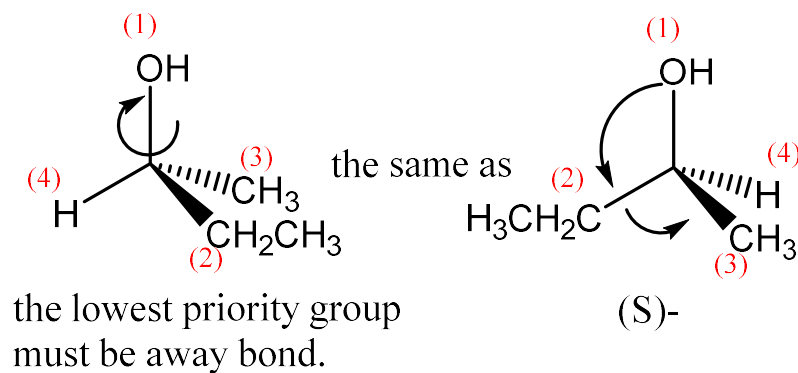
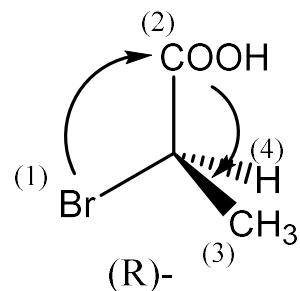
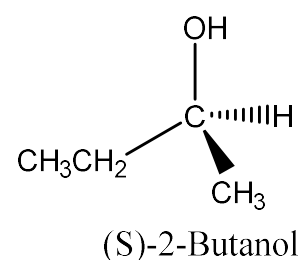
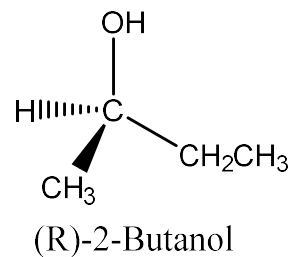
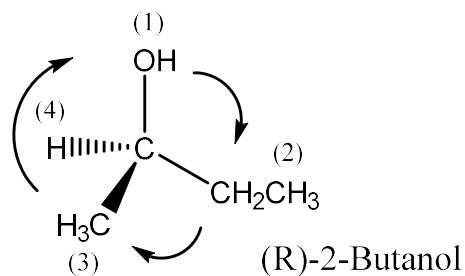


Nomenclature of Chiral Compounds (R-S Notation System)

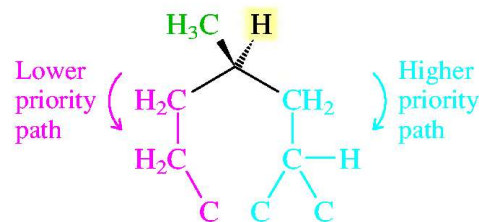
(Cahn-Ingold-Prelog system)

- The four groups attached to the stereogenic carbon are assigned priorities from highest (1) to lowest (4)
- Atoms directly attached to the stereogenic center are compared. Priorities are assigned as follows
 - Atoms with higher atomic number are given **higher priority (1)**
 - Align the lowest priority group (4) behind the chiral carbon.
 - The molecule is rotated to put the lowest priority group back
 - if the direction of 1→2→3 is **clockwise**, the enantiomer is **R**
 - if 1→2→3 is **counterclockwise**, the enantiomer is **S**
 - If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined

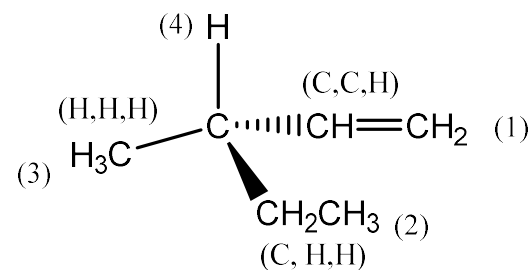
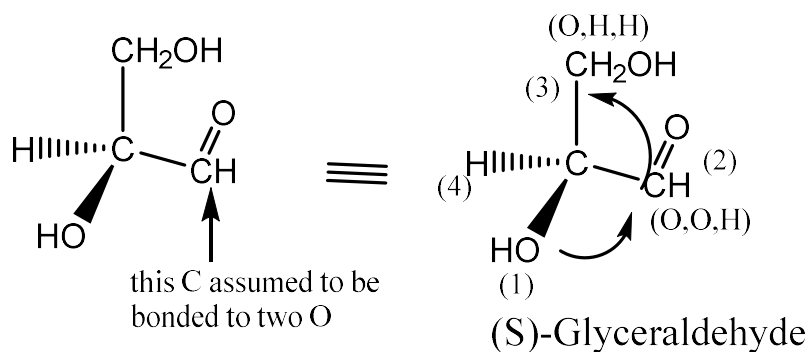




is treated as



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



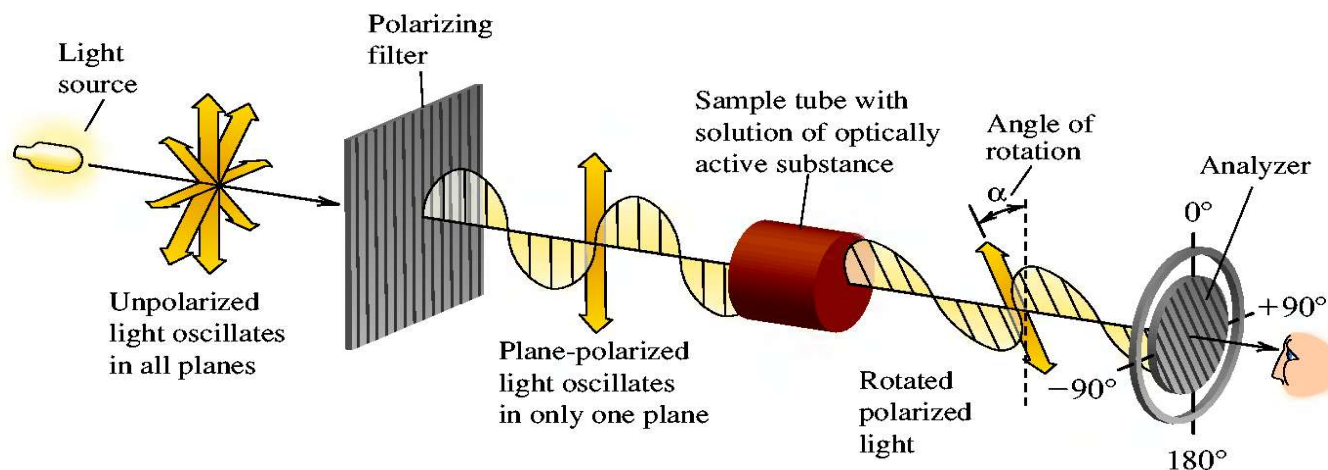
Properties of Enantiomers

- Enantiomers have almost all identical physical properties (melting point, boiling point, density)

Physical Properties	(R)-2-Butanol	(S)-2-Butanol
Boiling point	99.5 °C	99.5 °C
Density(g/mL)	0.808	0.808
Refractive index	1.397	1.397

- Enantiomers rotate the plane of plane-polarized light in equal but opposite directions (Optical Activity)

Optical activity is the ability of a chiral substance to rotate the plane of plane-polarized light and is measured using an instrument called a **polarimeter**.



- Chiral compounds rotate the plane of plane-polarized light. Rotation measured in degrees

clockwise (dextrorotatory) = +

counterclockwise (levorotatory) = -

Specific Rotation $[\alpha]$: standard amount of optical rotation by 1 g/mL of compound in a standard 1

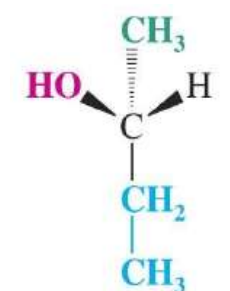
$$[\alpha] = \frac{\alpha}{c \cdot l}$$

where $[\alpha]$ = the specific rotation

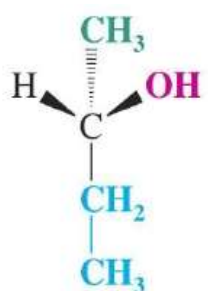
α = the observed rotation

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)

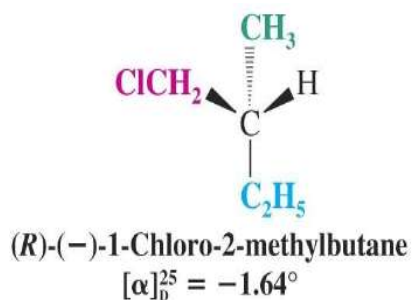


(*R*)-2-Butanol
 $[\alpha]_D^{25} = -13.52^\circ$

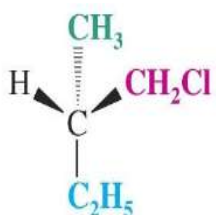


(*S*)-2-Butanol
 $[\alpha]_D^{25} = +13.52^\circ$

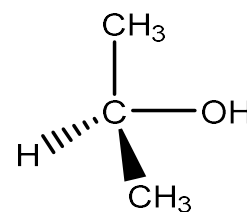
- There is no straightforward correlation between the *R*, *S* designation of an enantiomer and the direction [(+) or (-)] in which it rotates plane polarized light



(*R*)-(-)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = -1.64^\circ$



(*S*)-(+)-1-Chloro-2-methylbutane
 $[\alpha]_D^{25} = +1.64^\circ$

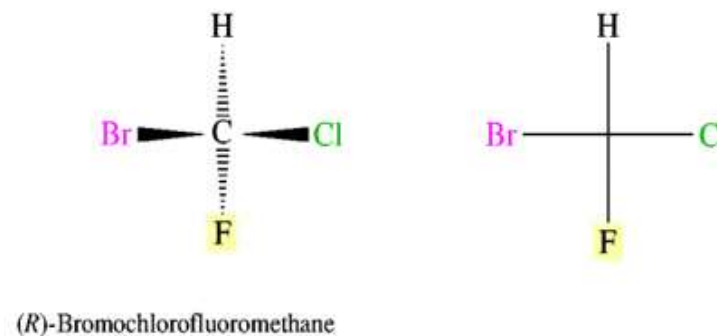
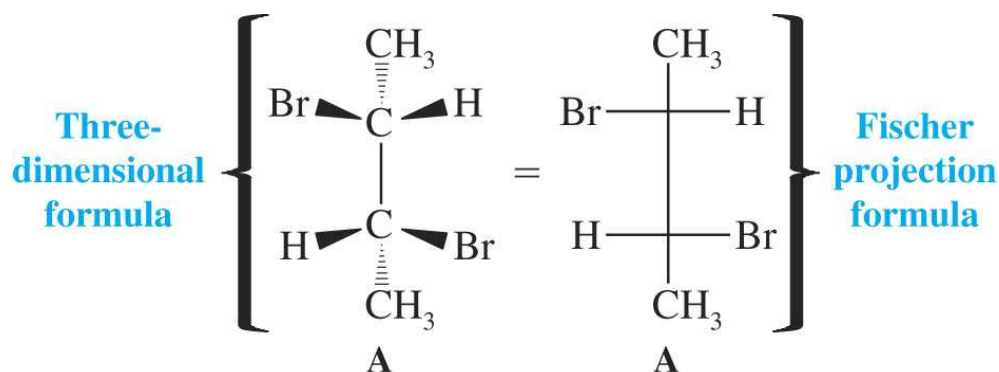


$[\alpha] = 0$
 Achiral

Fischer Projections

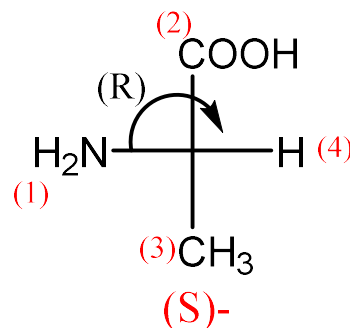
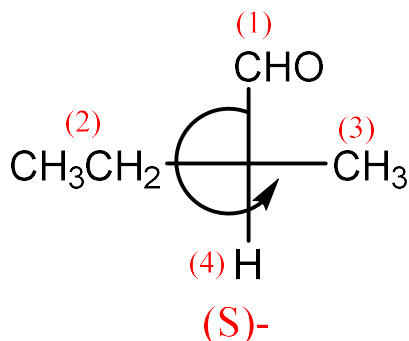
It is a 2-dimensional representation of chiral molecules.

- 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

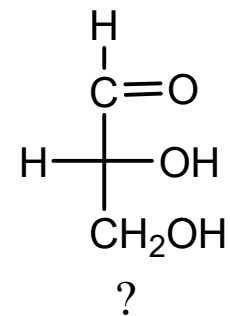
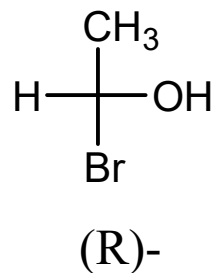
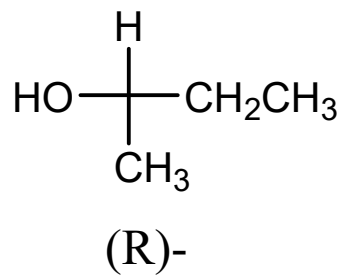
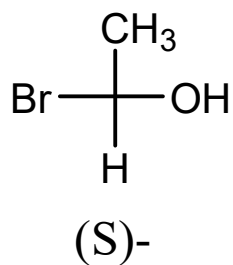


R/S in Fischer

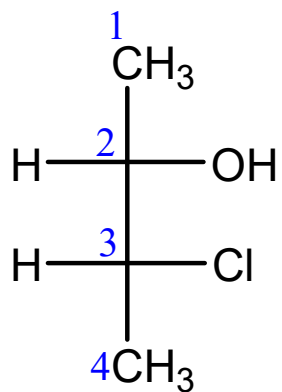
- When the lowest priority is on the top or bottom, we can assign R/S directly as the usual R/S rule.
- When the lowest priority is on horizontal line, we can assign R/S by taking the opposite direction of R/S rule.



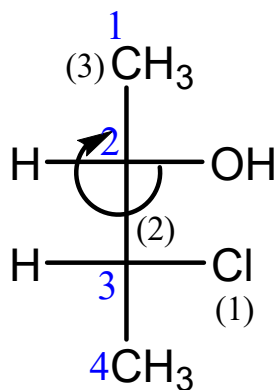
the lowest priority H is on horizontal



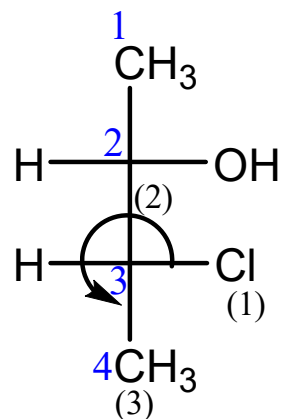
Assigning R/S for molecules with more than one chiral center.



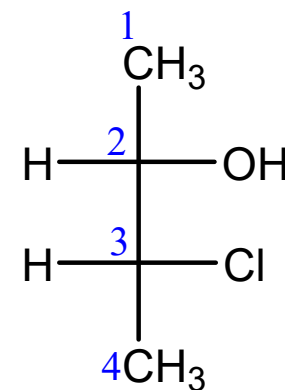
has two chiral centers
at C2 and C3



The configuration of
Carbon-2 is 2S



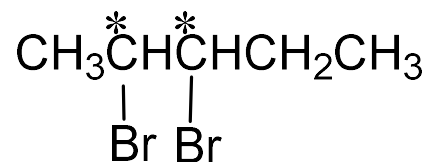
The configuration of
Carbon-3 is 3R



(2S, 3R)

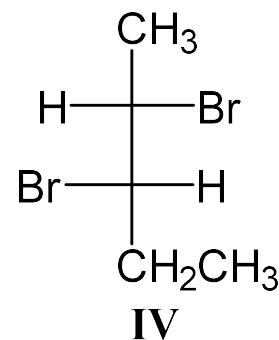
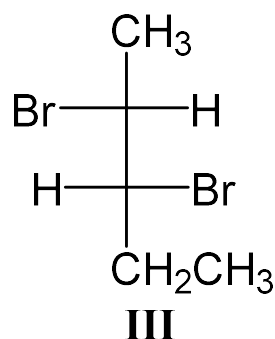
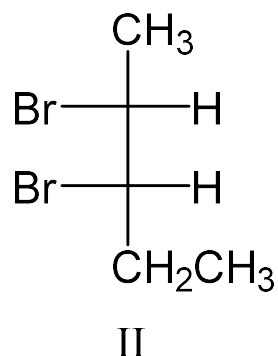
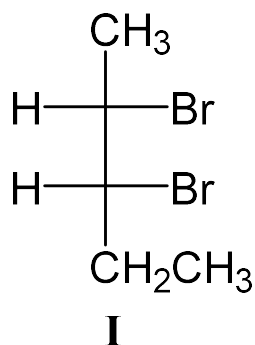
Multiple Stereogenic Centers: Diastereomers

- Molecules with More than One Stereogenic Center



Four stereoisomers possible.

2,3-dibromopentane



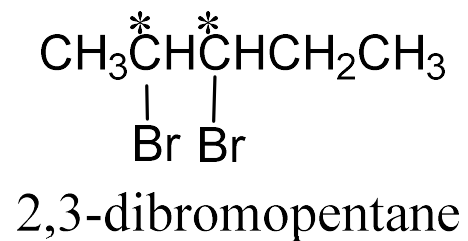
- Stereoisomers I and II are enantiomers.
- Stereoisomers III and IV are enantiomers

What is the relation between I and III?

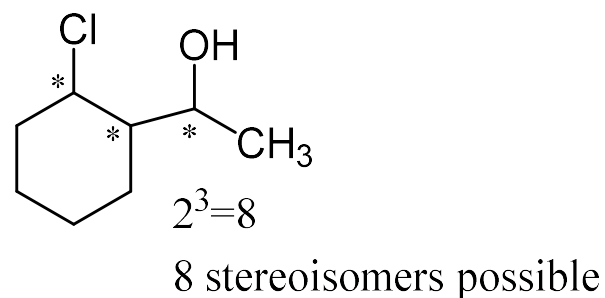
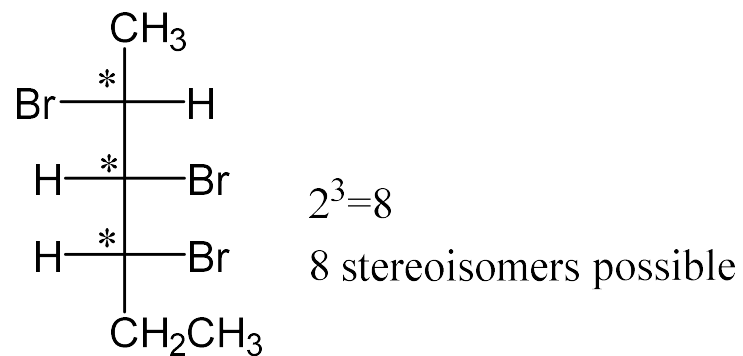
Diastereomers are stereoisomers which are not mirror image of each other.

- I and III are diastereomers.
- I and IV are diastereomers.

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



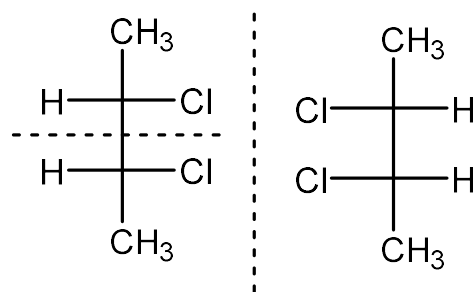
$$n=2$$
$$2^2 = 4 \text{ stereoisomers}$$



Meso Compounds

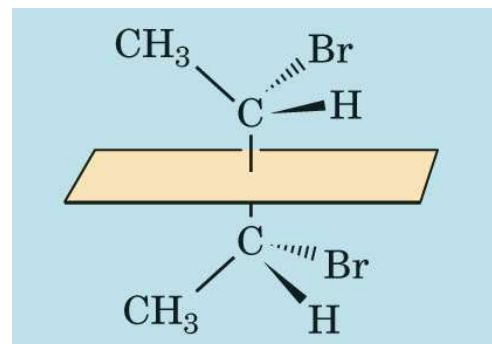
- Compounds with chiral centers but which are not chiral.

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

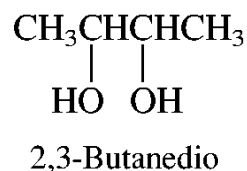


(2R,3S)-2,3-dibromobutane (same as its mirror image)

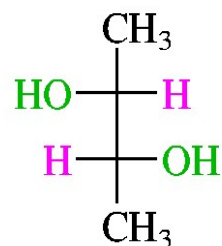
Meso compound



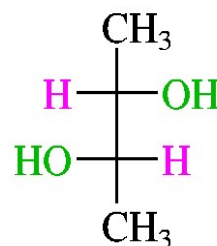
Sometimes molecules with 2 or more stereogenic centers will have less than the maximum amount of stereoisomers



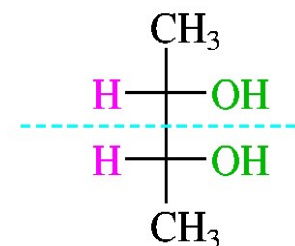
Only three, not four, stereoisomeric 2,3-butanediols are possible.



(2R,3R)-2,3-Butanediol

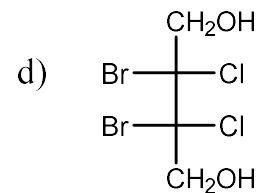
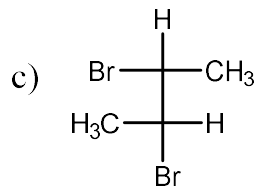
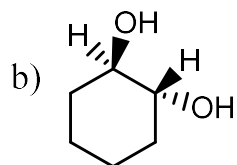
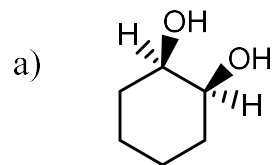


(2S,3S)-2,3-Butanediol



meso-2,3-Butanediol

Which of the following structure represent a meso compound?



Which of the following has a meso form?

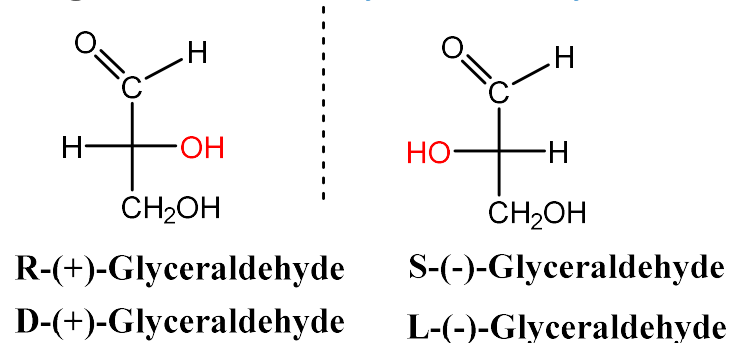
a) 2,3-dibromobutane

c) 2,4-dibromopentane

b) 2,3-dibromopentane

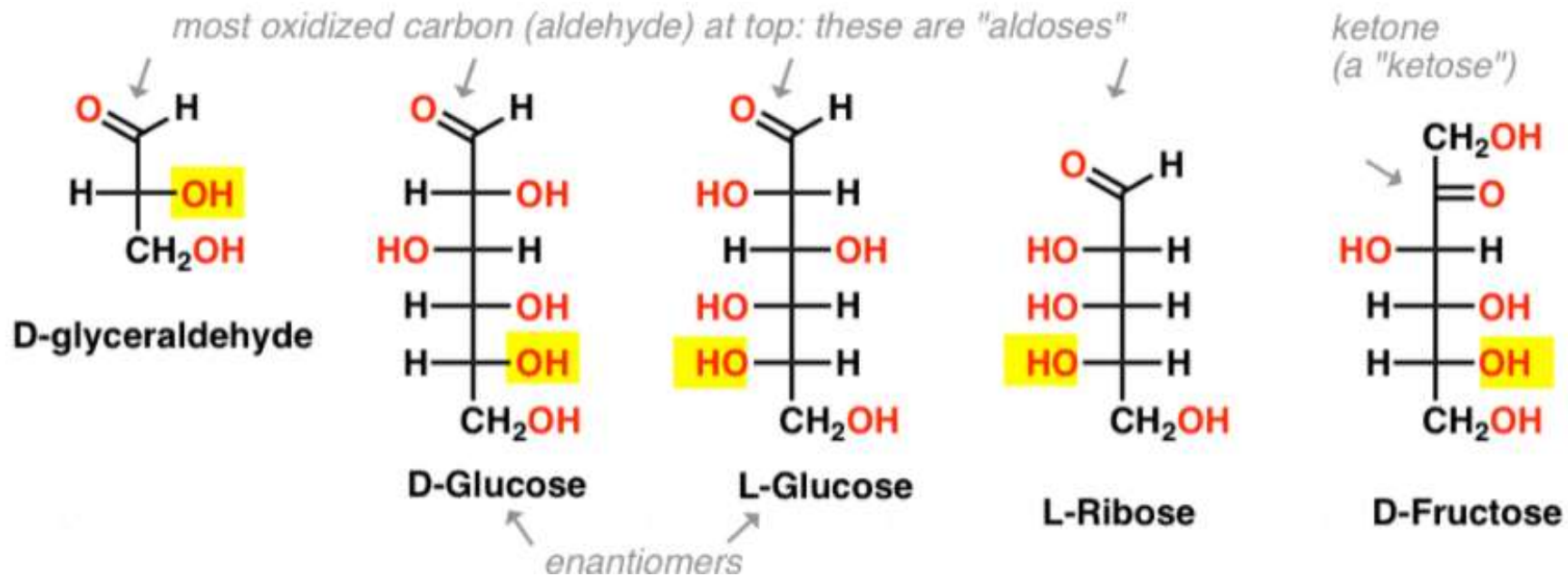
The D,L-system

- Sugars commonly follow the D, L system of nomenclature.
- Based on the configuration of **Glyceraldehyde**.



For a sugar drawn in the Fischer projection with the most oxidized carbon at the top:

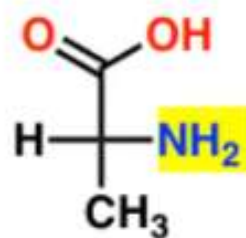
- If the OH on the bottom chiral center points to the **right**, the sugar is **D**
- If the OH on the bottom chiral center points to the **left**, the sugar is **L**



The D- L- system can also be applied to other chiral molecules, e.g. amino acids:

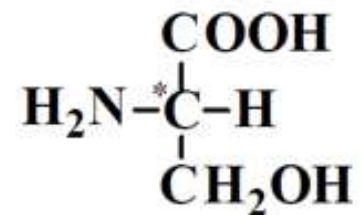


L-alanine



D-alanine

enantiomers



L-(-)-Serine

(S)-(-)-Serine

Racemic mixture

- an equimolar mixture of two enantiomers
(±)-2-butanol

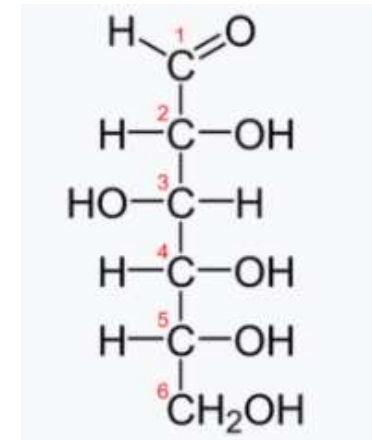
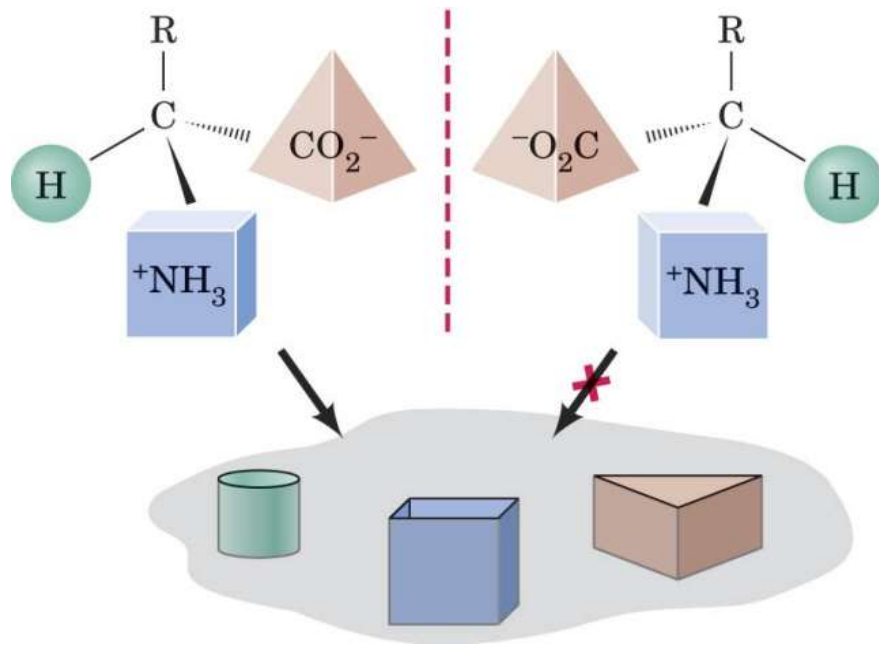
The Biological importance of Chirality

- Most of the molecules that make up plants and animals are chiral.

Amino acids and natural sugars are chiral

- Chiral molecules affect the human body in different way.

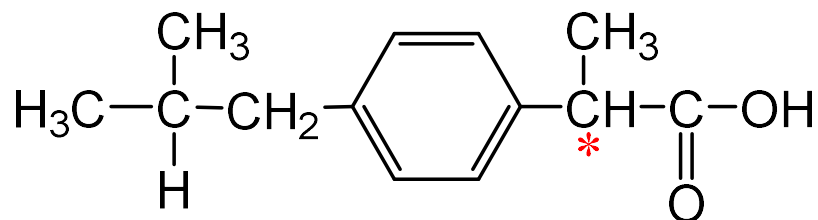
The binding specificity of a chiral receptor site for a chiral molecule is usually only favorable in one way



D-Glucose

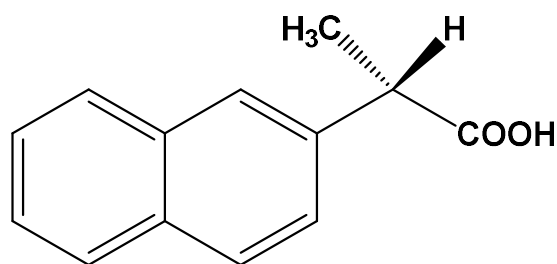
Only D-glucose found in nature and digestible.

Chiral drugs



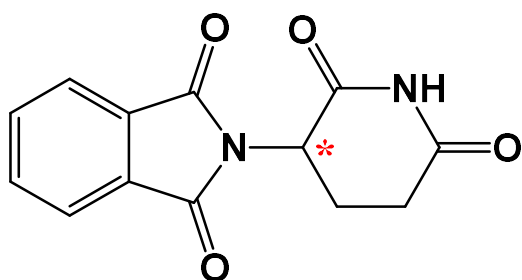
Ibuprofen

Generally the (±)-ibuprofene racemate is used, but only (S)-enantiomer has the anti-inflammatory action



(S)-Naproxen

an anti-inflammatory drug



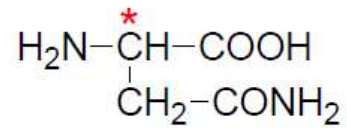
Thalidomide

The racemic mixture was used as antinausea drug for pregnant women in Europe (1959-1962).

(R)-thalidomide has antinausea effect.

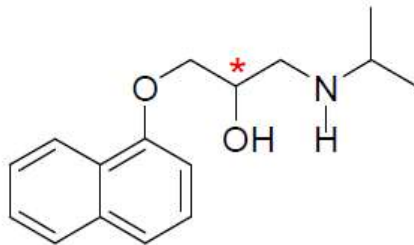
(S)-thalidomide has different biological activity and was shown to be responsible for over 2000 cases of birth defect in children born to women who took it while pregnancy.

Absolute configuration vs. biological activity



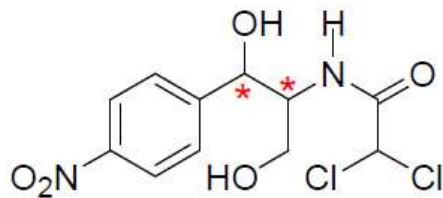
Asparagine

R- sweet
S- bitter



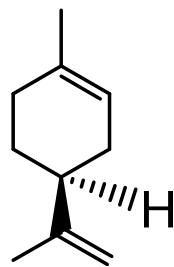
Propranolol

R- contraceptive
S- antihypertensive

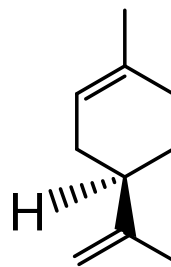


Chloramfenikol

R,R- antibiotic
S,S- inactive



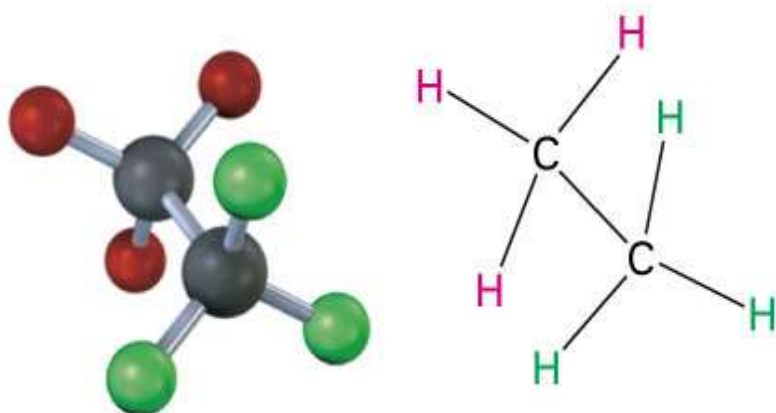
(*S*)-Limonene
(Lemon odor)



(*R*)-Limonene
(Orange odor)

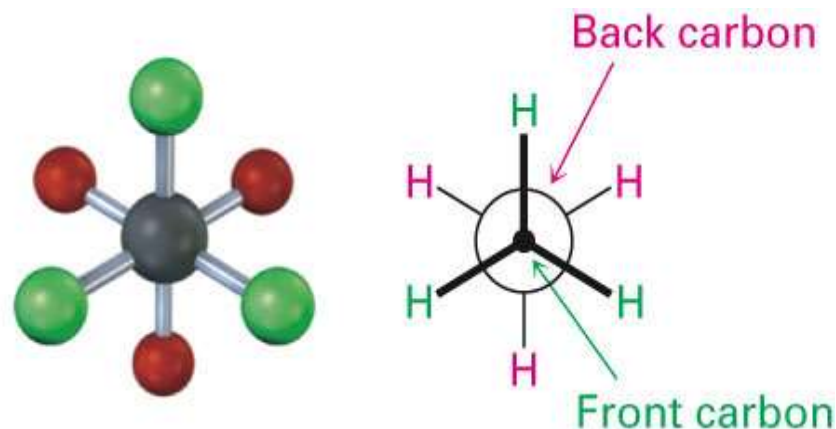
Conformational Isomerism

- **Conformations:** the **temporary molecular shapes** that result from **rotations of groups** about **single bonds**; structures related by bond rotations.
- **Conformational analysis:** the analysis of the **energy changes** that a molecule undergoes as **groups** rotate about **single bonds**.



**Sawhorse
representation**

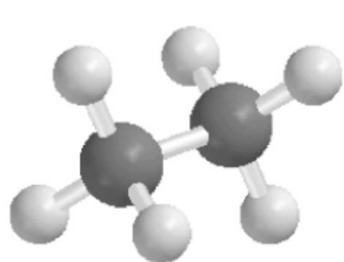
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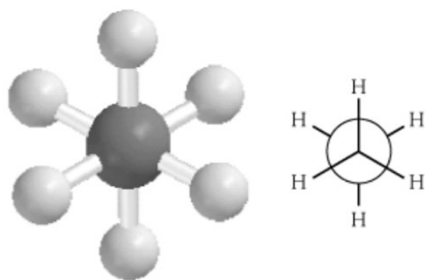
**Newman
projection**

Conformation of Ethane

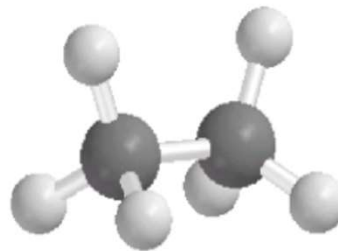
- Staggered and eclipsed.



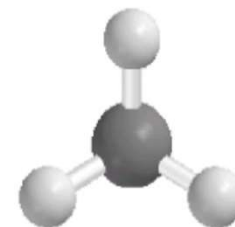
(a)



(b)



(a)



(b)

Staggered conformation

All the 6 C-H bonds are as far away as possible

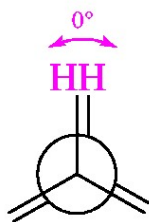
⇒ **most stable** conformation

Eclipsed conformation

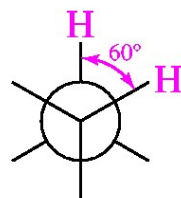
All the 6 C-H bonds are as close as possible to each other.

Repulsions between bonds on adjacent atoms destabilize the eclipsed conformation

Conformations in which the torsion angles between adjacent bonds are other than 60° are said to have **torsional strain**

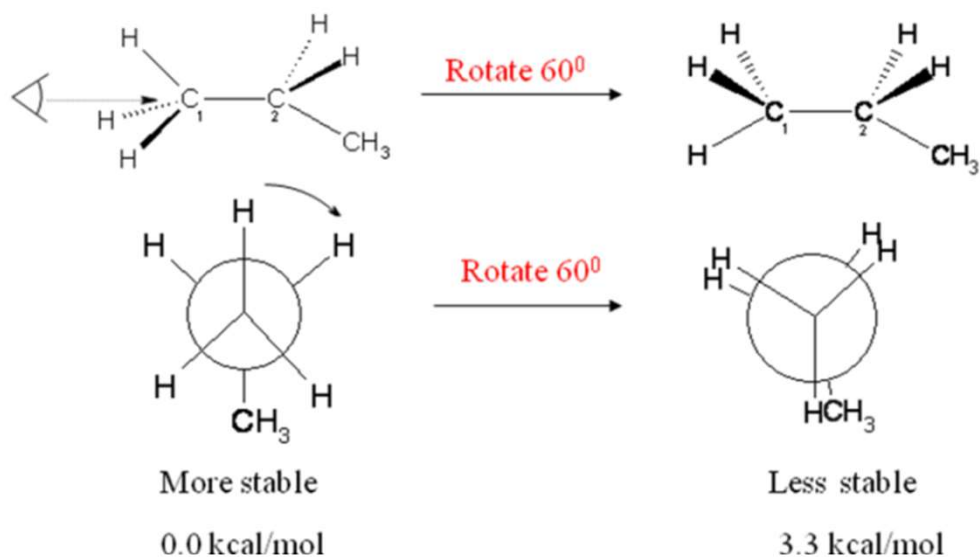


Torsion angle = 0°
Eclipsed

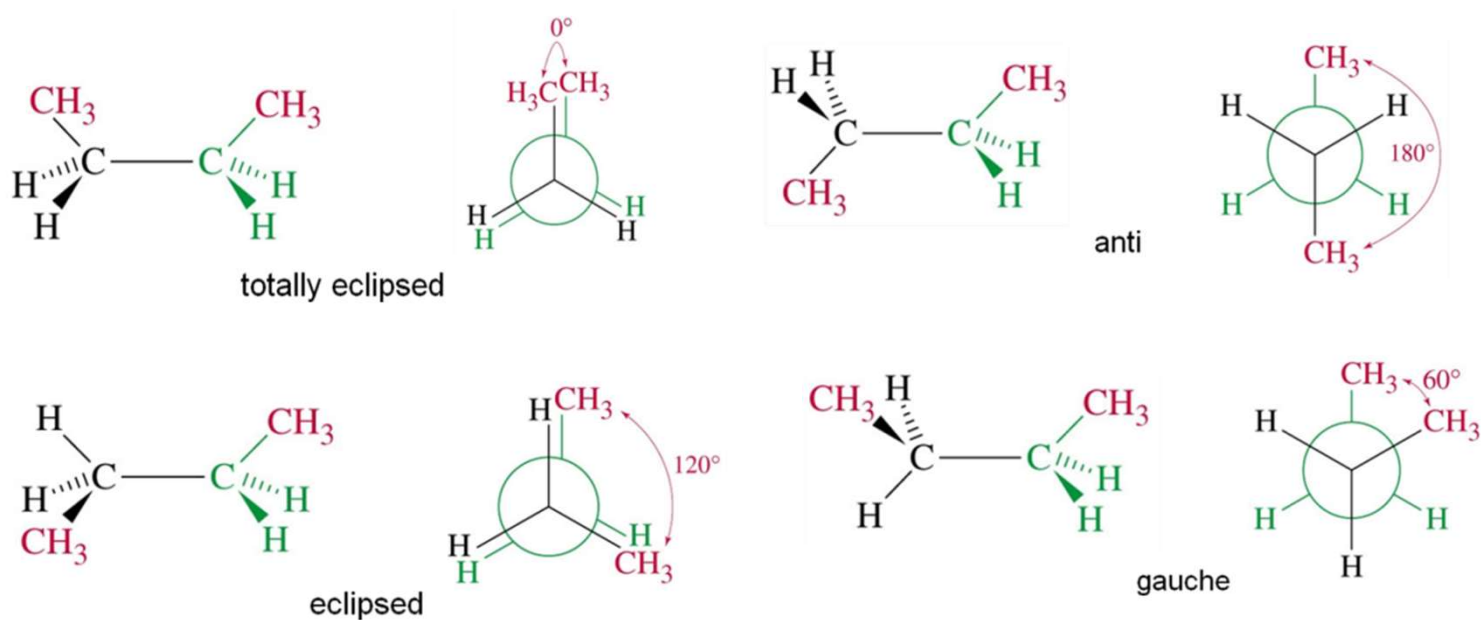


Torsion angle = 60°
Gauche

Conformations of Propane



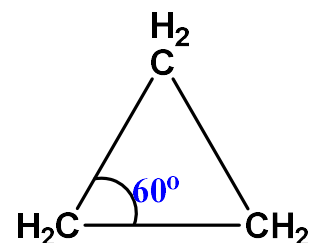
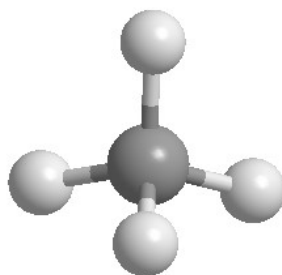
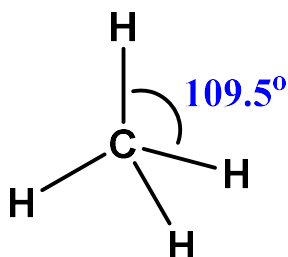
Conformations of Butane



Anti conformation is the most stable conformation of butane.

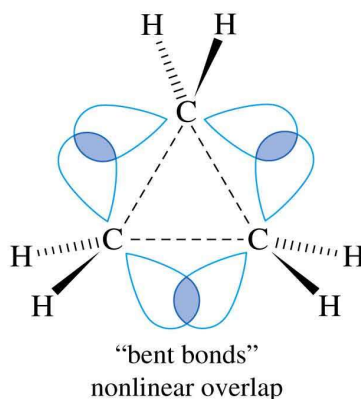
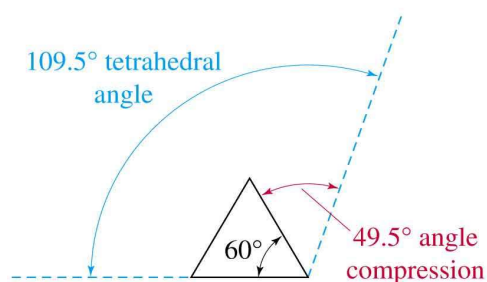
Conformations and Stabilities of Cycloalkanes

Angle Strain: the strain in a molecule due to its bond angles deviate from 109.5°



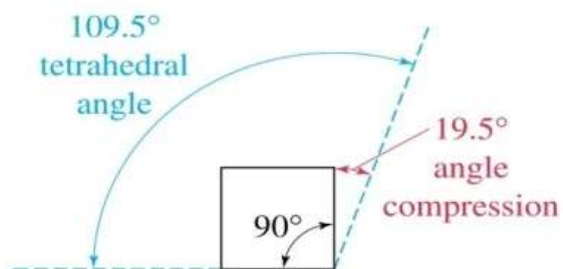
Ring Strain – total strain (sum of torsional, steric and angle strain) in a cycloalkane compared to an open, noncyclic reference compound.

Cyclopropane



- Large ring strain due to angle compression
- Very reactive, weak bonds

Cyclobutane

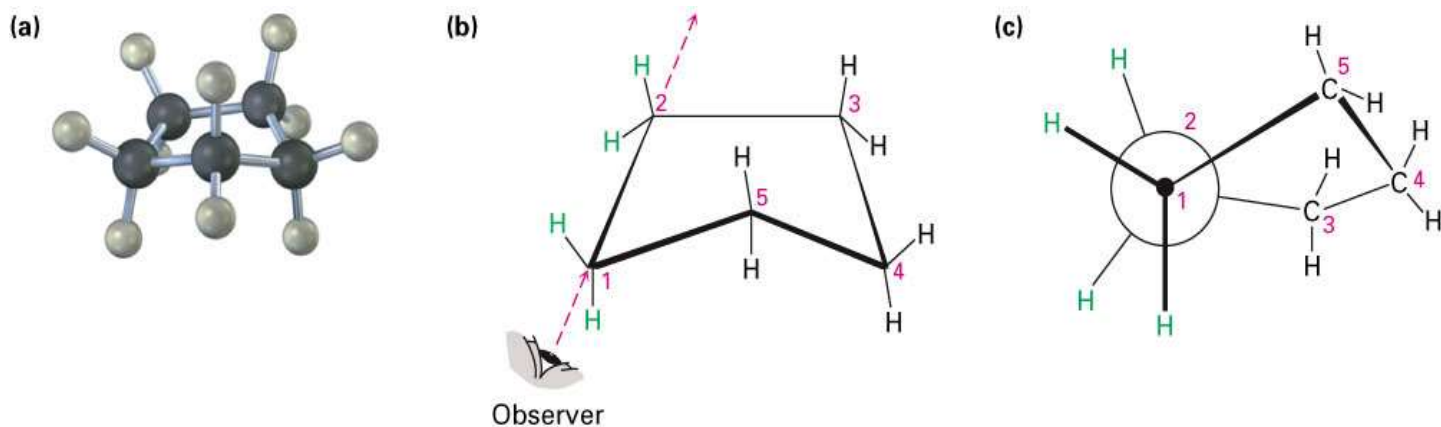


Angle strain due to compression

Torsional strain partially relieved by ring-puckering

Unstable molecule

Cyclopentane



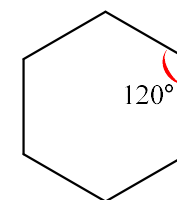
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Angle strain is relatively small because the 108° angles of a regular pentagon are not much different from the normal 109.5° bond angles of sp^3 -hybridized carbon.

- Small angle strain.
- Stable molecule

Cyclohexane

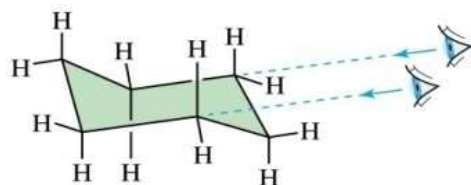
- The bond angles is 109.5° and all hydrogens are staggered.
- No angle strain and no torsional strain.
- Two conformations: **Chair** and **boat**



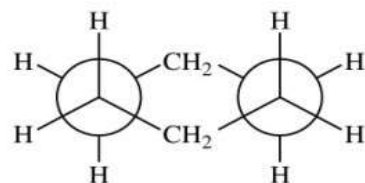
Regular hexagon



chair conformation



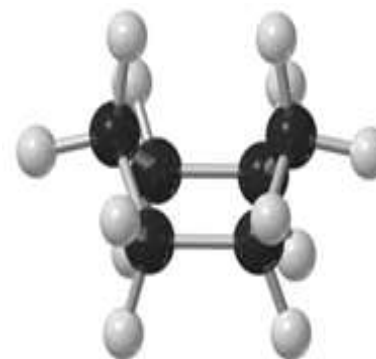
viewed along the "seat" bonds



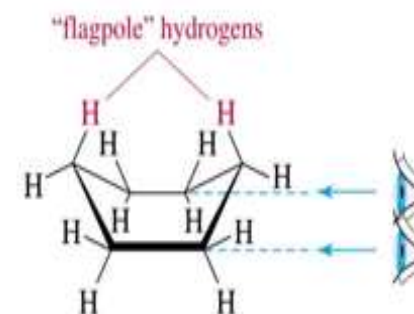
Newman projection

Chair Conformer

- C—C bond angles are all 109.5°
- free of angle strain.
- free of torsional strain



boat conformation



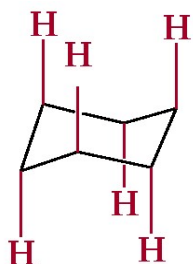
symmetrical boat

Boat Conformer

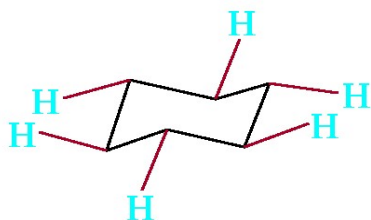
- free of angle strain.
- C—C bond angles are all 109.5°
- has torsional strain and **flagpole interaction**

Chair conformer is the most stable form of cyclohexane

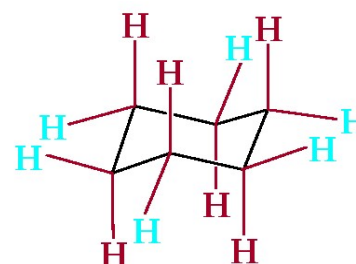
- **Axial hydrogens** - have their bonds parallel to a vertical axis that passes through the ring's center.
Directed up and down on adjacent carbons.
- **Equatorial hydrogens**-located approximately along the equator of the molecule.



Axial C—H bonds

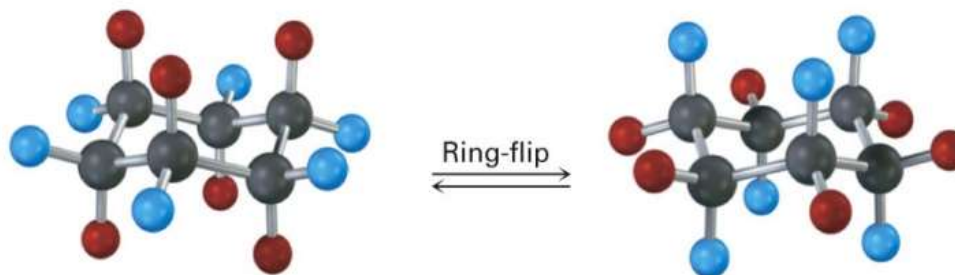


Equatorial C—H bonds

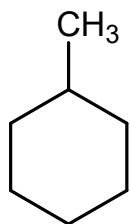


Axial and equatorial bonds together

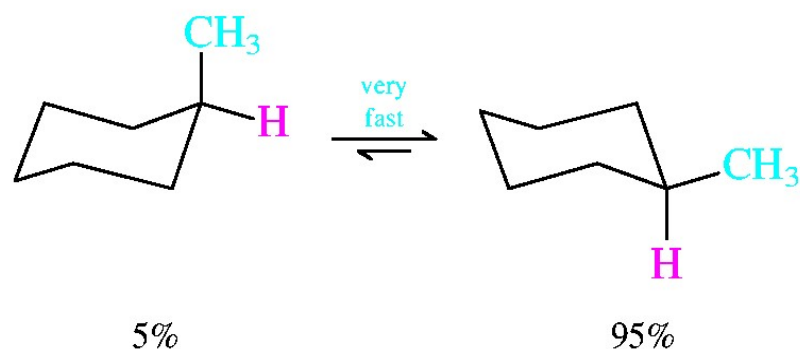
The axial and equatorial hydrogens are exchangeable by a process called “**ring flipping**”.



Monosubstituted Cyclohexanes

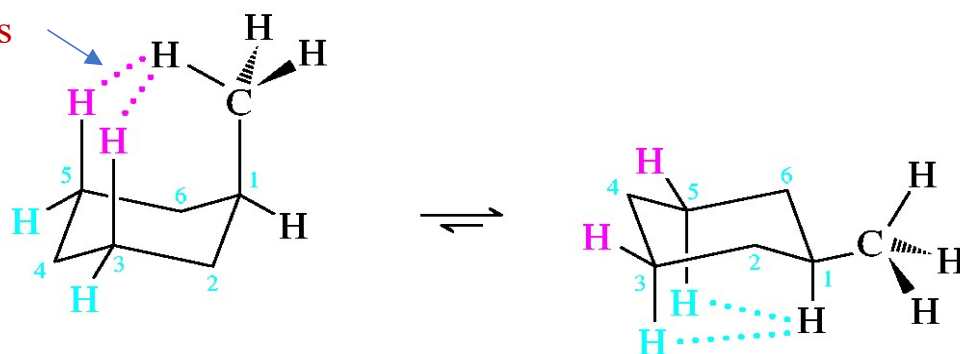


Methyl group prefer axial or equatorial position?



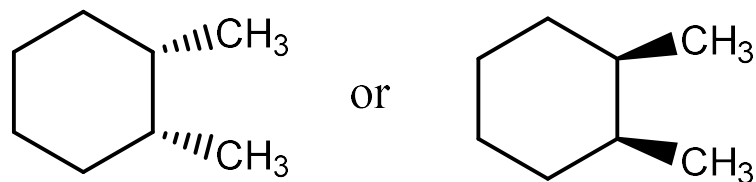
At room temperature approximately 95% of the molecules are in the chair conformation that has an **equatorial** methyl group

1,3-diaxial repulsions

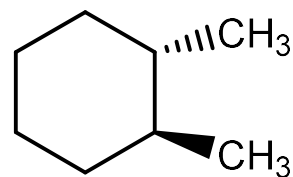


An axial substituent is crowded because of **1,3-diaxial repulsions**

Disubstituted Cyclohexanes

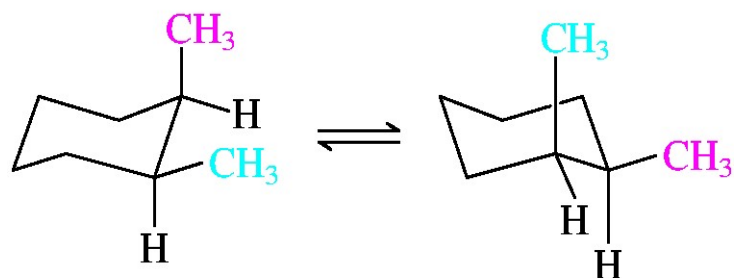


Cis-1,2 dimethylcyclohexane

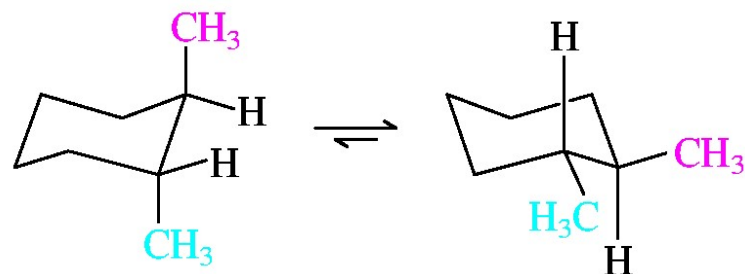


Trance-1,2 dimethylcyclohexane

The cis stereoisomer has two chair conformations of equal energy, each containing one axial and one equatorial methyl group.



cis-1,2-Dimethylcyclohexane



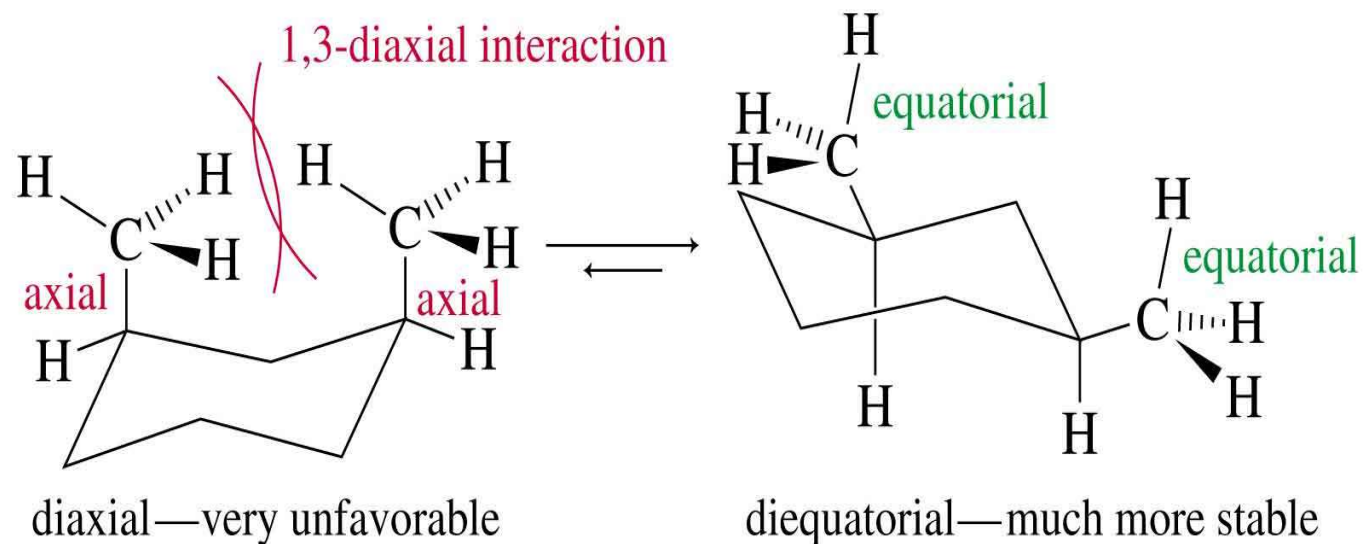
(Both methyl groups
are axial: less stable
chair conformation)

trans-1,2-Dimethylcyclohexane

(Both methyl groups are
equatorial: more stable
chair conformation)

Both methyl groups are equatorial in the most stable conformation of trans-1,2-dimethylcyclohexane.

Trans-1,3-Disubstituted cyclohexane with two **different alkyl groups**, the conformation of lower **energy** is the one having the **larger group** in the **equatorial** position



Name?

