

BP401T. PHARMACEUTICAL ORGANIC CHEMISTRY III (THEORY)

UNIT- II



PREPARED BY

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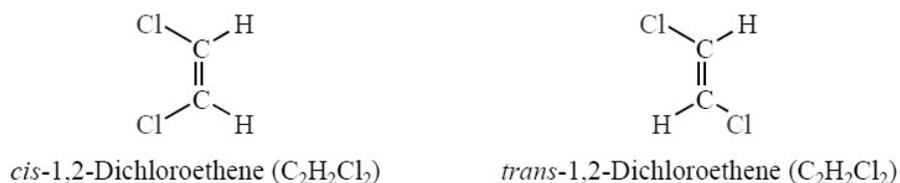
KANPUR-209217

GEOMETRICAL ISOMERISM (10 HOURS)

- Nomenclature of geometrical isomers (Cis Trans, EZ, Syn Anti systems)
- Methods of determination of configuration of geometrical isomers. Conformational isomerism in Ethane, n-Butane and Cyclohexane.
- Stereo isomerism in biphenyl compounds (Atropisomerism) and conditions for optical activity
- Stereospecific and stereoselective reactions

GEOMETRIC ISOMERISM (*Cis-Trans* Isomerism)

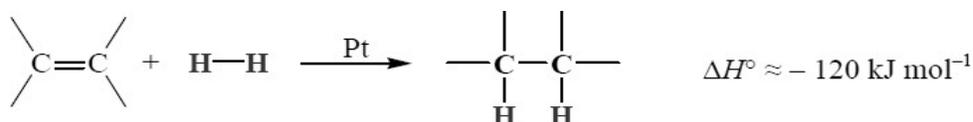
- The carbon atoms of the carbon-carbon double bond are sp^2 hybridized. The carbon-carbon double bonds consist of σ bond and π bond. The presence of π bond locks the molecule in one position, therefore rotation around the $C=C$ bond is not possible.
- This restriction of rotation about the carbon-carbon double bond is responsible for Geometric Isomerism.
- The *Cis isomers* is one in which two similar groups are on the same side of the double bond.
- The *Trans isomers* is one in which two similar groups are on the opposite sides of the double bond.



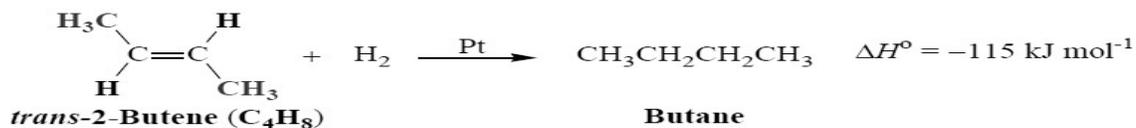
□ Overall Relative Stabilities Of Alkenes: trans isomer and cis isomer:

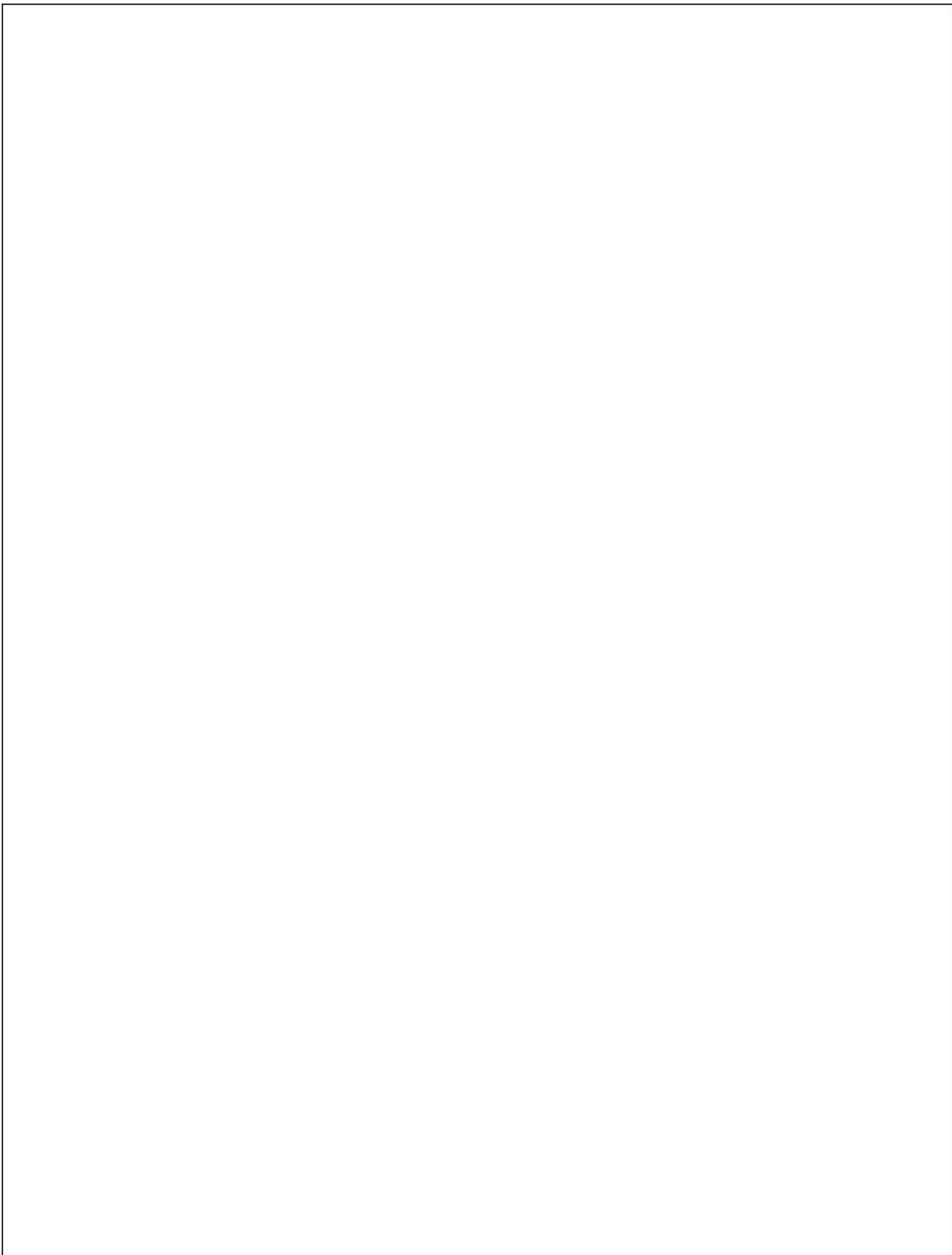
A. The reaction of an Alkene with hydrogen is an exothermic reaction; the enthalpy change involved is called the heat of hydrogenation.

- i. Most alkenes have heat of hydrogenation near -120 kJ mol^{-1} .



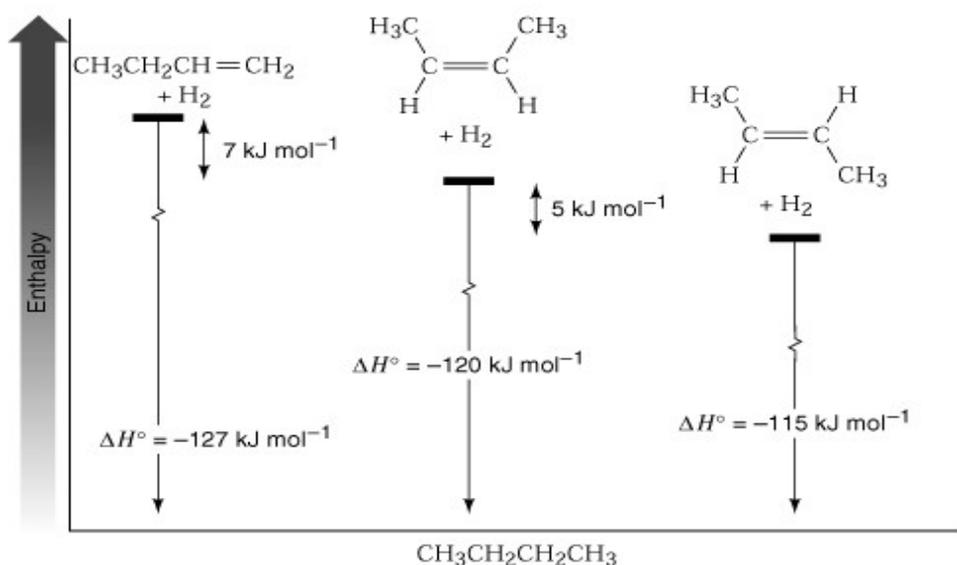
- ii. Individual alkenes have heats of hydrogenation may differ from this value by more than 8 kJ mol^{-1} .
- iii. The differences permit the measurement of the relative stabilities of alkene isomers when hydrogenation converts them to the same product.





B. In each reaction:

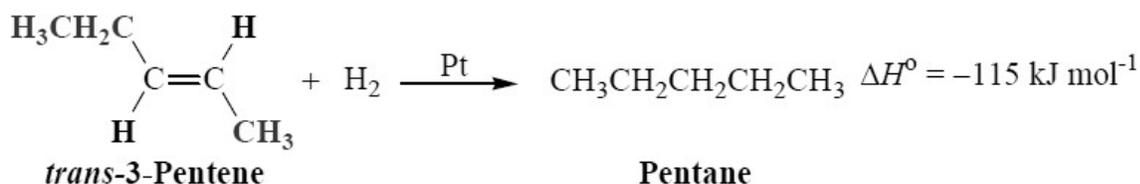
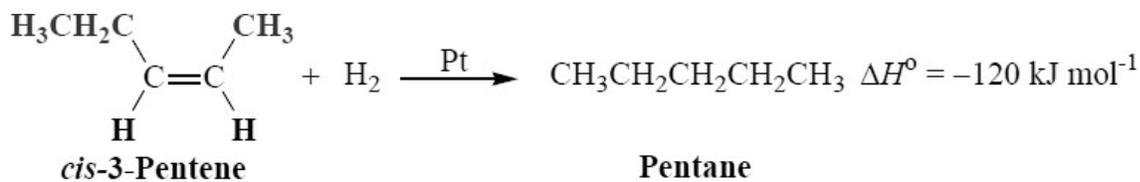
- The product (butane) is the same.
- One of the reactants (hydrogen) is the same.
- The different amount of *heat* evolved is related to different stabilities (different heat contents) of the individual butenes.



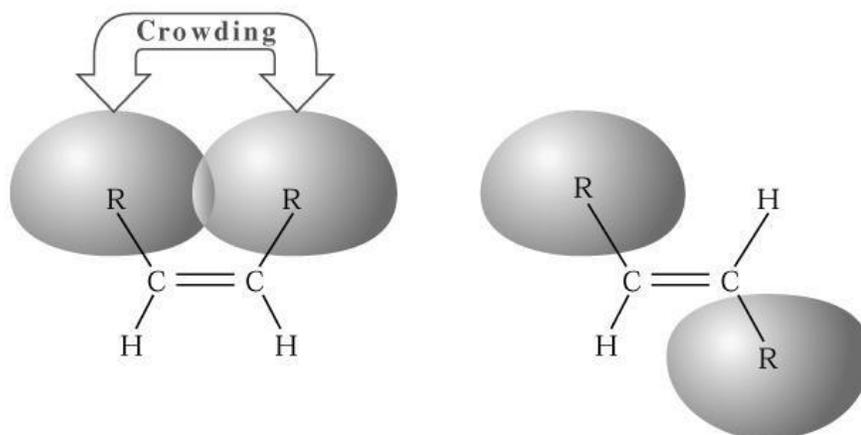
An energy diagram for the three butenes isomers. The order of stability is *trans*-2-butene > *cis*-2-butene > 1-butene.

- 1-Butene evolves the greatest amount of heat when hydrogenated, and *trans*-2-butene evolves the least.
- 1-Butene must have the greatest energy (enthalpy) and be the least stable isomer.
- Trans*-2-Butene must have the lowest energy (enthalpy) and be the most stable isomer.

C. Trend of stabilities: *trans* isomer > *cis* isomer

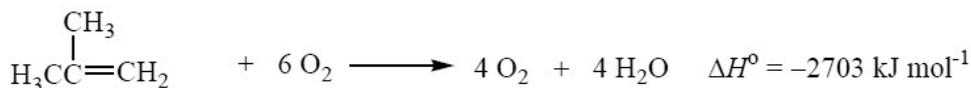
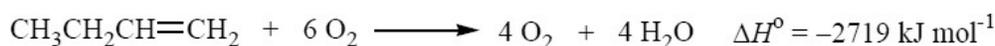
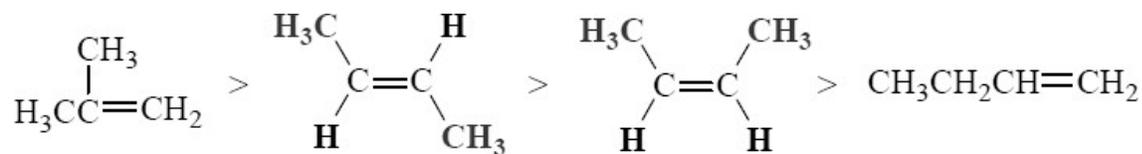


D. The greater enthalpy of cis isomers can be attributed to strain caused by the crowding of two alkyl groups on the same side of the double bond.



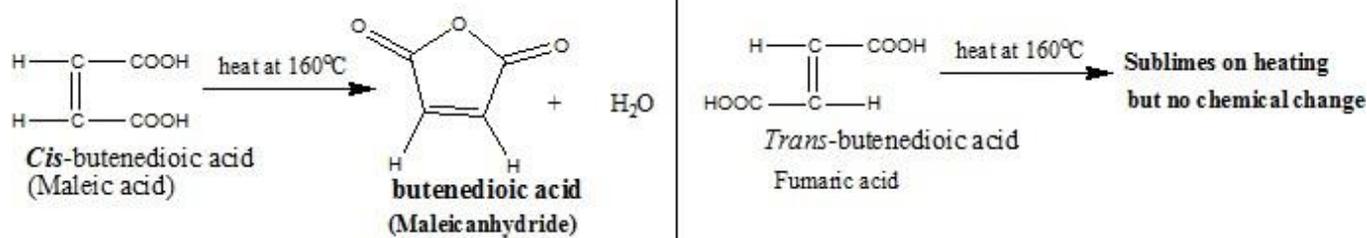
cis- and trans-Alkene isomers. The less stable cis isomer has greater strain.

E. The stability of the butenes isomers:



F. The geometric isomers of butenedioic acid

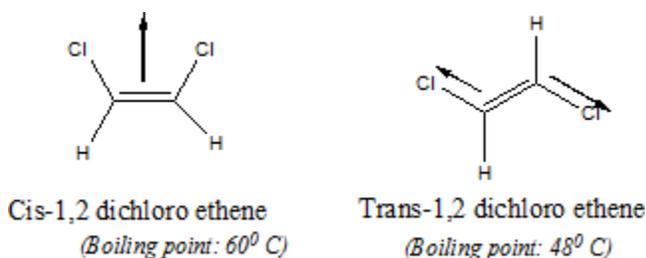
- Chemical properties of the cis- and trans- isomers are usually very similar, but an interesting exception to this is seen with butenedioic acid. Here the two isomers have such different reactivities.



- The differences in the properties of the cis- and trans- isomers of butenedioic acid become very evident when examples of their roles in biology are compared. Fumaric acid (trans-) is an intermediate in the Krebs cycle, an essential part of the reactions of aerobic respiration for energy release in cells. By contrast, maleic acid (cis-) is an inhibitor of reactions that interconvert amino acids, for example, in the human liver. Their different biological activities are a consequence of their different shapes affecting their binding to enzymes, the biological catalysts that control all these reactions.

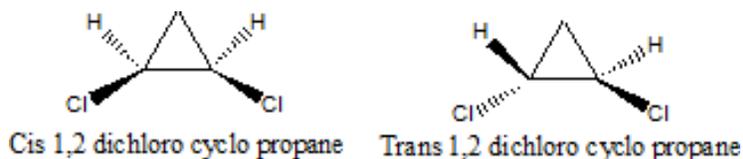
G. The geometric isomers of 1,2-dichloroethene

- The polarity strongly influences the relative boiling point as it determines the strength of the intermolecular forces.
- For example, cis-1,2-dichloroethene has a net dipole moment and dipole-dipole attractions between its molecules in addition to the *Van Der Waals'* forces, whereas trans-1,2-dichloroethene which is non-polar has only *Van Der Waals'* forces. The boiling point of the *cis-isomer* is therefore higher.



H. Cis and Trans for Cyclic molecules

- Cycloalkanes contain a ring of carbon atoms in which the bond angles are strained from the tetrahedral angles in the parent alkane and the ring prevents rotation around the carbon atoms, so when there are two different groups attached to two carbons in the ring, these molecules can exist as the cis- and trans- forms. For example:

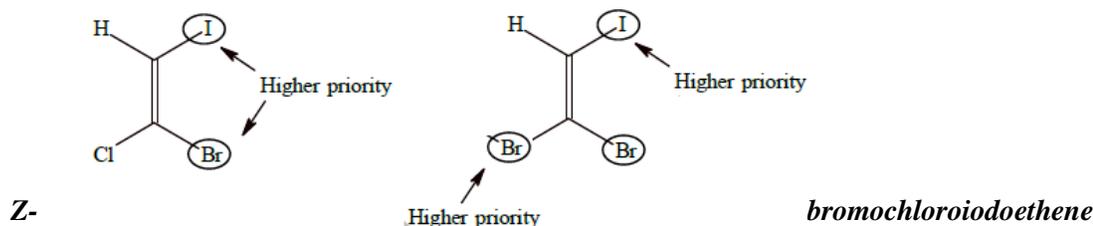


E & Z NOTATION FOR GEOMETRIC ISOMERISM

- The simple convention of denoting the geometrical isomers by **cis/trans** descriptors is not sufficient when there are more than two different substituents on a double bond. To differentiate the stereochemistry in them, a new system of nomenclature known as the **E & Z notation** method is to be adopted.
- According to this method, if the groups with higher priorities are present on the opposite sides of the double bond, that

isomer is denoted by **E**. Where **E = Entgegen** (the German word for 'opposite') or **E = Enemy**

- However, if the groups with higher priorities are on the same side of the double bond, that isomer is denoted by **Z**. Where **Z = Zusammen** (the German word for 'together')
- The letters **E** and **Z** are represented within parentheses and are separated from the rest of the name with a hyphen.
- Step by step procedure to determine the **E** and **Z** configuration: *The following procedure is to be adopted to denote the geometrical isomers by E & Z descriptors.*
 - ✓ First determine the higher priority group on each end of the double bond.
 - ✓ If the higher priority groups are on the opposite sides of double bond, the isomer is denoted by the **descriptor, E**.
 - ✓ Otherwise if they are on the same side of double bond, the **Z descriptor** must be used.
- **The priorities are assigned by following Cahn-Ingold-Prelog sequence rules:**
 - **Rule 1:** Rank the atoms directly attached to the olefinic carbon according to their **atomic number**. **High priority** is given to the atom with **higher atomic number**.



- **Rule 2:** If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass. **E.g.** the Deuterium isotope (H^2 or **D**) has more priority than protium (H^1 or **H**). The C^{13} isotope has more priority than C^{12} .

- **Rule 3:** If the relative priority of two groups cannot be decided by Rule 1, it shall be determined by applying to the next atom group 'X'. organic molecules where **X** is more than one atom
-

X = $-\text{CH}_2\text{CH}_2\text{CH}_3 > -\text{CH}_2\text{CH}_3 > -\text{CH}_3 > -\text{H}$ i.e. the longer the hydrocarbon carbon chain the higher its priority,

Rule 4: Treat double and triple bond as if each were a bond to a separate atom. For this methods, imagine that **pi** (π) bond is broken and the atoms at both ends duplicate. (**or**) Atoms participating in double/triple bonds are considered to be bonded to an equivalent number of similar “phantom” atoms by single bonds. Note: “phantom” atoms are bonded to no other atoms.

METHODS OF DETERMINATION OF CONFIGURATION OF GEOMETRICAL ISOMERS

The common methods attributed in the determination of configuration of geometrical isomers includes,

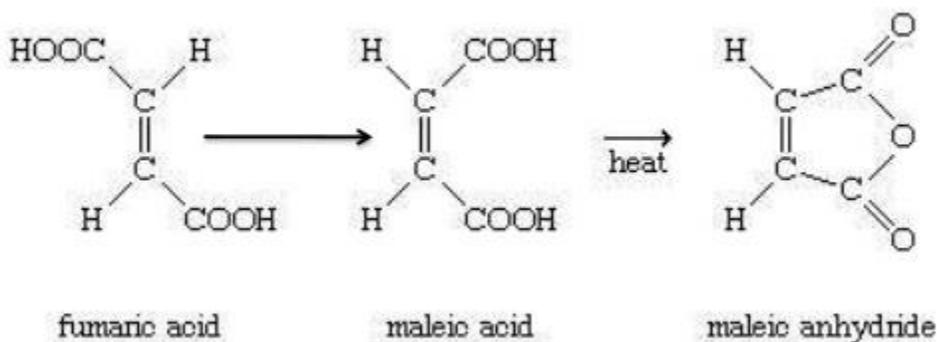
1. Method of cyclization
2. By converting into the compound of known configuration.
3. Optical activity
4. Method based on physical property
5. By stereo selective addition and elimination reaction.

1. Method of Cyclization

This method is applied in which either of the form capable of forming a ring .

This method is based on the principle that the intermolecular reaction occur easily when the reacting groups are closed together .

For Eg: among two acids Malic and Fumaric only the former give the anhydride on gentle heating,so in malic acid the two reactive groups (-COOH) are closer and hence it is cis and fumaric acid is trans.



2. By Converting Into The Compound Of Known Configuration.

Geometrical isomer pairs can be converted in to a compound of known configuration.

For Eg: the conversion of one form of the trichlorocrotonic acid into fumaric acid on hydrolysis , so the above trichlorocrotonic acid must be the trans isomer moreover the same trichlorocrotonic acid gives crotonic acid (m.p 72 degree Celsius) on reduction. The other isomer of the trichlorocrotonic acid does not give fumaric acid on hydrolysis and form isocrotonic acid (m.p 15.5 degree Celsius) on reduction.

Hence the isocrotonic acid and the corresponding trichlorocrotonic acid are cis –isomers.

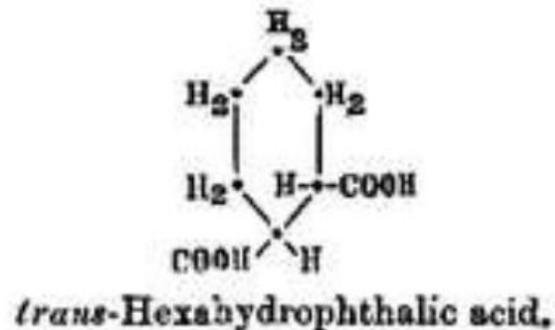
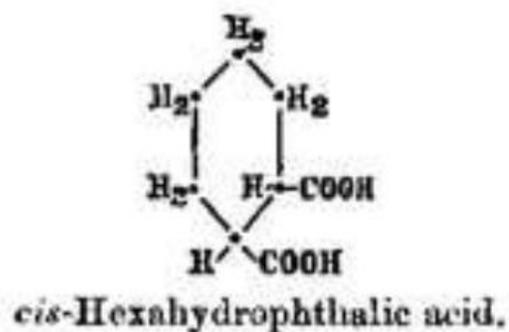


3. Optical activity

Among the two members of geometrical isomers only one form is optically active whereas the other is optically inactive due to presence of an element of symmetry. The optically active form can be resolved and may be used to establish its configuration.

Eg: Hexahydrophthalic acid the trans form of which has been resolved.

Cis is optically inactive due to the plane of symmetry and trans is optically active and hence resolved.



6. Method based on physical property

Physical properties often be used for establishing the configuration of various physical properties which helps in determining the configuration are,

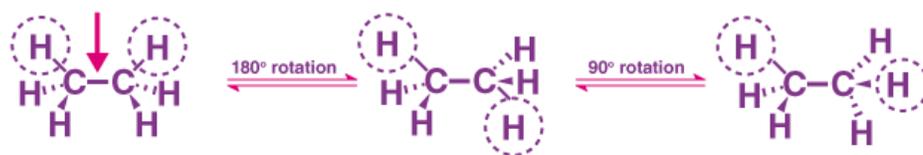
- Dipole moment
- Melting point
- Boiling point
- Solubility
- Refractive index
- Acid strength
- Electron diffraction.

CONFORMATIONAL ISOMERISM IN ETHANE, N-BUTANE AND CYCLOHEXANE

Conformational Isomerism is a form of stereoisomerism where interconversions of isomers are possible by rotations referring to single bonds. These isomers are termed as conformational isomers. Rotational energy acts as a barrier in case of single bond rotation. It has to be overcome to interconvert one conformer to another. The energy barrier must be small for Conformational Isomerism to occur. There are several types of conformational isomers. For example Ethane and Butane.

Conformations of Ethane

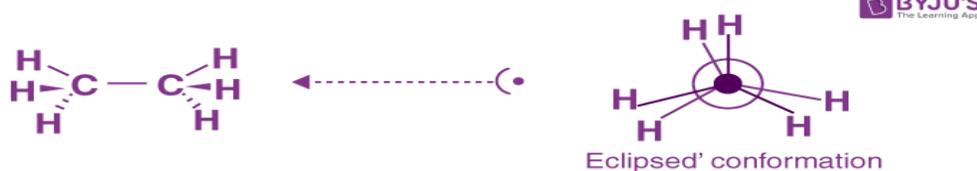
Ethane is an organic Chemical Compound. It is a colorless and odor gas at a standard temperature. Ethane molecule consists of seven sigma bonds. There will be a change in the shape of the molecule when there is a rotation of about six carbon-hydrogen bonds. But many possible differences occur when there is a rotation about the carbon-carbon bond.



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Conformations of Ethane

Now suppose we rotate CH₃ group clockwise at an angle of 60 degrees, there would be a possibility that hydrogen present at the front carbon is close to the hydrogen present at the back carbon. That is Eclipsed Conformation.



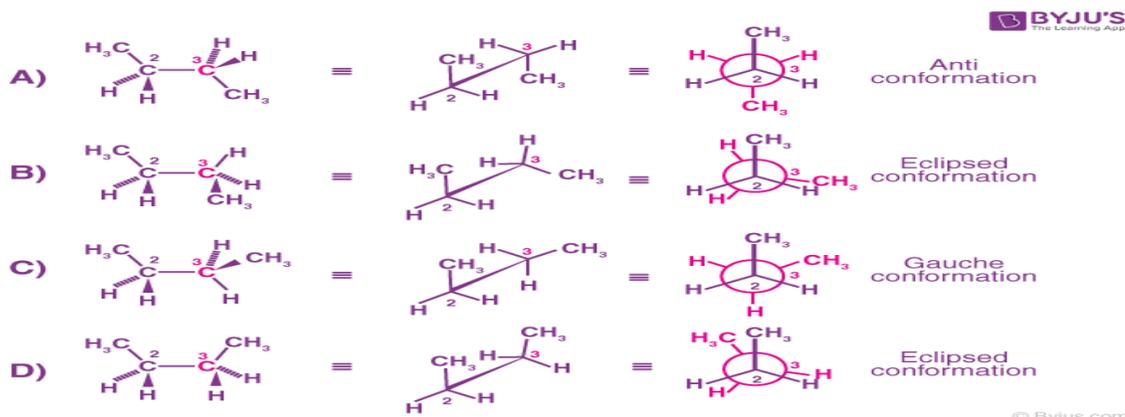
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Conformations Ethane

Eclipse Conformation is one of the highest Conformation. Another clockwise rotation at an angle of 60 degrees would lead to second eclipsed conformation. The solid line in the above figure represents the 6 carbon-hydrogen bond that is extended at an angle of 120 degrees from 2 carbons.

Uses Of Ethane: it is widely used in the production of Ethane. It is mainly done through steam cracking. It acts as a ripening agent for food. It is a primary ingredient in mustard gas.

Conformations of n Butane



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Butane is an organic compound which consists of an alkane with 4 carbon atoms. It may refer to a mixture of 3 isomers. At atmospheric pressure, Butane is a gas. They are liquefied gas that is highly flammable.

Compared to ethane, hydrogen butane consists of the complex set of conformations that is related to the constitution. The

below figure represents the 4 conformations of butane.

The above diagram explains the rotation about C2-C3 bond due to the change in potential energy.

What is Conformation of Cyclohexane?

Cyclohexane has a non-polar structure that makes it almost free from ring strain. The most important conformations that it can have included chair conformation and boat conformation. The chair conformation is more stable than the boat conformation. The boat conformation can sometimes be more stable than it is usually, by a slight rotation in the C-C bonds and is called the skew boat conformation. Nevertheless, the chair conformation is the most stable cyclohexane form.

A Conformation of cyclohexane can refer to many 3-Dimensional shapes assumed by a cyclohexane molecule without disturbing the integrity of the chemical bonds in it.

Cyclohexane Conformation

A regular hexagon shape contains internal angles of 120° . However, the carbon-carbon bonds belonging to the cyclohexane ring have a tetrahedral symmetry, with the bond angles corresponding to 109.5° .

This is the reason why the cyclohexane ring has a tendency to take up several warped conformations (so that the bond angles are brought closer to the tetrahedral angle (109.5°) and there is reduced overall strain energy).

Examples of common conformations of cyclohexane include the boat, the twist-boat, the chair, and the half-chair conformations, which are named based on the shape that the cyclohexane molecule assumes in them.

These four cyclohexane conformations have been illustrated below along with some insight on their stability.

Conformations of Cyclohexane

It can be noted that the cyclohexane molecule has the ability to switch between the conformations listed above and that only the chair and the twist-boat conformations can be isolated into their respective pure forms.

Due to hydrogen-hydrogen interactions in these conformations, the bond length and the bond angle vary slightly from their nominal values.

The chair conformations of cyclohexane have lower energies than the boat forms. However, the rather unstable boat forms of cyclohexane undergo rapid deformation to give twist-boat forms which are the local minima corresponding to the total energy.

The Hydrogen atoms belonging to the carbon-hydrogen bonds that are at a perpendicular angle to the mean plane are called Axial hydrogens, whereas those belonging to the carbon-hydrogen bonds which are parallel to the mean plane are called equatorial hydrogens. These bonds are also referred to as axial and equatorial bonds respectively.

Cyclohexane is the most widely occurring ring in compounds of natural origin. Its prevalence, undoubtedly a consequence of its stability, makes it the most important of the cycloalkanes. The deviation of bond angle in cyclohexane molecules is more than in cyclopentane, it should be more strained and less reactive than cyclopentane. But actually it is less strained and more stable than cyclopentane.

In order to avoid the strain, cyclohexane does not exist as a planar molecule as expected. It exists as a puckered ring

which is non-planar and the bond angles are close to tetrahedral bond angles. Two such puckered rings for cyclohexane called boat and chair conformations.

Conformation of Cyclohexane Stability

Generally, in the chair shaped conformation of cyclohexane, there are three carbon-hydrogen bonds of each of the following types:

Axial 'up'

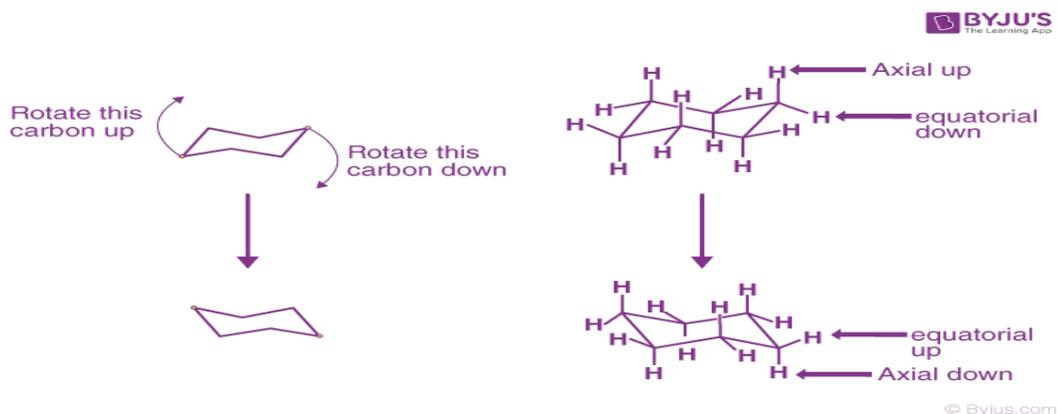
Axial 'down'

Equatorial 'up'

Equatorial 'down'

This geometry of chair cyclohexane conformations is generally preserved when the hydrogen atoms are replaced by halogen atoms such as fluorine, chlorine, bromine, and iodine. The phenomenon wherein the cyclohexane molecule undergoes a conversion from one chair form to a different chair form is called chair flipping (or ring flipping).

An illustration detailing chair flipping is provided below.



Ring Flipping of Chair Cyclohexane Conformation

When chair flipping occurs, axial carbon-hydrogen bonds become equatorial and the equatorial carbon-hydrogen bonds become axial. However, they retain the corresponding 'up' or 'down' positions.

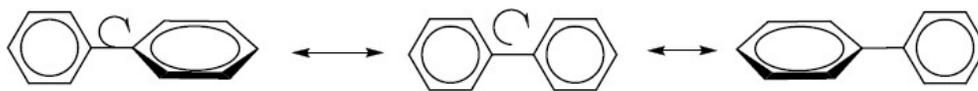
It can be noted that at a temperature of 25°C, 99.99% of the molecules belonging to a given cyclohexane solution would correspond to a chair-type conformation.

The boat conformation of cyclohexane is not a very stable form due to the torsional strain applied to the cyclohexane molecule. The stability of this form is further affected by steric interactions between the hydrogen atoms. Owing to these factors, these conformations are generally converted into twist-boat forms which have a lower torsional strain and steric strain in them.

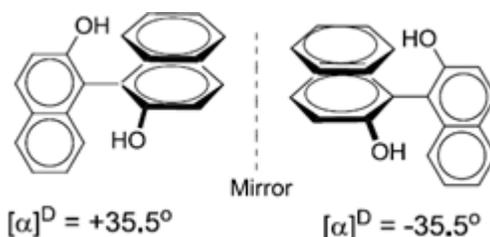
These twist-boat conformations of cyclohexane are much more stable than their boat-shaped counterparts. This conformation has a concentration of less than 1% in a solution of cyclohexane at 25°C. In order to increase the concentration of this conformation, the cyclohexane solution must be heated to 1073K and then cooled to 40K.

Atropisomerism

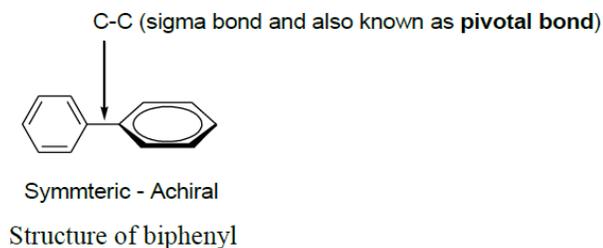
- **Biphenyls** are compounds whereby a phenyl ring is connected to another through a central σ bond.



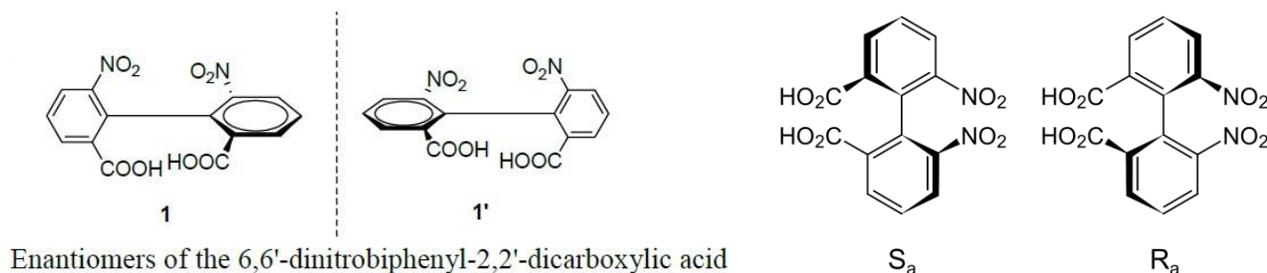
- In unsubstituted **biphenyl**, there is sufficient amount of freedom of rotation around the central single bond to allow for free interconversion between the various conformers or rotamers so that the various rotamers cannot exist independently.
- However, **biphenyls** with large substituents at the *ortho* positions on either side of the **central σ bond** experience restricted rotation along this bond due to **steric hindrance**. If the substituents are different, a chiral molecule existing as a pair of enantiomers called **atropisomers** is obtained.
- Polynuclear aromatic systems such as **binol** also exist as **enantiomers**.

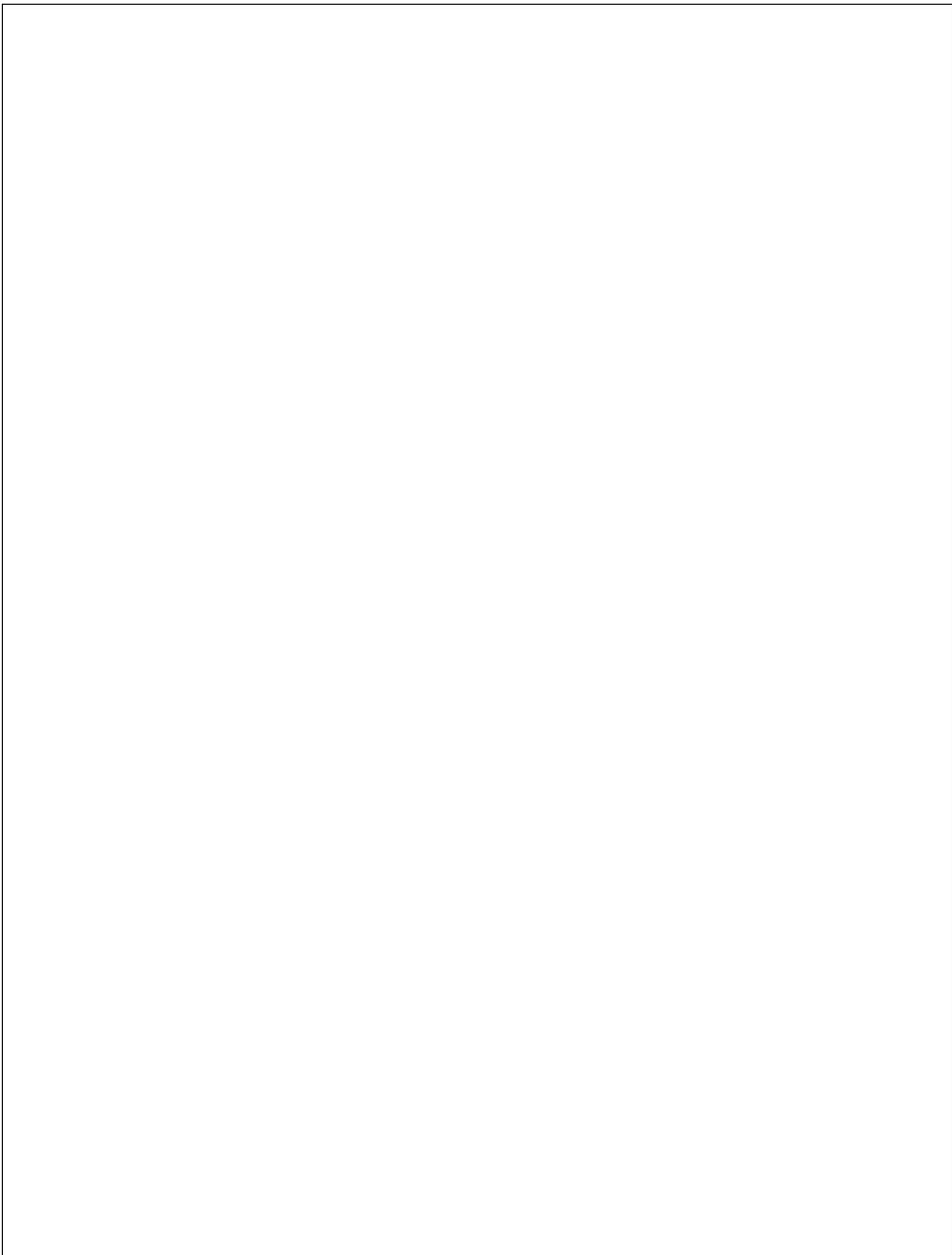


- Atropisomerism are stereoisomers as a result of restricted rotation about a single bond.
- Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers (from Greek, a = not and tropos = turn).
- If bulky group on *ortho* position of *bi-phenyl* or strained ring structural features. Bulky substituents or strained rings may enhance the barrier to rotation between two distinct conformations to such an extent as to allow observation of **atropisomers**.
- **Atropisomerism** is also called **axial chirality** and the chirality is not simply a centre or a plane but an **axis**.



- Biphenyl substituted on *ortho* position, which contains a chiral axis along the biphenyl linkage. The biphenyl rings are perpendicular to each other in order to minimize steric clashes between the four *ortho* substituents meaning that rotation about the biphenyl bond through pivotal bond is restricted.



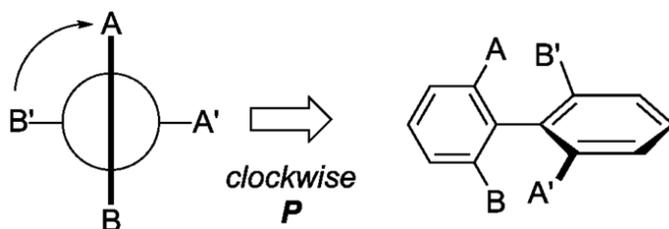
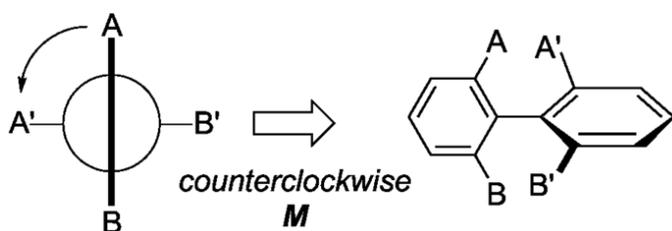


Conditions of Atropisomerism:

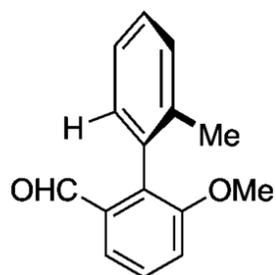
1. A rotationally stable axis
2. Presence of different substituents on both sides of the axis
3. The configurational stability of axially chiral biaryl compounds is mainly determined by three following factors:
 - i. The combined steric demand of the substituent in the combined steric demand of the substituents in the proximity of the axis.
 - ii. The existence, length and rigidity of bridges.
 - iii. Atropisomerisation mechanism different from a merely physical rotation about the axis, e.g. photochemically or chemically induced processes.

- Stereochemical assignment

- o Determining the axial stereochemistry of biaryl atropisomers can be accomplished through the use of a Newman projection along the axis of hindered rotation.
- o The ortho, and in some cases *meta* substituents are first assigned priority based on Cahn–Ingold–Prelog priority rules.
- o Starting with the substituent of highest priority in the closest ring and moving along the shortest path to the substituent of highest priority in the other ring, the absolute configuration is assigned **P** or **Δ** for clockwise and **M** or **Λ** for counterclockwise.

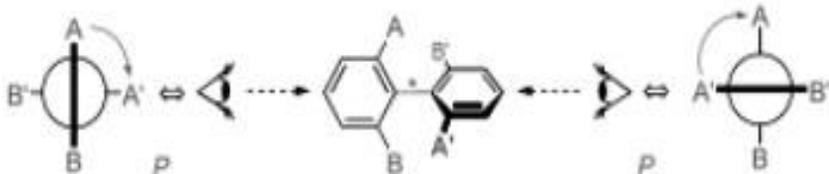
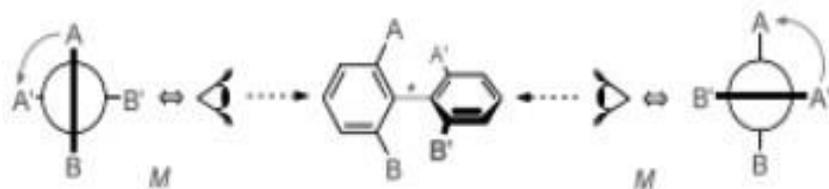


example:



M counterclockwise

chirality in biaryl compounds (priority: A > B):



counterclockwise : **M** (minus)
clockwise : **P** (plus)

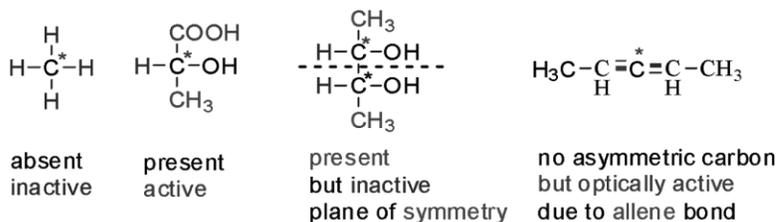
□ CONDITIONS FOR OPTICAL ACTIVITY

- 1) To exhibit optical activity molecule must possess asymmetric carbon: Asymmetric carbon compounds are optically active. But, presence of asymmetric is not only the requirement.

Asymmetry:

if asymmetric centre present = optically active (may / may not check for other criteria)

if asymmetric centre absent = optically inactive (may / may not check for other criteria)

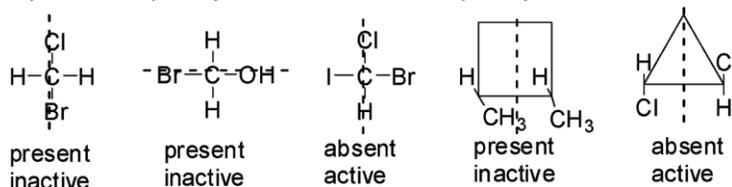


- 2) To exhibit optical activity molecule must not have the symmetry elements, (a) plane of symmetry (b) centre of symmetry (c) n-fold alternating access of symmetry. If these three are absent then only the compounds exhibits optical activity.

(a) **Plane of symmetry:** A plane which bisects the molecules into two mirror images are called plane of symmetry. If the plane of symmetry is present then the molecule is optically inactive, if absent then optically active.

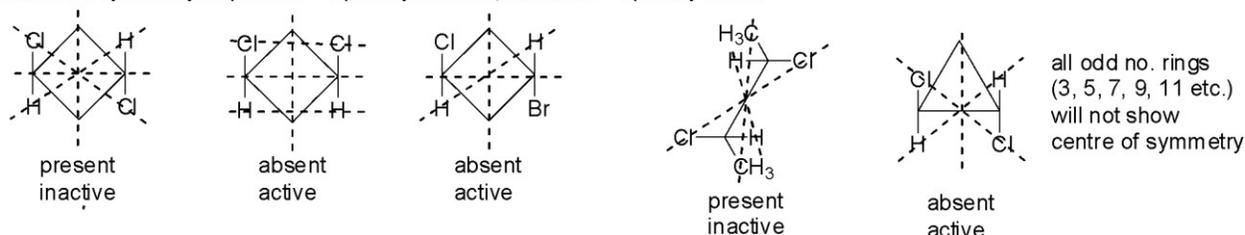
Plane of symmetry:

if present = optically inactive; if absent = optically active



(b) **Centre of symmetry:** If all the lines two identical groups pass through a single point or a central point is called centre of symmetry.

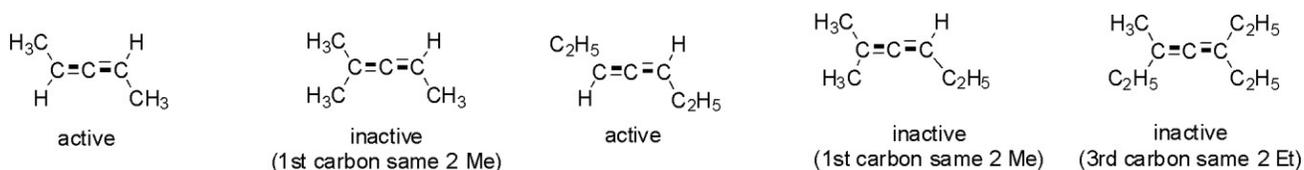
Centre of symmetry: if present = optically inactive; if absent = optically active



(c) **n-Fold alternating access of symmetry:** If a rotation by $360^\circ/n$ degrees ($n = 1, 2, 3, \dots$) followed by reflection in plane perpendicular to the axis taken results in identical molecule the compound said to be possess n-fold alternating access of symmetry. If plane of symmetry or centre of symmetry is present then n-fold alternative access of symmetry is present. If plane of symmetry or centres of symmetry are absent then n-fold alternating access of symmetry will be absent. If the n-fold alternating access of symmetry present then the molecule is optically inactive, if absent then optically active.

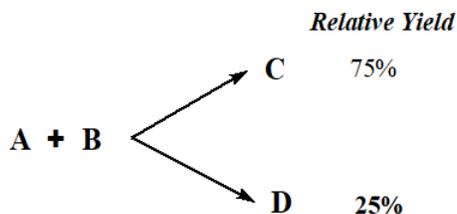
Allenes are optically active because absence of plane of symmetry.

However, if on first or third carbon two same groups present it will be inactive.



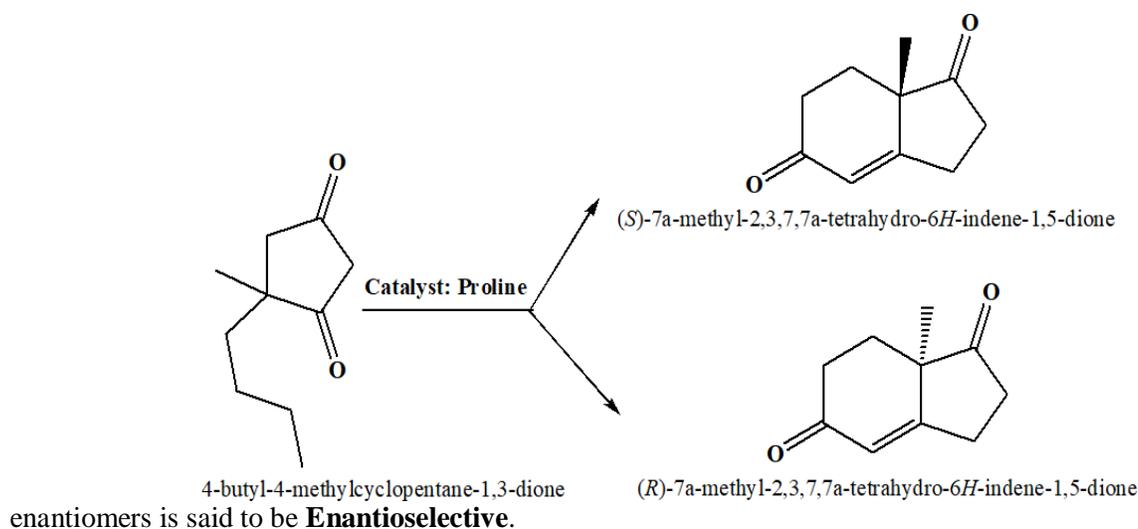
STERESELECTIVE REACTIONS

- A stereoselective process is one in which one stereoisomer predominates over another when two or more may be formed.
- If more than one reaction could occur between a set of reactants under the same conditions giving products that are stereoisomers and if one product forms in greater amounts than the others, the overall reaction is said to be **stereoselective**.



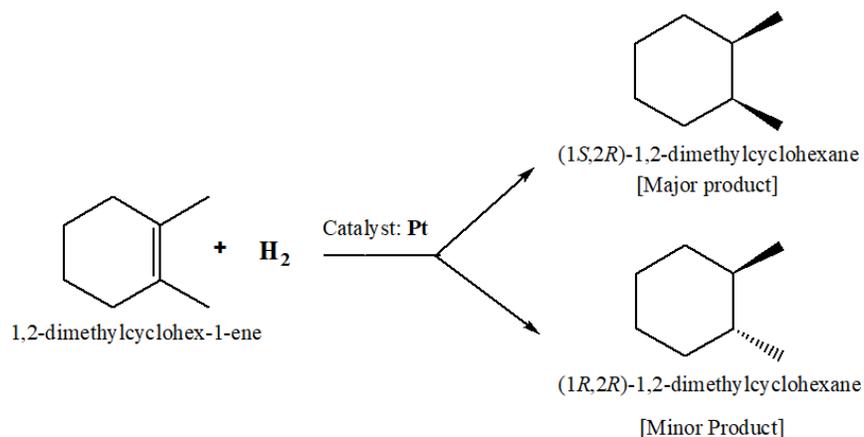
The overall reaction between A and B is stereoselective.

- A **stereoselective reaction** in which the possible products are

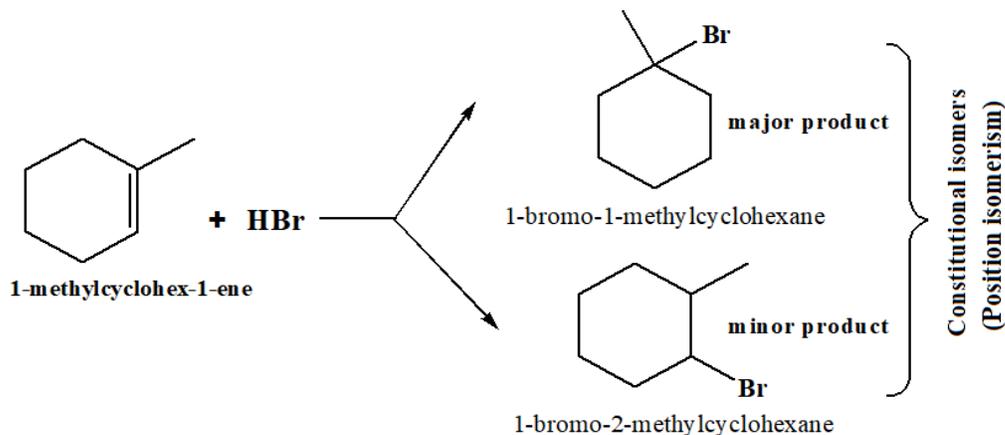


enantiomers is said to be **Enantioselective**.

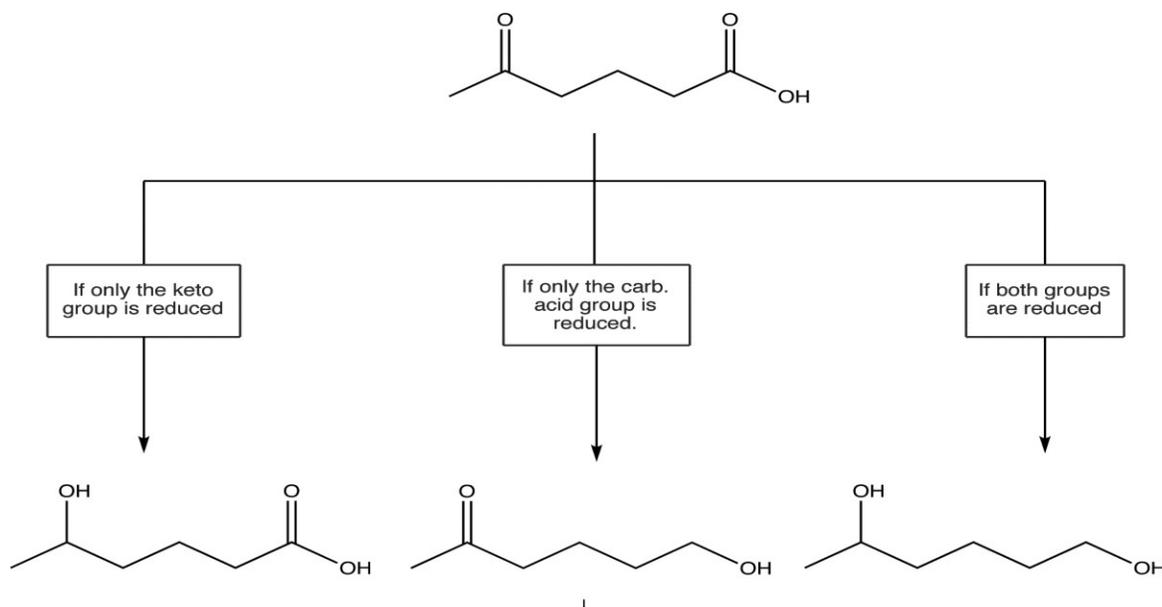
- A **stereoselective reaction** in which the possible products are diastereomers is said to be **Diastereoselective**.



Regioselective: If more than one reaction could occur between a set of reactants under the same conditions giving products that are **constitutional isomers** and if one product forms in greater amounts than the others, the overall reaction is said to be **regioselective**.



- **Chemoselective:** If an organic compound contains more than one different functional groups or more than one like functional groups that are not equivalent (see equivalent ligands), and, if a reagent reacts exclusively or predominately with one of them, the reaction is said to be **Chemoselective**.



• Difference Between Stereospecific and Stereoselective Reactions

	<i>Stereospecific Reactions</i>	<i>Stereoselective Reactions</i>
Definition	A stereospecific reaction is a reaction in which the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option.	A stereoselective reaction is a reaction in which there is a choice of pathway, but the product stereoisomer is formed due to its reaction pathway being more favorable than the others available.
Number of Products	A stereospecific reaction gives a specific product from a certain reactant.	A stereoselective reaction can result in multiple products.

Effects	The final product of a stereospecific reaction depends on the stereochemistry of the reactant.	The selectivity of the reaction pathway depends on differences in steric effects (presence of bulky groups cause steric hindrance) and electronic effects.
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