Chapter III
Isomerism and Diastereoisomerism

I/ Isomerism

Isomers are compounds with the same molecular formula, but different structural formulas (different by the nature of the chemical bonds or by the arrangement of the atoms in space).

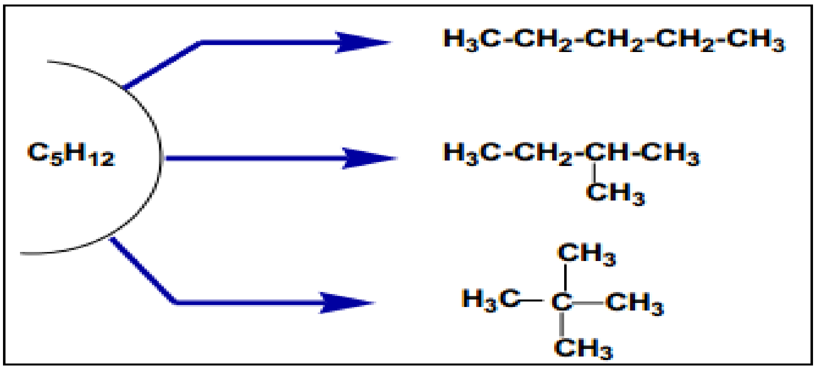
1. Planar isomer (constitutional or structural isomer)

Two planar isomers are two separable pure substances that have the same molecular formula but are distinguished by their planar structural formulas.

a. Chain isomers

Two chain isomers have the same molecular formula, but differ in the shape of the hydrocarbon chain.

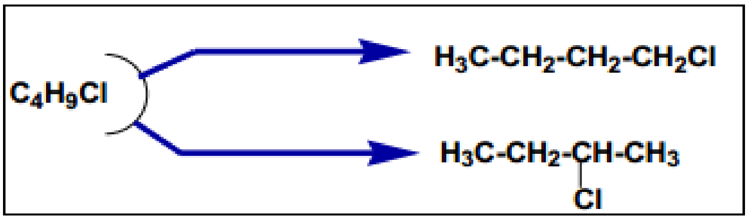
Example:



b. Position isomers

Two position isomers have the same molecular formula but differ in the position of a substituent on the hydrocarbon chain.

Example:



c. Functional isomers

Two functional isomers have the same molecular formula, but differ in their main functional group.

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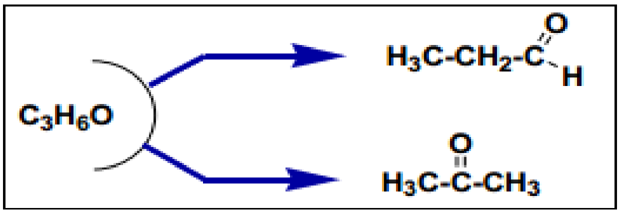
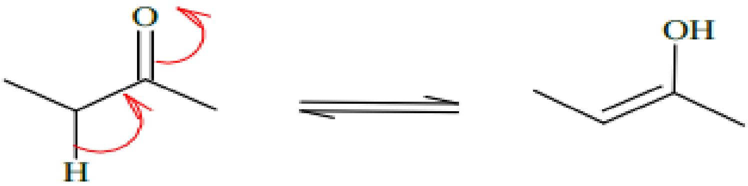


Tautomer

Tautomer is a form of functional isomer that occurs through the migration (movement) of a hydrogen atom to another atom. The two isomers obtained in this way are in equilibrium.

Example:

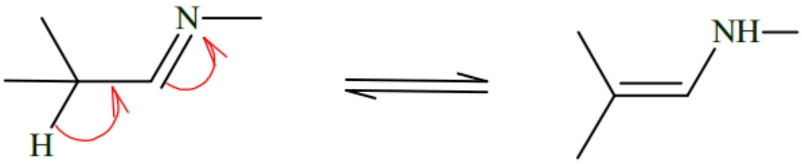
- **Keto-enol tautomer**



Keto form **Enol form**

- **Imino-enamine tautomer**

The imine form is often predominantly present.



Keto form **Enol form**

II/ Stereoisomerism

Stereoisomers differ only in the arrangement of atoms in space; they have the same planar structural formulas. Stereoisomerism encompasses two types of specific isomers. The following distinctions are made:

- **Conformational Stereoisomers:** Conformational stereoisomer occurs when a molecule changes its conformation by rotating around one or more single bonds. This change in conformation happens without breaking any bonds. The molecular structures that differ by their conformations are called conformers.

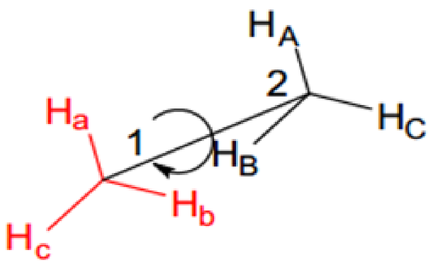
- **Configurational Stereoisomers:** Configurational stereoisomers of a given constitutional molecule are the complete set of arrangements of its atoms in space, without considering conformations.

1. Representation of Molecules in Space

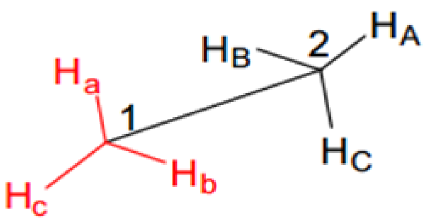
There are several ways to represent stereoisomers: perspective representation (cavalier), projective or Cram representation, Newman projection, and Fischer projection.

a. Perspective Representation (Cavalier)

The conformation of a molecule refers to the different arrangements of its substituents that result from free rotation around a C–C bond.

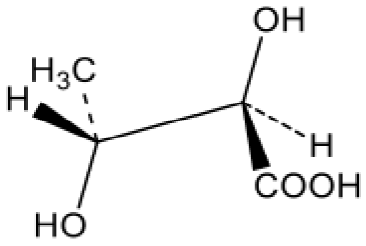


Eclipsed form

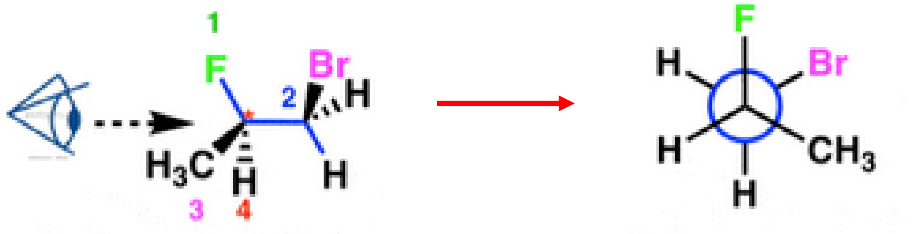


Staggered form

a. Perspective or Cram Representation

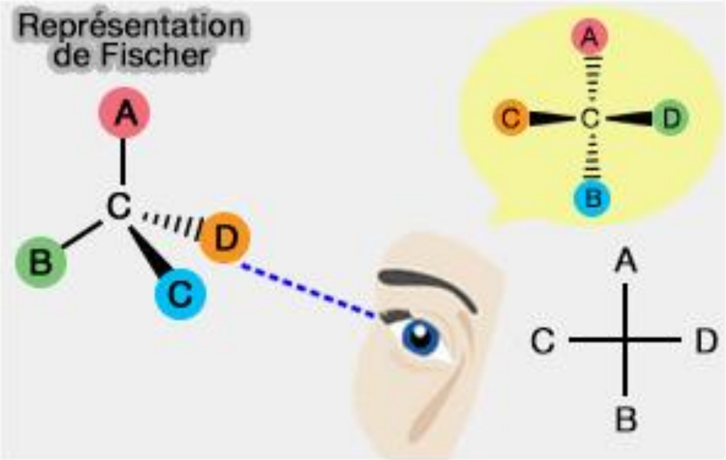


b. Newman Projection



c. Fischer Projection

This representation is commonly used with sugars and amino acids.



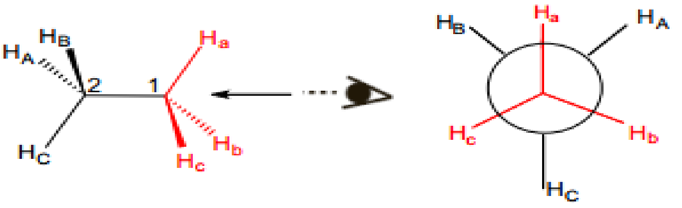
2. Conformational Isomers

a. Conformation of Ethane

Ethane is the simplest compound containing a single C-C bond. The rotation of one methyl group relative to the other results in an infinite number of arrangements, each corresponding to different conformations. Conformers (or rotational isomers) are stereoisomers connected by the rotation of a part of the molecule relative to the rest of the molecule around a bond as the axis of rotation, without breaking the bond.

Newman Projection: This representation involves viewing the molecule along the chosen C1-C2 axis and then projecting the atoms onto the plane of the paper.

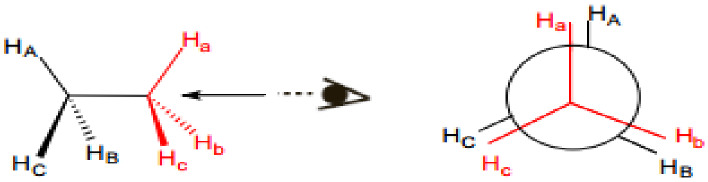
Eclipsed form



Cram

Newman

Staggered form



Cram

Newman

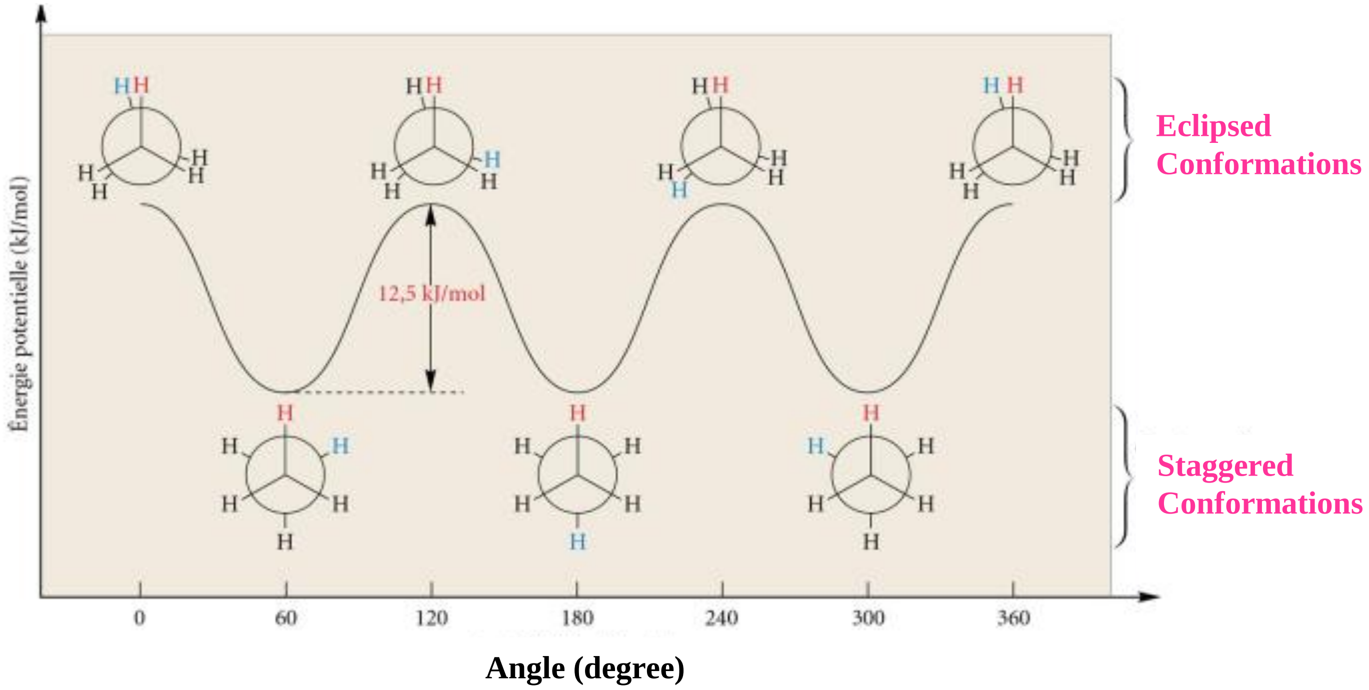
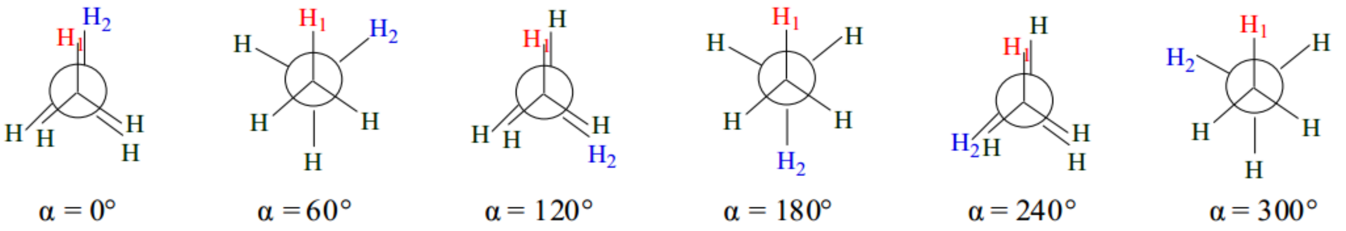


Figure 1: Potential energy diagram associated with the conformations of the ethane molecule.

The Newman projections in **Figure 1** represent the staggered and eclipsed conformations resulting from rotation in 60° increments around the bond.

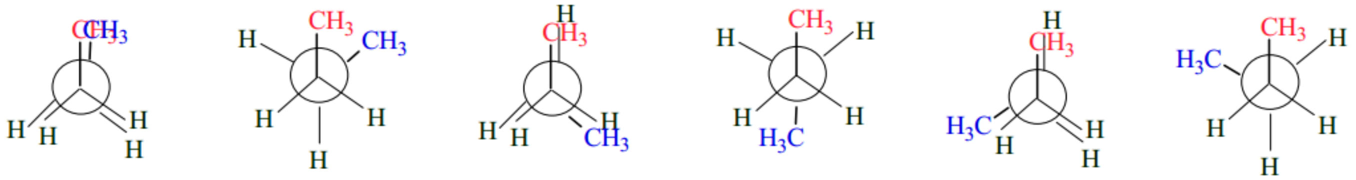


During the rotation of one methyl group relative to the other, the energy of the ethane molecule varies. This energy is minimized in the staggered conformations and maximized in the eclipsed conformations.

Therefore, the staggered conformation is the most stable and thus the most probable.

a. Conformation of Butane

The molecule is observed along the C2-C3 axis.



	α = 0°	α = 60°	α = 120°	α = 180°	α = 240°	α = 300°
Conformation	**Eclipsed**	**staggered**	**eclipsed**	**staggered**	**eclipsed**	**staggered**

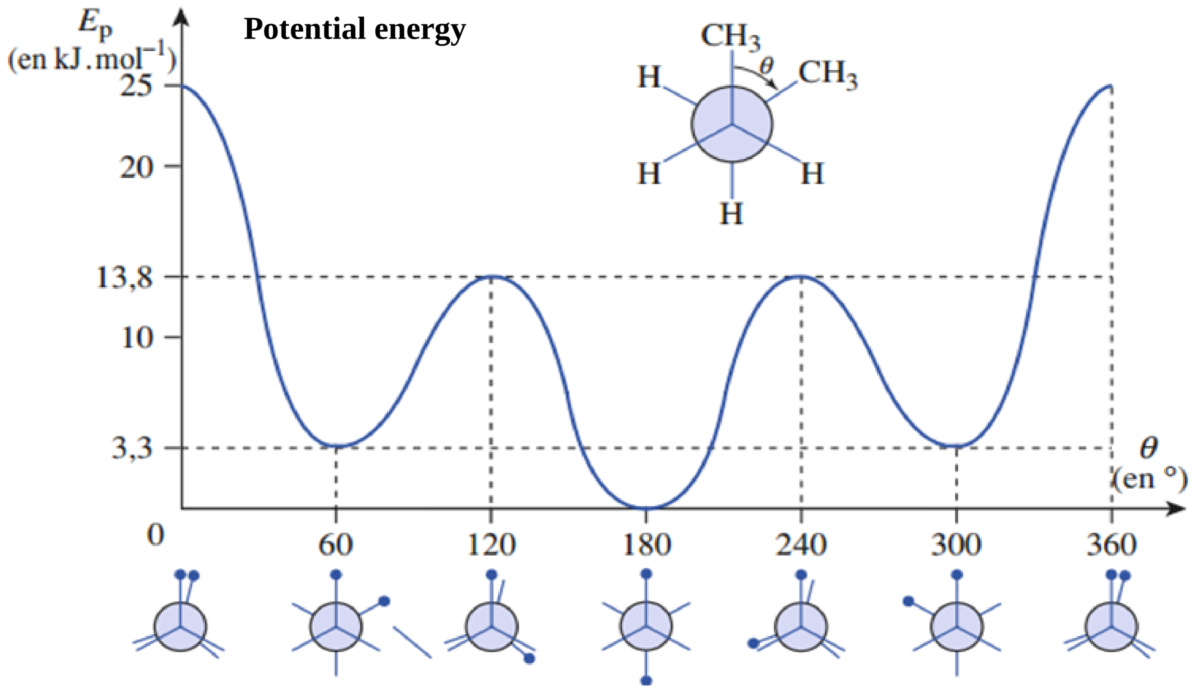


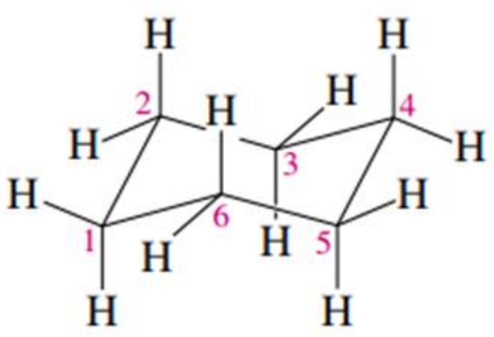
Figure 2: Potential energy diagram associated with the conformations of the butane molecule.

According to **Figure 2**, the energy difference between the maximum and minimum values constitutes what is known as the energy barrier. There is a dynamic equilibrium among all conformations due to thermal agitation. Staggered conformations are statistically the most abundant. However, the most stable conformations are the staggered ones. The conformation with the lowest energy is the most stable of all (***the anti conformation at α = 180° is the most stable*** because the two methyl groups -CH_3 are as far apart as possible).

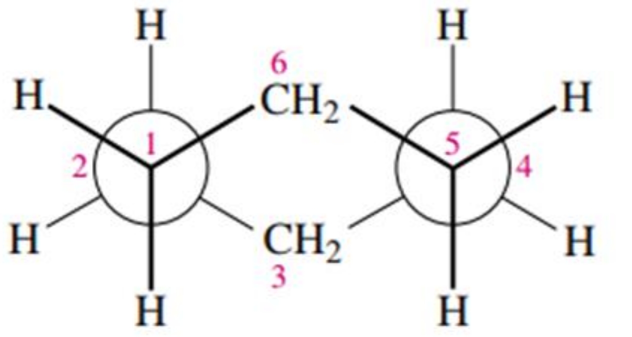
The conformation in which the two CH_3 groups are in an eclipsed position is the least stable. Eclipsed conformations have higher energy.

a. Conformation of cyclohexane

Six-membered rings are the most common in natural cyclic compounds because they can adopt a conformation known as the **chair conformer**.

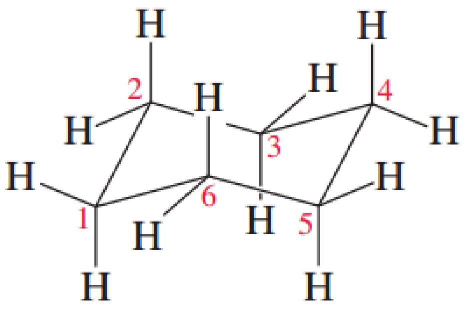


Chair Conformer of Cyclohexane

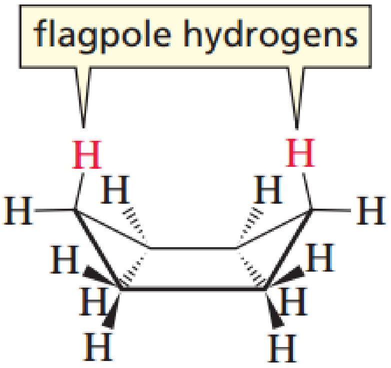


Newman Projection of the Chair Conformer

Cyclohexane exists in the **chair conformation** and the **boat conformation**

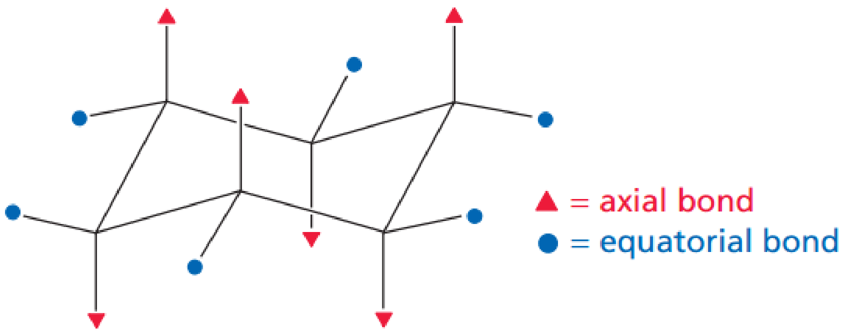


chair conformer of cyclohexane



boat conformer of cyclohexane

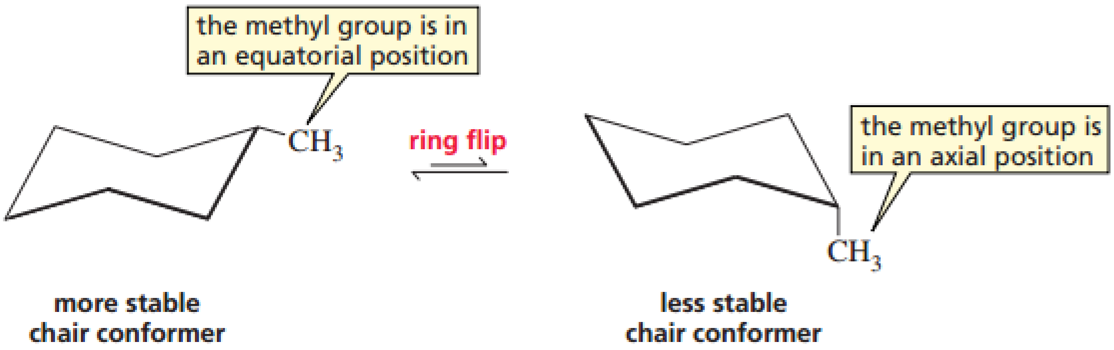
The **chair conformation** is much more stable than the **boat conformation**.



- Hydrogen in the ***axial*** position ***(a)***.
- Hydrogen in the ***equatorial*** position ***(e)***.

The presence of one or more substituents alters this equilibrium. When cyclohexane is substituted, the conformation that has maximum stability is the one where the substituents (or the largest ones) are in the equatorial position.

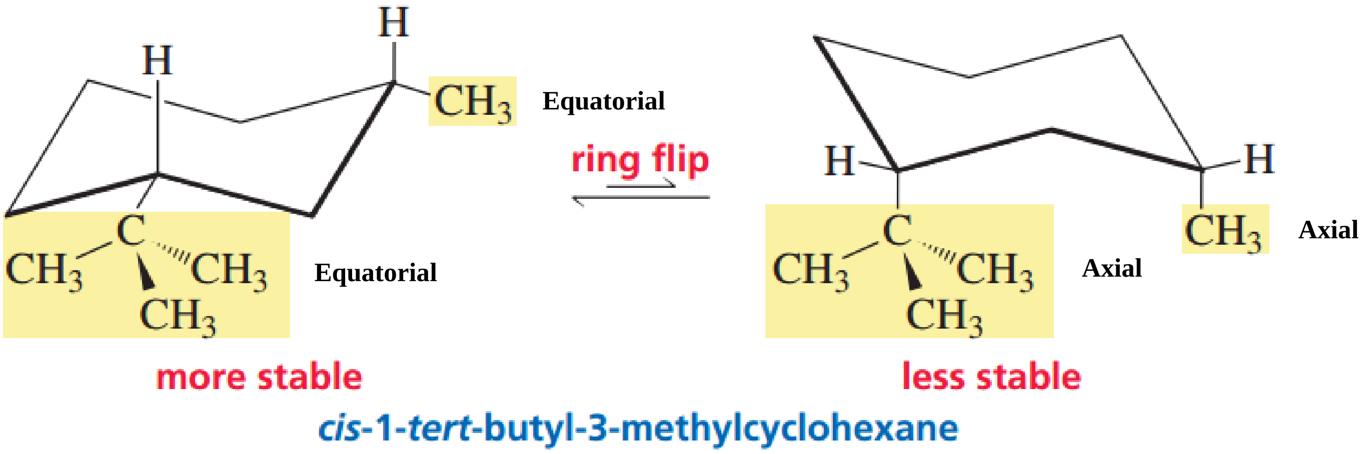
b. *Conformation of monosubstituted cyclohexane*



The most stable conformation of a monosubstituted cyclohexane is the chair conformation in which the substituent is ***in the equatorial position***.

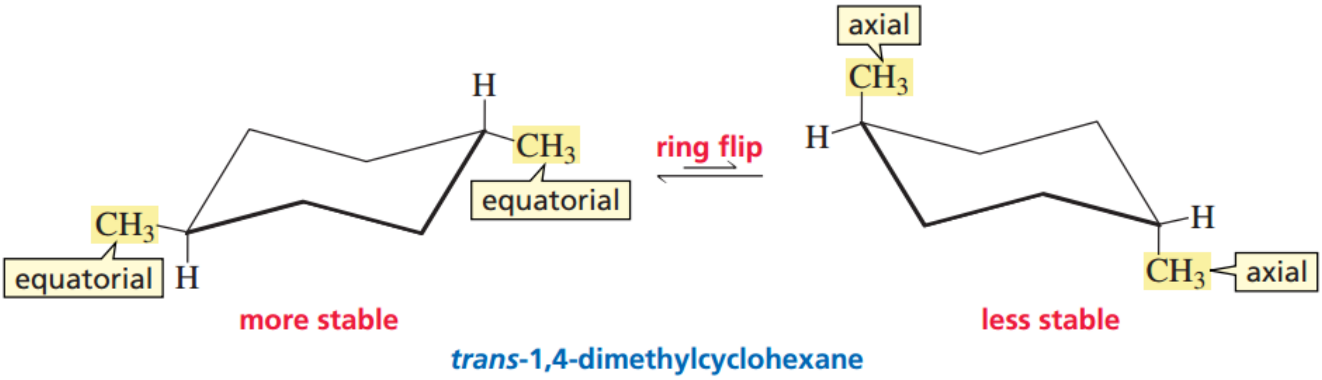
c. *Conformation of disubstituted cyclohexane*

- **The two conformers of cis-1-*tert*-butyl-3-methylcyclohexane**



Two substituents are in the axial position in one conformer and in the equatorial position in the other. The one on the left is therefore ***more stable***.

- **Two conformers of trans-1,4-dimethylcyclohexane**

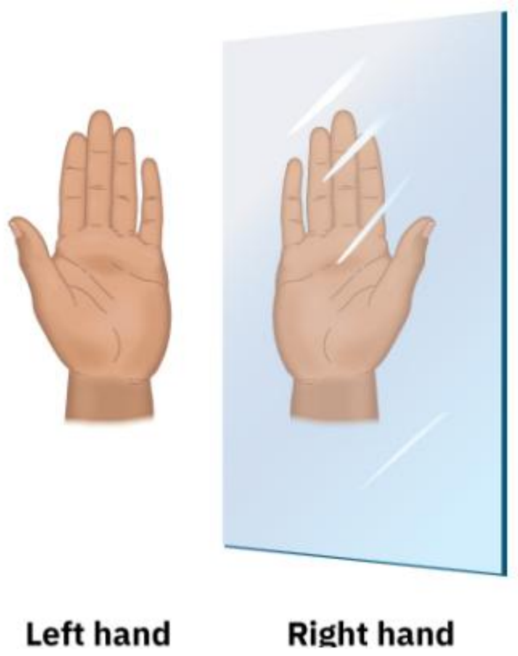


The two chair conformers of trans-1,4-dimethylcyclohexane do not have the same stability, as the two methyl groups occupy an equatorial position in one and an axial position in the other. The more stable conformer is the one on the left, which has both methyl groups in the equatorial position.

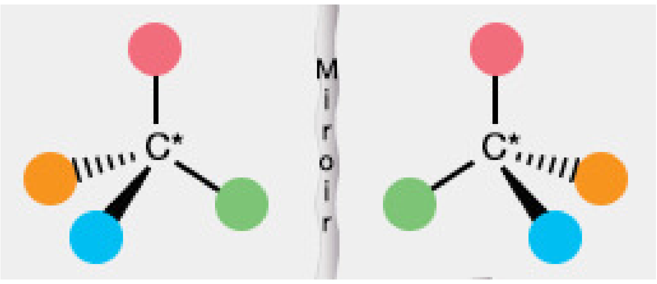
2. Optical Isomers (Configurational Isomers)

a. *Definition of Chirality*

A molecule is said to be chiral if it is not superimposable on its mirror image. A molecule containing an asymmetric carbon (C*) is chiral.

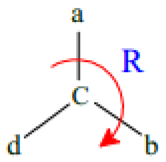


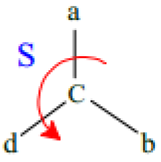
An asymmetric carbon is an sp^3-hybridized carbon bearing four different substituents. It is conventionally represented by C*.



b. *Absolue configuration (R/S)*

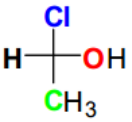
The absolute configuration indicates the arrangement of the different atoms or groups of atoms (substituents) around the asymmetric carbon. To determine the absolute configuration of an asymmetric carbon, one simply needs to apply the ***Cahn-Ingold-Prelog rules*** mentioned below:





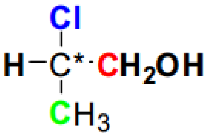
c. Cahn, Ingold et Prelog Sequential Rules

- ***The atom with the higher atomic number takes precedence over the one with the lower atomic number.***



Cl 〉O 〉C 〉H

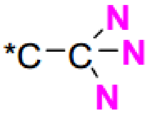
- ***If the atoms are identical, move to the next one and so on.***



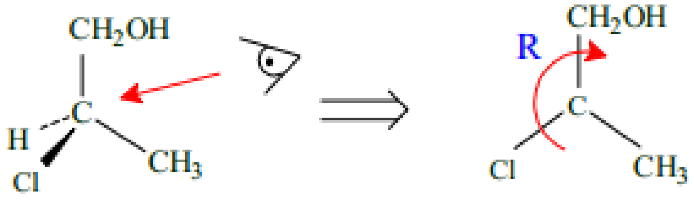
Cl〉 $-CH_2OH$〉-CH3〉H

- ***For identical atoms in double (or triple) bonds, they are considered to be bonded twice (or three times) to the same atom.***

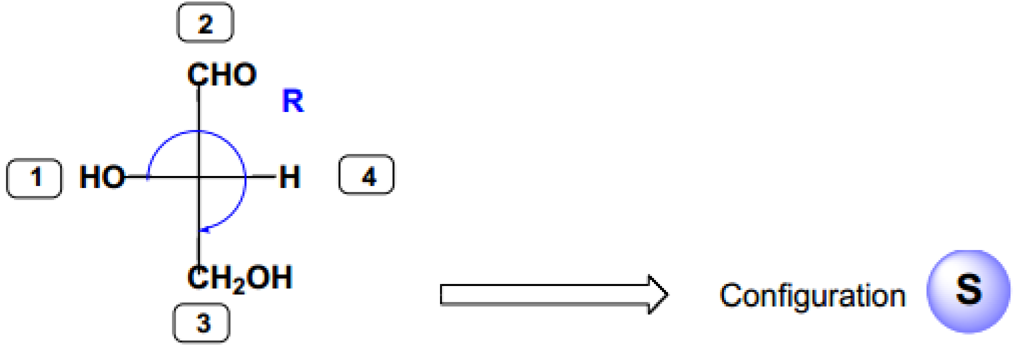
$^*C-C\equiv N$



Example:



- **Absolute configurations of molecules represented according to Fischer.**



d. Optical Activity

A property of chiral molecules is optical activity. This refers to the ability of a chiral molecule to rotate the plane of polarized light that passes through it either to the right (***dextrorotatory molecule***, ***positive optical rotation***) or to the left (***levorotatory molecule***, ***negative optical rotation***).

Biot's Law

To characterize an optically active substance, its specific rotation $[\alpha]_\lambda^t$ is defined. The value of the specific rotation is given by ***Biot's Law***:

$$[\alpha]_\lambda^t = \frac{\alpha}{l \times C}$$

α : Angle of rotation observed in degrees (°).

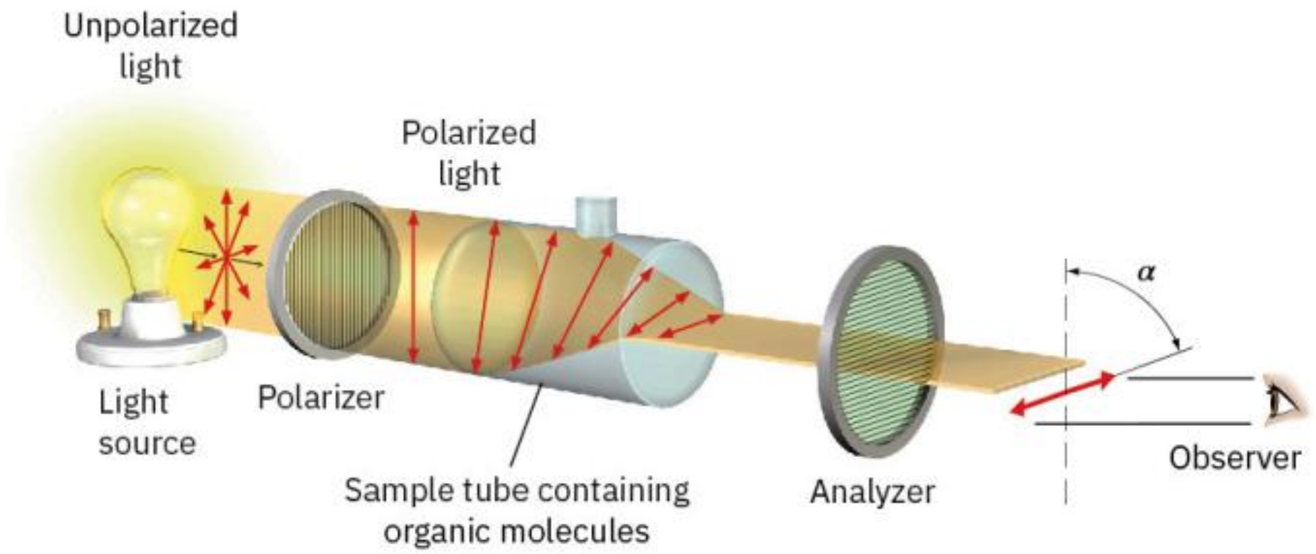
l : Length of the cell in dm.

c : Concentration of the substance in g per cm^3.

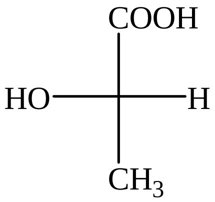
t : Temperature of the solution in °C.

λ : Wavelength of the polarized light.

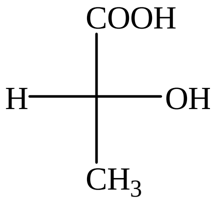
$[\alpha]_\lambda^t$: Specific rotation characteristic of the compound.



Example: Lactic Acid



(1)



(2)

These two compounds are enantiomers; their optical rotation is equal in absolute value but of opposite sign.
For 1: [α] = +3,5°

For 2: [α] = - 3,5°

The sign of [α] depends on the sign of the angle α.

α is counted positively when the observer rotates the analyzer to the right to achieve extinction. The substance is then ***dextrorotatory*** and denoted as ***(d)*** or ***(+)***. Conversely, the substance is ***levorotatory*** and denoted as ***(l)*** or ***(−)*** when the angle is negative (rotation of the analyzer to the left).

Thus, the two previous enantiomers are named:

(1): the acid (**+**)-lactic acid or (**d**)-lactic acid.

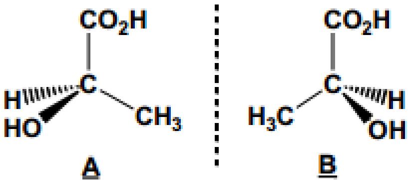
(2): the acid (**−**)-lactic acid or (**l**)-lactic acid.

- ✓ If **α = 0**, then either the molecule is ***achiral***, or it is a ***racemic mixture*** (an ***equimolar mixture*** of two enantiomers at ***50%-50%***).

III/ Enantiomers and Diastereomers

1. Definition

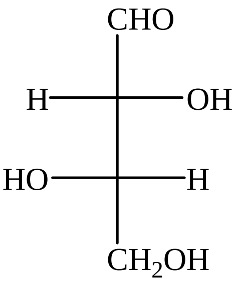
Two chiral molecules that are mirror images of each other are called ***enantiomers***.



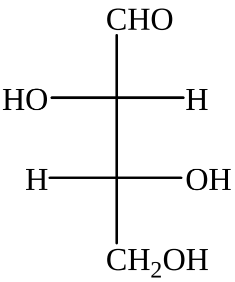
Plane mirror

Example: Represent the different stereoisomers of the molecule in Fischer projection.

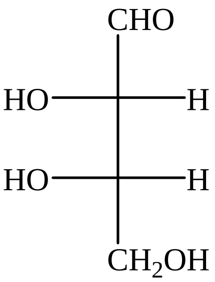
2,3,4-trihydroxybutanal



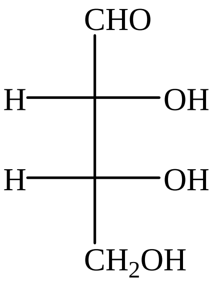
(2R, 3S)
I



(2S, 3R)
II

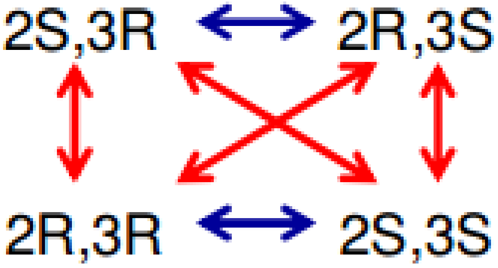


(2S, 3S)
III



(2R, 3R)
IV

I et II	→	**Enantiomer Couple**	**III et IV**	→	**Enantiomer Couple**
I et III	→	**Diastereomer Couple**	**I et IV**	→	**Diastereomer Couple**
II et III	→	**Diastereomer Couple**	**II et IV**	→	**Diastereomer Couple**

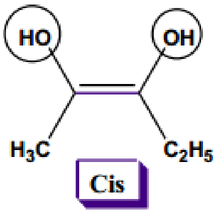


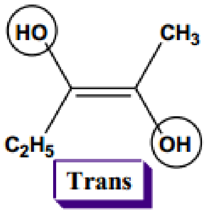
→ **Enantiomer Couple** → **Diastereomer Couple**

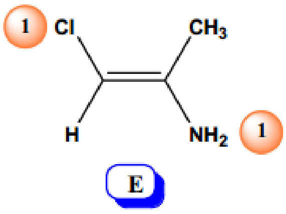
Two asymmetric carbons represent 4 stereoisomers.

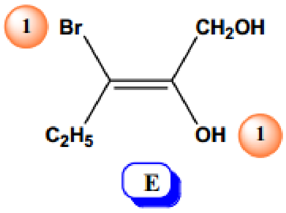
In general, when a molecule has n different asymmetric carbons, it exhibits 2^n ***stereoisomers***.

1. *Geometric Isomers*

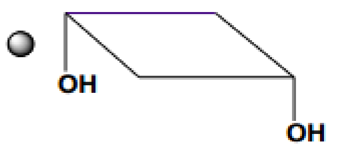




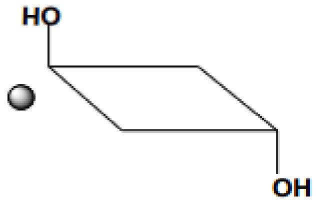




Case of Cycles



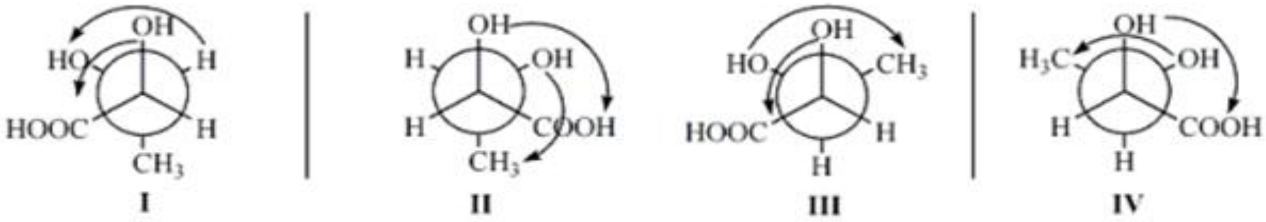
■ (Cis)-cyclobutane-1,4-diol



■ (Trans)-cyclobutane-1,4-diol

2. Nomenclature Erythro, threo and meso nomenclature

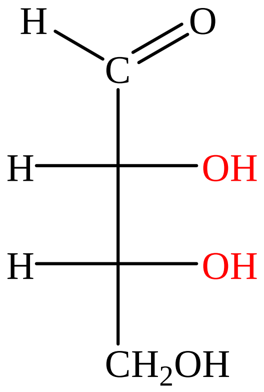
3. Newman Projection



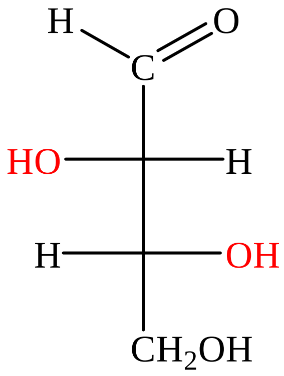
Erythro couple **Threo couple**

(2S, 3S) **(2R, 3R)** **(2S, 3R)** **(2R, 3S)**

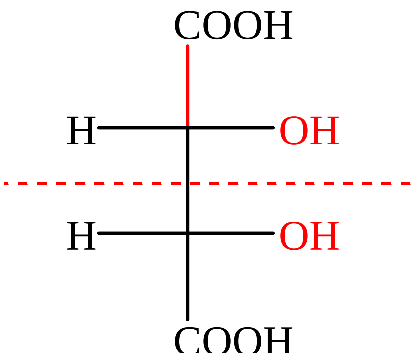
➢ Fisher Projection



Erythro



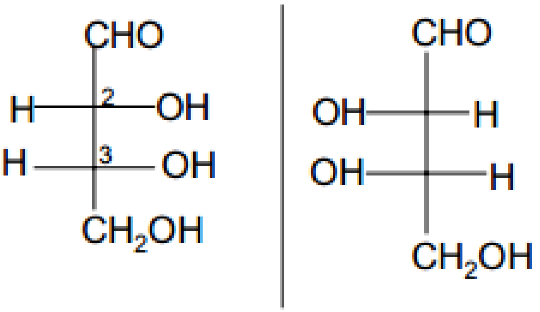
Threo



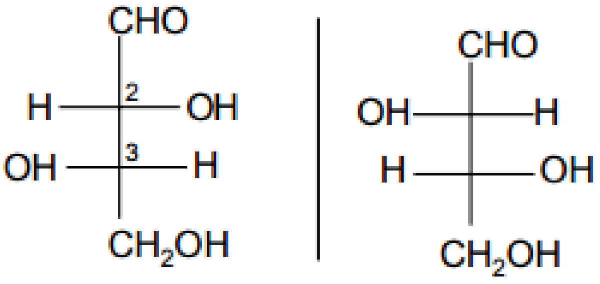
Meso

Example: Represent the different stereoisomers of the molecule in Fischer projection.

2,3,4-trihydroxybutanal



Erythro couple



Threo couple

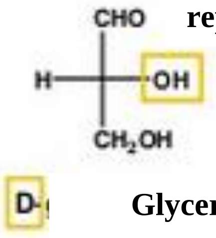
(2R, 3R) **(2S, 3S)** **(2R, 3S)** **(2S, 3R)**

Erythrose (2R, 3R) **Erythrose (2S, 3S)** **Threose (2R, 3S)** **Threose (2S, 3R)**

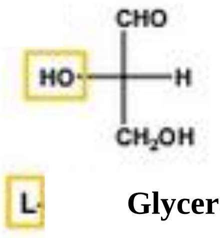
4. D and L Nomenclature

This nomenclature is used in the series of sugars and amino acids.

Fisher representation

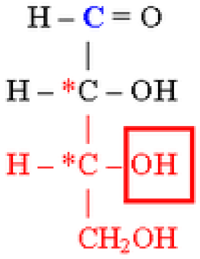


Glyceraldehyde

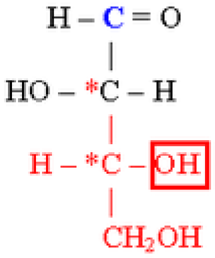


Glyceraldehyde

According to Fischer projection, when -OH is on the right, it is designated as **D**; when it is on the left, it is designated as **L**.

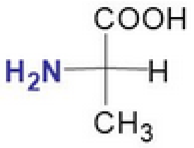


(D-Erythrose)

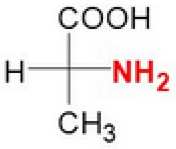


(D-Thréose)

Amino acids are named ***D*** or ***L*** based on the position of the NH_2 group. When $-NH_2$ is on the right, it is designated as ***D***; when it is on the left, it is designated as ***L***.



L-Alanine



D-Alanine