

Unit 1: Stereochemistry

Introduction:

Isomerism: The phenomenon of existence of molecules with same molecular formula but different structural formulae is called isomerism. Isomers can be constitutional isomers, where molecules have the same molecular formula but different connectivity between the atoms, such as 1-bromo- and 2-bromobutane. There are different types of constitutional isomerism as chain isomerism, positional isomerism and functional group isomerism; when the compounds have same molecular formula but differ in chain size, position of the functional group and the functional group itself respectively. When all these chain size, functional group and its position etc are same; but molecules differ only in the arrangement of groups or atoms in space, it is called stereoisomerism. Hence, Stereoisomerism: The phenomenon where isomers have same molecular and structural formula but different spatial arrangement of groups or atoms. Stereochemistry is a branch of chemistry which deals with the study of spatial arrangement of atoms in a molecule. Stereochemistry is the study of the static and dynamic aspects of the three-dimensional shapes of molecules.

Significance of stereochemistry:

Nature is inherently chiral because the building blocks of life (amino acids, nucleotides, and sugars) are chiral and appear in nature in enantiomerically pure forms. Hence, this is an important issue for bioorganic chemists, and a practical issue for pharmaceutical chemists. The Food and Drug Administration (FDA) now requires that drugs be produced in enantiomerically pure forms. In addition, stereochemistry is highly relevant to unnatural systems. The properties of synthetic polymers are extremely dependent upon the stereochemistry of the repeating units. Finally, the study of stereochemistry can be used to probe reaction mechanisms. Hence, understanding stereochemistry is necessary for most fields of chemistry, making this chapter one of paramount importance.

Stereoisomerism :

It is the phenomenon where, the isomers have identical molecular and structural formula but differ only in the spatial arrangement of groups or atoms. There are two main types of the stereoisomerism as follows.

Type 1: Configurational Isomerism: This is an isomerism where the configuration of the molecule i.e. the arrangement of atoms and groups is different and the isomers cannot be interconverted without breaking a bond. Eg. **Optical and Geometrical isomerism**

Type 2: Conformational isomerism: This is an isomerism where the isomers are interconvertible by rotations about single bonds, and the **conformation** of a molecule concerns features related to rotations about single bonds.

Optical isomerism: This kind of **Configurational** stereoisomerism which occurs mainly due to presence of asymmetric carbon atom. The isomers are called optical isomers and are named as *d*- or *l*- isomers as they rotate the plane of plane polarised light to clockwise or anticlockwise direction respectively. Alternatively they are also named as + or - isomers. The phenomenon is called optical isomerism. The total number of stereoisomers possible is 2^n where **n** is the number of asymmetric carbon atoms in the molecule. **Asymmetric carbon** is a carbon bonded with four different groups or atoms. When two stereoisomers are nonsuperposable mirror images of each other, they are known as **enantiomers**. Stereoisomers that are not mirror images of each other are known as **diastereomers**. **Optical activity** refers to the ability of a collection of molecules to rotate plane polarized light. Whereas, the configuration or the arrangement of groups or atoms can be represented by D-L or R-S systems.

Geometrical Isomerism: This kind of **Configurational** stereoisomerism occurs due to presence of restricted rotation like double bond or a small ring in the molecule. The phenomenon is called geometrical isomerism and the isomers are named as cis-trans / E-Z isomers.

[Note 1: We have studied these two types optical and geometrical isomerism in detail in the paper III of semester II in the last Year B.Sc. I]

** All these different types and the methods of nomenclature used in those respective types are represented in the Fig 1.*

Type 2: Conformational Isomerism: This year, we are going to learn the other kind of stereoisomerism viz conformational isomerism. Conformational isomerism is a form of isomerism that describes the phenomenon of molecules with the same structural formula but with different shapes due to rotations about one or more bonds. Different conformations can

have different energies, are usually **interconvertible** but are very rarely isolated from other conformers.

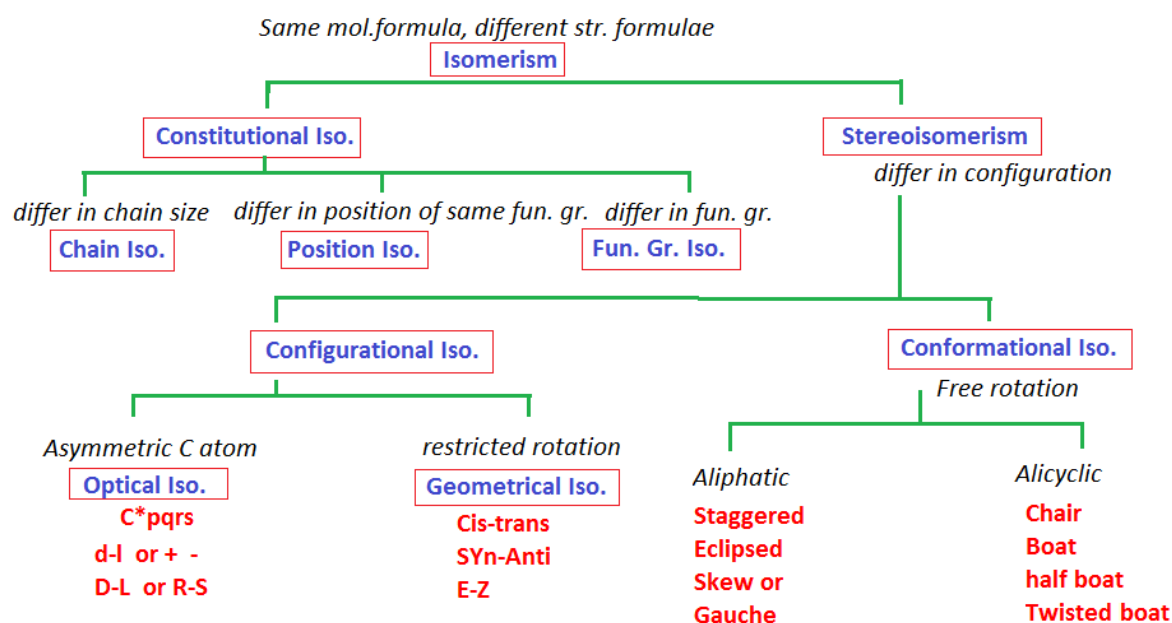


Fig 1: Types of stereoisomerism reasons and nomenclature

1.1 Conformational isomerism – Introduction.

In saturated acyclic systems it was believed that rotation about the most C-C bonds can be entirely free. Though it is not so free or easy as expected, the molecule can exist in different forms obtained due to such free rotation. The different forms of the compound obtained due to such free rotation, are called conformational isomers. The term 'conformation' or 'conformer' is used to denote any one of the infinite number of momentary arrangements of the atoms in space that result from rotation about single bonds. This phenomenon is called conformational isomerism; which occurs due to free rotation around C-C bond.

Example: The simplest example of conformational isomerism is the ethane molecule having only one C-C bond, the rotation around which causes the ethane molecule to show different forms of the same molecule. [Fig. 2]

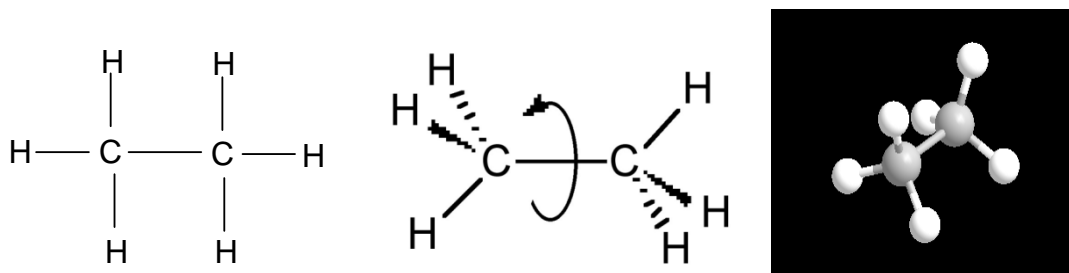


Fig.2 Ethane: molecular formula, Free rotation and 3D structure

Conformers: The term conformation or conformer is used to denote any of the infinite number of momentary arrangements of the atoms in space resulting from the free rotation about single bonds. Due to this free rotation, the molecule attains different forms such that in one extreme form the two groups on the two atoms are as far away as possible. This is called **staggered** conformer. The other extreme condition is when the two groups on the two atoms are as near to each other as possible. This is called **eclipsed** conformer. All the remaining 'in between' conformers are called **gauche** or **skew** forms.

These different three dimensional forms are represented in two dimensional drawings by different methods as shown below.

1.2 Representation of conformations of ethane by using Saw- Horse, Fischer (dotted line wedge) and Newman's projection formulae.

In all these three methods , one has to view at the three dimensional structure from different **direction** and then represent the molecule in different specified ways as shown in Fig.3

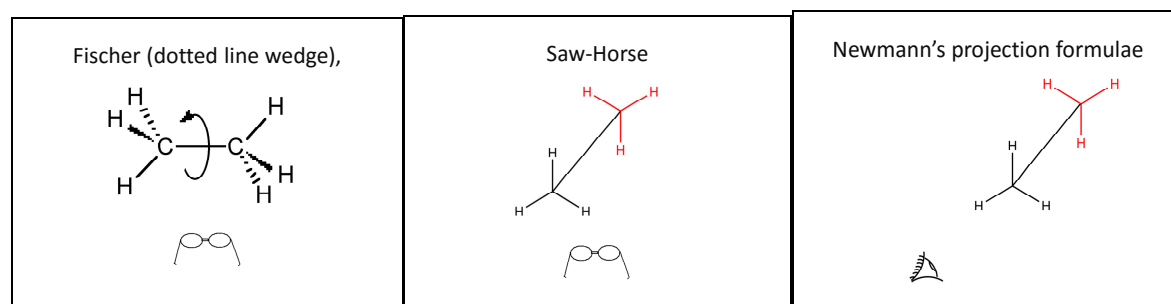
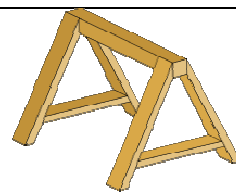


Fig.3 direction of viewing before drawing the molecule

Note 2: A **saw-horse** (saw-buck, trestle, buck) is a beam with four legs used to support a board or plank for sawing



a. Saw- Horse method: (See note 2)

In this method the molecule is seen from the angle towards a bond under rotation. This is shown by a straight line drawn at angle of about 45° to the lines of notebook. The two ends of the line are considered to be the two carbon atoms. The substituents of these carbon atoms are shown by three lines drawn from the terminal points of the line representing the C-C bond, making an angle of about 120° with each other. The extreme isomers of ethane are represented by Saw-Horse method are as shown in Fig. 4

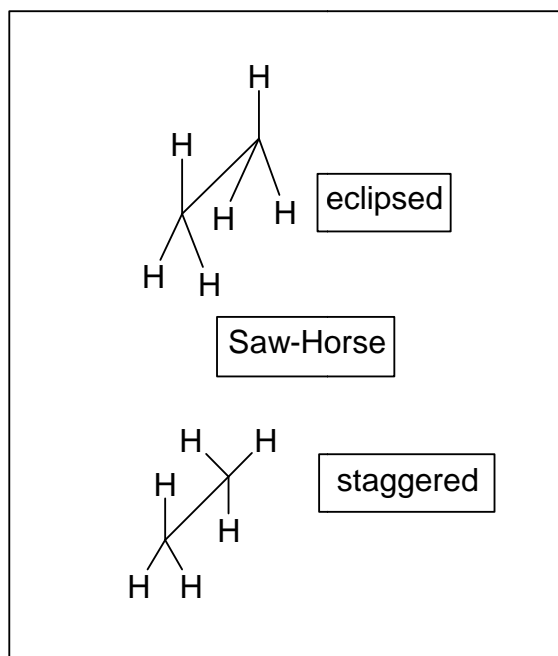


Fig 4: conformers of ethane (Saw-Horse method)

b. Fischer (dotted line-wedge) method:

In this method the molecule is seen from the side of the bond under rotation and this bond and the bonds in the same plane are represented by simple lines, the bonds going back from the plane of the paper are represented by dotted lines and the bonds coming towards the viewer are represented by wedges or solid lines as shown in Fig.5

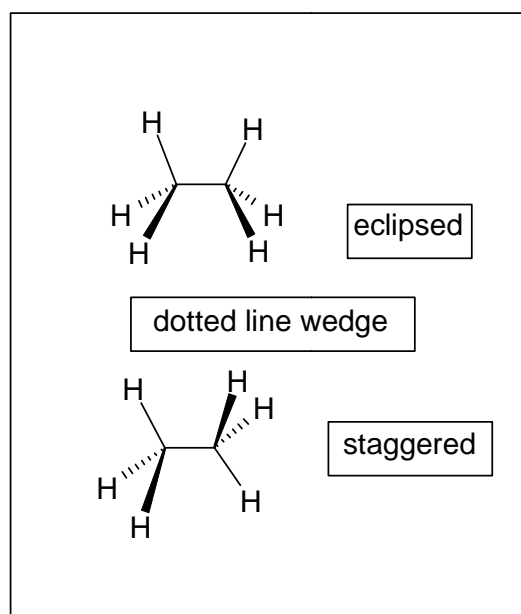


Fig.5 : conformers of ethane (Fischer dotted line wedge method)

c. Newman's projection formulae method:

In this method, the molecule is viewed from the direction of the bond itself. The front carbon is represented by a simple dot. The back carbon is shown by a small circle drawn around the dot representing the front carbon atom. The bonds to the front carbon are shown by simple lines drawn from the dot in angle 120° . The bonds of the back carbon are represented by lines drawn from the circumference of the circle representing the back carbon atom. This method is significant as the Gauche or Skew forms also can be shown effectively by this method as shown in Fig. 6

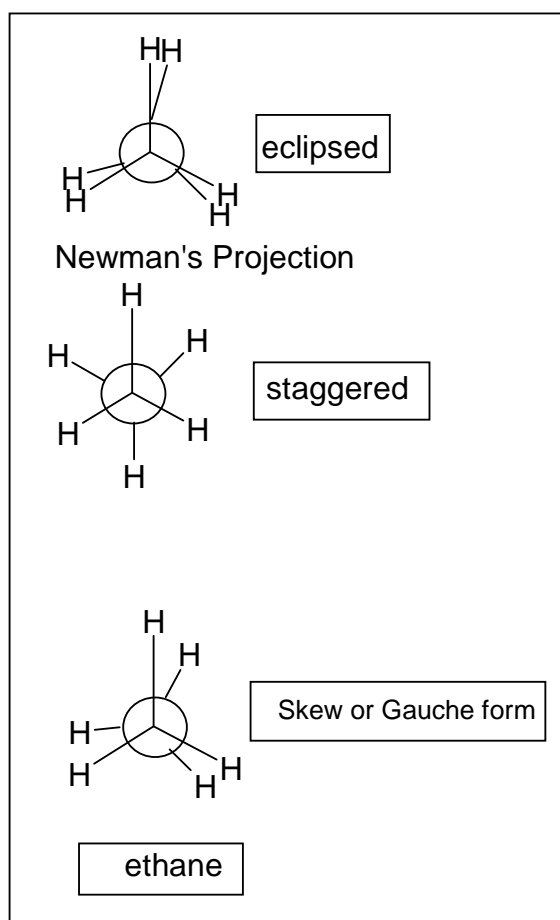


Fig. 6: Conformers of ethane (Newman's projection formulae method)

In short the three methods are useful in representation of the conformers effectively as shown in Fig.7

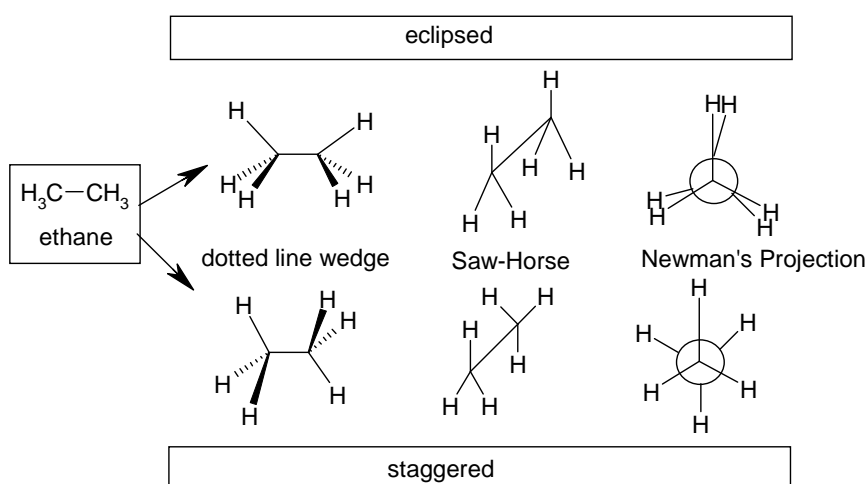


Fig.7: Conformers of ethane by all three methods

Similarly, the conformers of the n-butane where the rotation around the C₂-C₃ bond is considered can be shown by these three methods as shown in Fig.8.

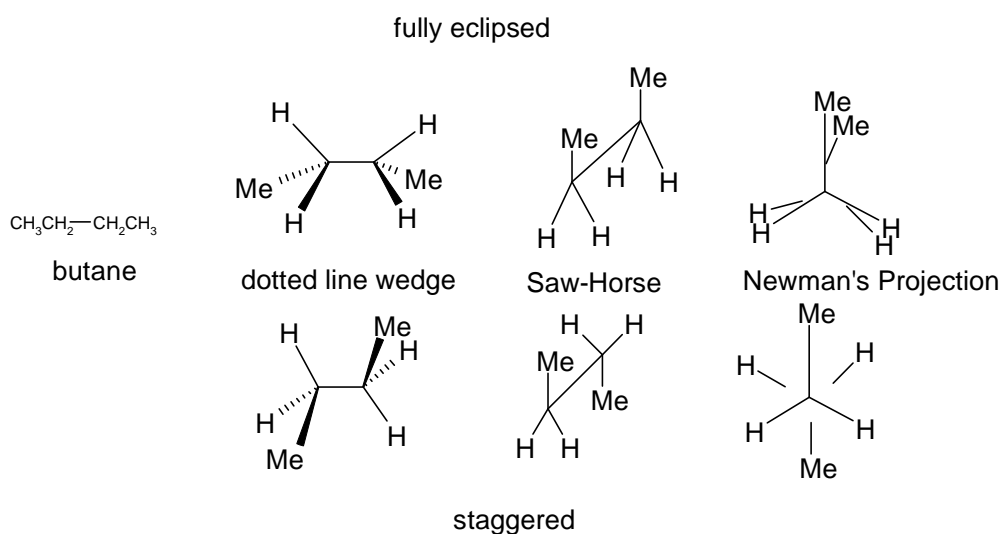


Fig.8: Conformers of butane by all three methods

The gauche or skew forms are better shown by Newman's Projection formula as shown in Fig.9

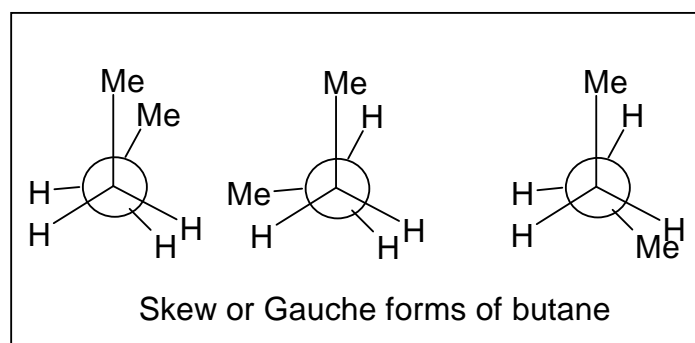


Fig.9: Skew or Gauche forms by Newman's projection method

1.3 Conformations and conformational analysis of ethane and n-butane by Newman's Projection formula with the help of energy profile diagrams.

Conformational isomerism is a form of stereoisomerism in which the isomers can be interconverted exclusively by rotations about single bonds. Such isomers are generally referred to as **conformations** or **conformers** or **rotamers**. These different conformations of ethane can be represented as shown in Fig.10

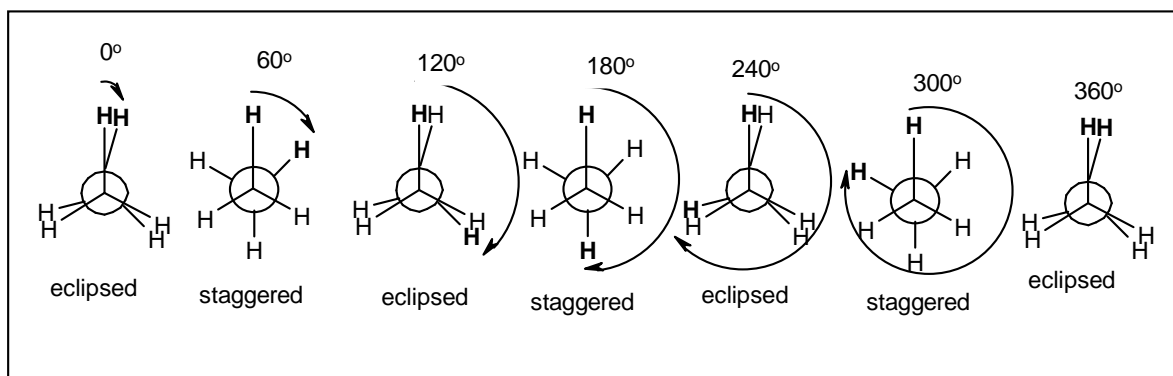


Fig.10: conformational isomers of ethane

Rotations about single bonds are restricted by a rotational energy barrier which must be overcome to interconvert one conformer to another. The study of the energetics between different rotamers is referred to as **conformational analysis**.

Conformational Analysis: Ethane

Every conformer is associated with some potential energy due to the torsional strain in the molecule. Torsional strain is due to torsional interaction, i.e. the strain due to nearest bond electrons which try to repel each other. This bond electron repulsion causes more strain when the electrons are nearest to each other. Hence the distance between the two substituent electrons depends on the angle between the adjacent C-H bonds. This angle between any two nearest carbon-hydrogen bonds is called the dihedral angle. As this angle is 0° in eclipsed conformations, there is extreme bond electron repulsion due to the torsional (bond opposition) strain and hence the eclipsed conformer is less stable and is associated with the potential energy of 3 Kcal/mol (12 KJ/mol).

When the molecule of ethane is rotated along the C-C bond, with the change in angle of rotation (from 0° to 360°), the angle between any two nearest carbon-hydrogen bonds called the dihedral angle also changes between 0° to 60°.

In the staggered conformer the dihedral angle is 60°, the C-H bond electrons remain as far away from each other as possible. Hence there is comparatively less severe bond repulsion and the staggered conformer is most stable and the potential energy of the molecule is at the minimum for the staggered conformation.

Consequently, the potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown below. This variation of energy associated with different conformers of ethane w.r.t. the angle of rotation is called conformational analysis. The potential energy of the molecule is at the minimum for the staggered conformation which increases with rotation and reaches maximum at the eclipsed conformation. This energy profile is represented as shown in Fig.11

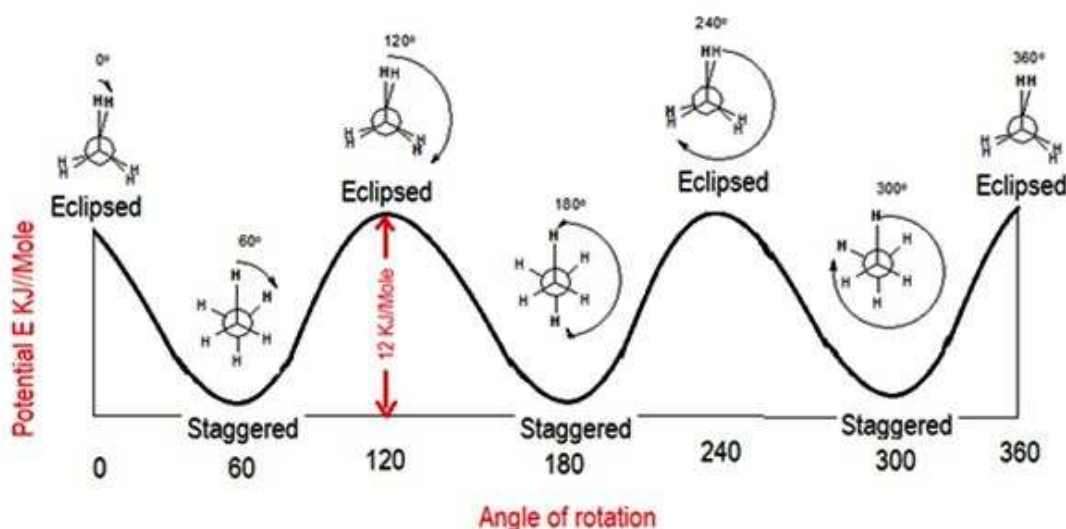


Fig.11: Conformational Analysis of ethane

In short, the energy required to rotate the ethane molecule about the C-C bond is called torsional energy. The relative instability of the eclipsed or skew forms is due to the torsional strain caused from interaction among the electron clouds of the C-H bonds. Hence the dihedral angle i.e. the angle between the two C-H bonds of the two carbon atoms affects the stability. When the rotational angle is 0° , 120° , 240° and 360° , ethane molecule is in the eclipsed conformation. Here the electron clouds of the C-H bonds are very near to each other. Therefore, the eclipsed conformers are associated with potential energy of 12 KJ per mole. However, when the rotational angle is 60° , 180° , 300° ; ethane molecule is in the most stable staggered conformation and is associated with minimum or zero potential energy. Hence, most of the ethane molecules naturally exist in the staggered conformation or, any molecule spends most of its time in the most stable staggered conformation.

Conformational Analysis: Butane

In butane we have three C-C bonds, still, focussing our attention on the middle C-C bond, we see a molecule similar to ethane, but with a methyl group replacing one hydrogen on each carbon. Butane shows conformations as shown in Fig. 12

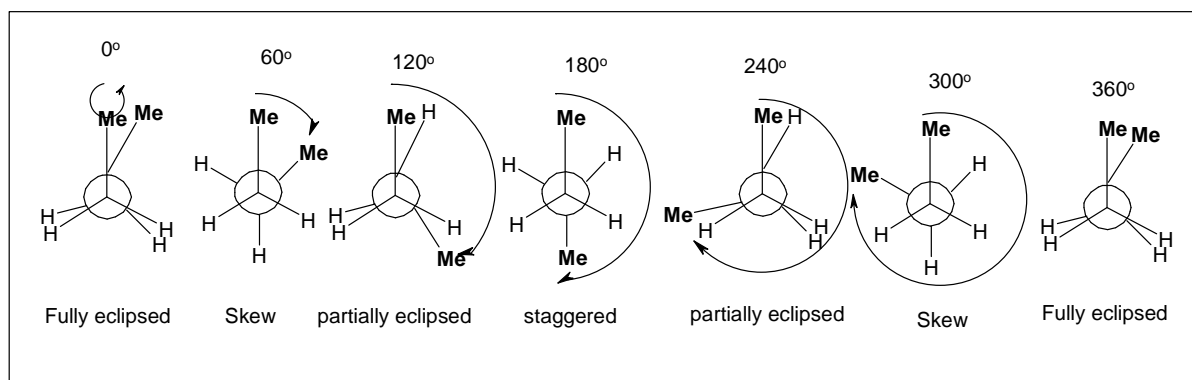


Fig. 12: Conformers of butane

Fully eclipsed or Synperiplanar: The conformers with dihedral angle 0° or 360° , where the methyl group of one carbon and methyl of the other are overlapping each other; are associated with energy 18.4 to 25.5KJ than the staggered conformation, hence are called fully eclipsed conformers.

Skew/gauche or Synclinal: The conformers with dihedral angle 60° and 300° , where the two bulky methyl groups are at the angle of 60° from each other; are associated with energy 4 KJ than the staggered conformation, hence are called skew or gauche conformers.

Partially eclipsed or Anticlinal: The conformers with dihedral angle 120° and 240° , where the methyl group of one carbon and hydrogen of the other are overlapping each other; are associated with energy 14.7 KJ than the staggered conformation, hence are called partially eclipsed conformers.

Staggered or Anti or Antiperiplanar: As with ethane, staggered conformation has lowest torsional energy and hence it is most stable conformation with methyl groups as far apart as possible with dihedral angle 180° .

The staggered conformers are highly stable hence less energetic. The fully eclipsed forms are least stable and hence highly energetic. The partially eclipsed forms are less stable

than the skew forms and more stable than the fully eclipsed forms. The energy difference indicates the energy required to convert one form into another. This energy profile is represented as shown in Fig.13

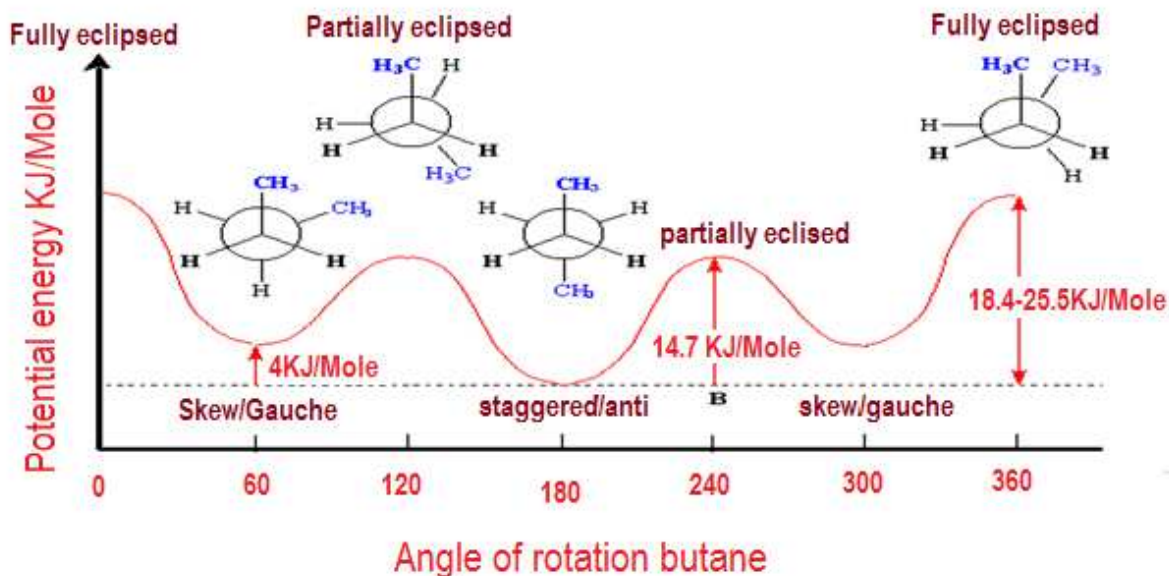







Fig.13: Conformational Analysis of butane

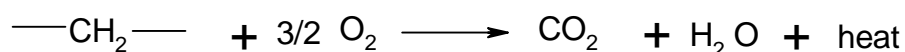
1.4 Cycloalkanes relative stability - Baeyer's strain theory, Theory of strainless rings.

Aliphatic saturated cyclic derivatives of the hydrocarbons are called cycloalkanes. The cycloalkanes may have 3/4/5/6/7 or more members in the ring. Depending upon the number of atoms in the ring they are named as cyclo derivatives of the parent hydrocarbon.

Structure					
Common Name:	Tri methylene	Tetra methylene	Penta methylene	Hexa methylene	Hepta methylene
IUPAC name:	Cyclo propane	Cyclo butane	Cyclo pentane	Cyclo hexane	Cyclo heptane

The relative stability of these different cycloalkanes is judged from their tendency to undergo ring opening reactions and heats of combustion.

Heat of combustion is the quantity of heat evolved when one mole of a compound is burned to carbon dioxide and water.



Heat of combustion can often furnish valuable information about the relative stabilities of organic compounds. The table.1 represents the values of heats of combustion of different cycloalkanes.

Ring size	Heat of combustion per CH ₂ ,Kcal/mol	Ring size	Heat of combustion per CH ₂ ,Kcal/mol
Open chain	157.4	9	158.8
3	166.6	10	158.6
4	164.0	11	158.4
5	158.7	12	157.6
6	157.4	13	157.8
7	158.3	14	157.4
8	158.6	15	157.5

Table 1: Heats of combustion for different cycloalkanes

We notice that for cyclopropane, the heat of combustion per -CH₂-group is 9kcal higher than the open chain value of 157.4. For cyclobutane it is 7 kcal higher than the open chain value. This indicates that they contain more energy per -CH₂- group. Hence cyclopropane and cyclobutane are less stable than open chain compounds. However, the rings larger than cyclopentane do not show much deviation from the open chain value, indicating the comparable stability of the rings with open chain compounds.

Baeyer strain theory: In 1885 Adolf von Baeyer proposed a theory to account for certain aspects of the chemistry of cyclic compounds. His argument was based on the deviation of bond angles from the ideal tetrahedral angle (109.5°) of the aliphatic carbon atom. When carbon is bonded to four other atoms, the angle between any pair of bonds is the tetrahedral angle 109.5°.

Hence according to Baeyers strain theory, The stability of the cycloalkanes is affected by the C-C bond angles of the carbons in the ring. When the deviation of these C-C bond angles from the tetrahedral angle is more, the molecule is more unstable. Hence, cyclopropane and cyclobutane are highly strained due to the angle of 60° and 90°

respectively. The angles of a pentagon (108°) are very close to the tetrahedral angle 109.5° and hence should be virtually strain free. Thus according to Baeyer, The angles of regular hexagon (120°) are somewhat larger than the tetrahedral angle and thus cyclohexane should be associated with certain strain and hence must be unstable. Hence, rings larger than cyclohexane also should be unstable due to expected deviation of their angles from tetrahedral angle and strain associated with it.

However, the observations of the heats of combustion values show that none of the rings larger than four carbons does the heat of combustion per $-\text{CH}_2-$ deviate much from the open chain value. Hence in fact all these rings are stable enough and show little tendency to undergo ring opening reactions.

This is because, the angles that Baeyer used for each ring were based on the assumption that the rings are flat. For such flat rings the angles are more than the tetrahedral angle. i.e for hexagon it is 120° and for decagon it is expected to be 144° . But actually, the cyclohexane ring is not a regular flat hexagon, but is puckered such that each bond angle of carbon can be a tetrahedral angle 109.5° . Hence cyclohexane is present in the puckered form as shown in Fig. 14

1.5 Conformations and stability of cyclohexane and monosubstituted cyclohexanes Cyclohexanol, bromocyclohexane and methyl cyclohexane.

If we look more closely at the puckered ring of cyclohexane, we find that the molecule can have different forms as shown below.

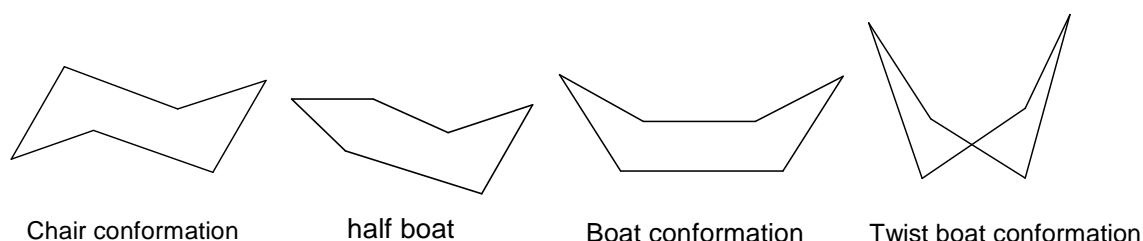


Fig.14: Different conformers of cyclohexane

These different forms are named as the chair conformation, half boat, boat conformation and twist boat (or skew boat) conformation respectively. Out of which the chair

conformation must be the highly stable conformation. The Newman's projection formulae of the conformations are shown as below.

Note 3: while drawing the cyclohexane molecule in Newman's projection formulae one has to view the model from the direction such that the C_2 and C_6 are shown by dots or points and C_3 and C_5 are shown by the circles and the position of C_1 and C_4 are shown by joined lines from the respective carbons. (As shown in Fig. 15)

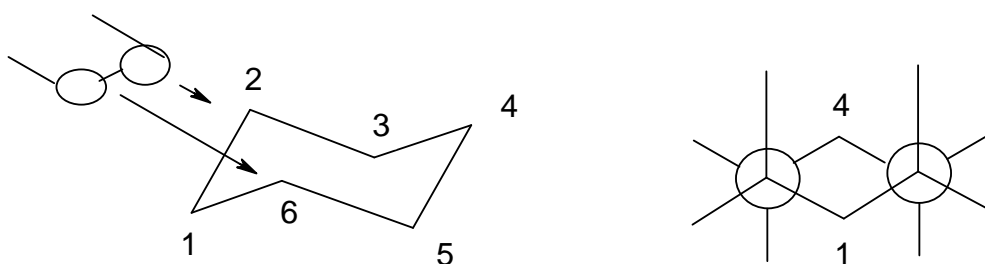


Fig.15: Newman's projection formula for cyclohexane (Chair form)

Chair conformation shows that every carbon in the conformation has a staggered form which is highly stable. Hence chair conformation is the most stable conformation of the cyclohexane. The C-H bonds on each carbon are of two types namely axial and equatorial as shown in the Fig.16.

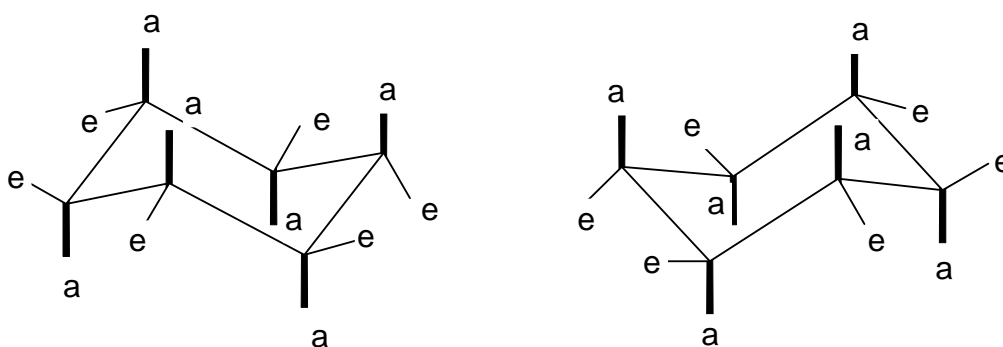


Fig.16: two chair forms of cyclohexane (Axial: a, Equatorial: e)

The conversion from one chair shape to the other is called **ring flipping** or **chair-flipping**. Carbon-hydrogen bonds that are axial in one configuration become equatorial in the other, and vice-versa.

In cyclohexane, the two chair conformations have the same energy. At 25°C, 99.99% of all molecules in a cyclohexane solution will be in a chair conformation.

If this chair form is flipped by rotation around the C-C bonds, we get the another conformation called Boat conformation. The Newmann's projection formulae of the conformations are shown in Fig.17

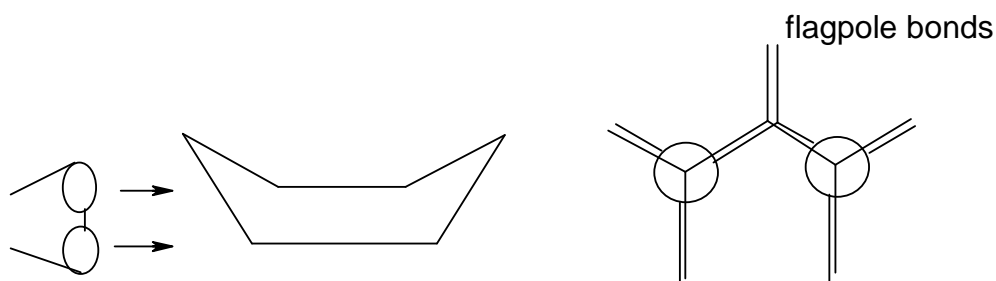


Fig.17: Newman's Projection formulae of boat conformation

This conformation is least stable due to the flag pole bonds which are very much close to each other. As shown in Fig.18

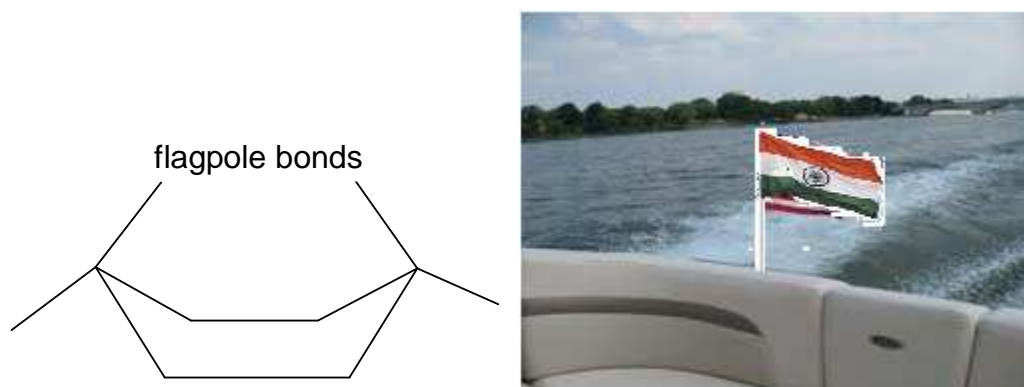


Fig.18: Flagpole bond interaction

Conformational analysis:

Chair form is the most stable form as there is no angle strain, as well as no bond opposition (eclipsing) strain. Hence it is having minimum potential energy (point a in Fig.19).

When the bottom part of the chair is bent upward, we get the half boat conformation. During this transformation, some angular distortion is required because several

bonds have to be rotated at the same time. Hence the molecule passes through high potential energy of about 10-11 Kcal/mole (point b in fig. 19).

Half boat form is immediately converted to comparatively more stable boat form. In the boat form though there is no angle strain as all angles are about 109.5° , but there is bond opposition strain of the type that is seen in eclipsed form of ethane. The pair of hydrogens at the flagpoles are only 1.8 Å apart, where the van der Waals radii of two hydrogens is 2.4 Å. This is called bowsprit-flagpole interaction, due to which the boat form is considerably less stable than the chair (Point d in fig. 19).

While passing from one boat form to another boat form the molecule goes through different twists showing different flexible forms called as skew boat or twist boat conformations. These forms have some relief in the bowsprit flagpole interaction as well as eclipsing of adjacent hydrogens. Hence it is having less energy than the boat form (point c in fig. 19)

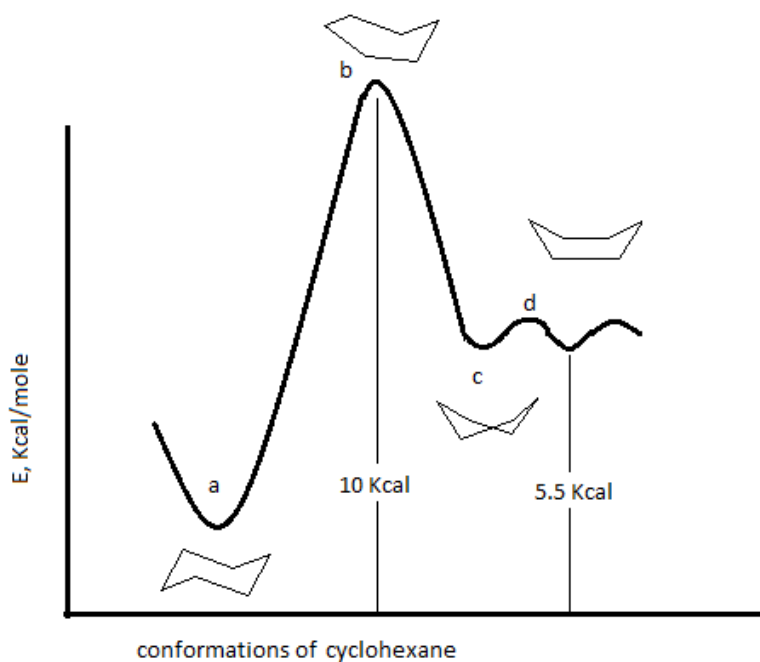


Fig.19: Conformational Analysis of cyclohexane

Conformations of monosubstituted cyclohexane:

When one hydrogen from cyclohexane is replaced by a substituent like OH, Br or CH_3 group; we get monosubstituted cyclohexanes namely cyclohexanol,

bromocyclohexane and methyl cyclohexane respectively. These monosubstituted cyclohexane molecules also show conformational isomerism such that the most stable conformers of them are chair conformations. But, unlike unsubstituted cyclohexane, there are two different chair conformations as shown in Fig.20, which have different energies, depending upon the identity and location of the substituents.

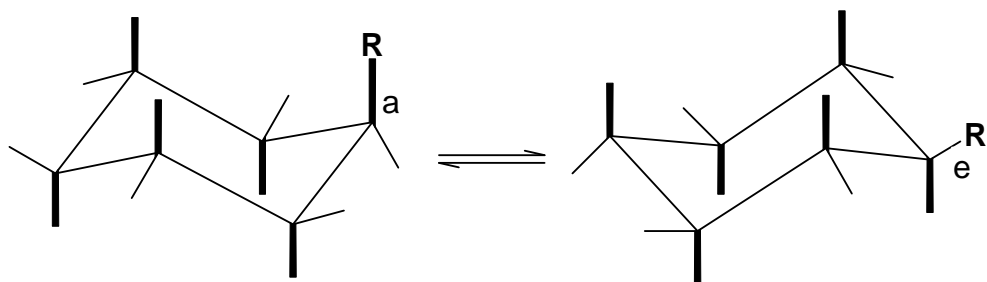


Fig 20: A form & E form: substituent is at axial or equatorial position

For example, in methylcyclohexane the lowest energy conformation is a chair one where the methyl group is in equatorial position i.e. 'E' form is more stable than A form. This is because, E configuration has less interactions between the methyl group (on C₁) and the hydrogens at C₃ and C₅; more importantly, the methyl group at C₁ and C₃ are away from each other and thus there is no interaction between them as seen in the gauche form of butane. Whereas, in 'A' form the methyl group at C₁ and C₃ are close to each other and thus there is interaction between them as seen in gauche form of butane. This is seen clearly from the Newman's projection formulae of the E and A chair forms, where the substituent is at equatorial and axial position respectively as shown in Fig.21.

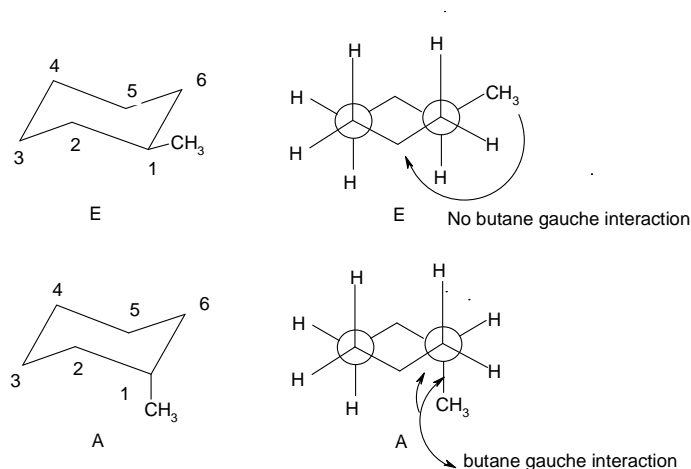


Fig.21: Butane gauche interactions in A and E forms

In addition to the axial/equatorial placement of the alkyl group, the orientation of the atoms within the alkyl group will affect the energy.(Fig.22)

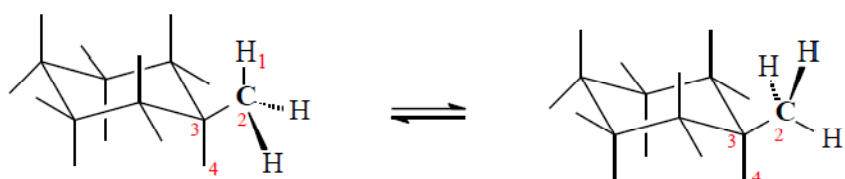


Fig.22: Orientation of methyl hydrogens and C₁ hydrogens

In the left-hand conformer, the C-H bonds in the methyl group are all staggered with the ring carbons and axial hydrogen; in the right-hand conformer, the methyl hydrogens eclipse the C-C and C-H bonds of the ring, a higher energy conformation (e.g. H₁ and H₄).

Hence the most stable conformation in methyl cyclohexane is the chair form in which the methyl group is at equatorial position and in staggered conformation with the C₁.

Similarly cyclohexanol and bromocyclohexane too have their most stable conformers where the substituent OH or Br are at the equatorial position i.e. E forms. However the equatorially substituted chair can be readily converted into axially substituted chair form by ring flipping. At room temperature, both isomers are present in rapidly established equilibrium; with about 95% of the molecules in the E form and remaining in the A form.

The energy difference between the E and A conformational isomers depends on the nature of substituent as given in the table 2.

Derivative	Energy difference Kcal/mole
Methyl cyclohexane	1.6-1.8
Cyclohexanol	0.4-0.9
Bromocyclohexane	0.2-0.7

Table 2: Energy difference in E and A forms

1.6 Locking of conformation in t-butyl cyclohexane.

We have seen that the monosubstituted cyclohexane molecules also show conformational isomerism such that the most stable conformers of them are chair conformations and the two chair conformations E and A have different energies, depending upon the identity and location of the substituents. In general, large groups will generally prefer to occupy an equatorial position where there is an absence of 1,3-diaxial (steric) interactions as shown in Fig.23

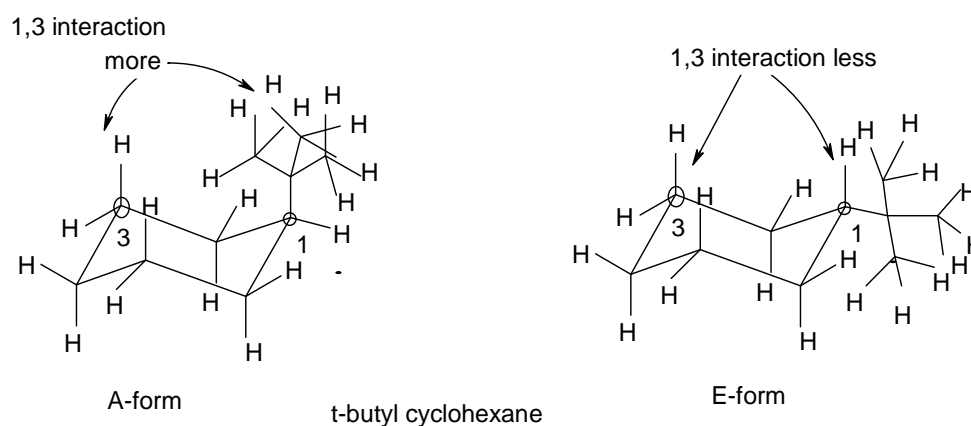


Fig 23: 1,3-diaxial interactions in A-form and E-forms of t-butyl cyclohexane

However, the axial conformation will also be present, but in smaller amount. But in case of t-butyl cyclohexane, the tertiary butyl group basically “locks” the ring in a chair with the *tert* -butyl group in the equatorial position as it is too big a group to go into the axial position such that there is so little axial conformer that it is difficult to measure any real value of free energy associated with it. The energy is said to be minimum 5 Kcal/mole. Hence the bulky tertiary butyl group almost remains locked as equatorial. This is evident from the equilibrium constant K_a which is in favour of the equatorial chair conformation as shown in Fig. 24

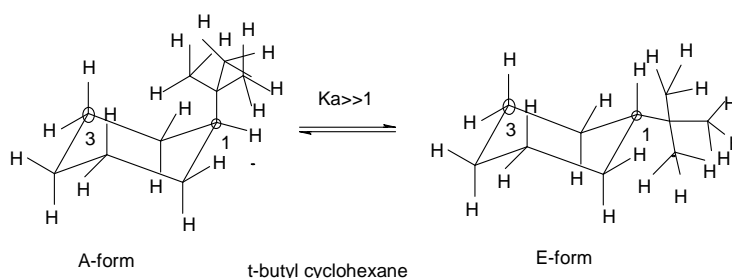


Fig.24: equilibrium between A and E forms

Hence almost all the molecules of t-butyl cyclohexane remain in E-chair form.

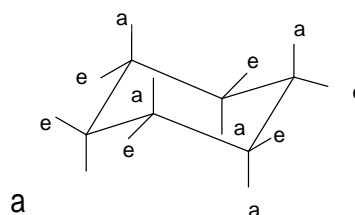
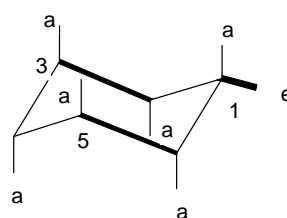
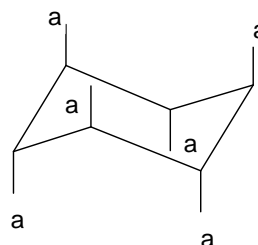
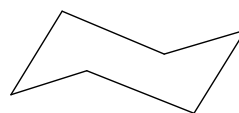
Note 4: How to draw stereoisomers of cyclohexane?

(1) Begin with the chair conformation of cyclohexane.

(2) Draw the axial bonds before the equatorial ones, alternating their direction on adjacent atoms. Always start by placing an axial bond “up” on the uppermost carbon or “down” on the lowest carbon. Then alternate such that all the axial bonds are parallel to one another

(3) Place the equatorial bonds so as to approximate a tetrahedral arrangement of the bonds to each carbon. The equatorial bond of each carbon should be parallel to the bonds of its second next neighbour carbons. Eg. Place equatorial bond at C-1 so that it is parallel to the bonds between C-2 and C-3 and between C-5 and C-6.

Following this pattern gives the complete set of equatorial bonds.



1.7 Stereoselective and stereospecific reactions:

When the reaction occurs, old bonds are broken and new ones are made. While these transformations are occurring in the molecule, the mechanism of the reaction i.e. the attack of the reagent on the reactant is highly important and decides the stereochemistry of the product. Taking into consideration the effect of the reaction on the stereochemistry of the products, the reactions can be named as stereoselective and stereospecific reactions as follows.

Stereoselective reactions:

A **stereoselective** reaction is one in which a single reactant can give two or more stereoisomeric products, and one or more of these products is preferred over the others—even if the preference is very small. Here, the given substrate produces diastereoisomeric products in different amounts. If one diastereoisomer predominates very much over the other, the

reaction is said to be highly stereo selective. If the two products are formed in almost equal amounts, the reaction is then said to be weakly stereo selective.

Stereospecific reactions:

The reactions in which stereoisomerically different starting material react differently and give rise to stereoisomerically different product. i.e one stereoisomer of the reactant gives one stereoisomer of the product, while a different stereoisomer of the reactant gives a different stereoisomer of product. Hence, to determine whether a reaction is stereospecific, one has to examine the product ratio from the different stereoisomers of the reactant. It is a reaction in which the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option.

*Note 5: "Selective" implies that there are factors which **favour** one product over the other, while "specific" is usually a sign that there's something inherent to the mechanism that leads to only **one** product.*

Example: The addition of halogens to alkenes is both stereoselective and stereospecific which gives us additional information about the stereochemistry of the addition and the mechanism for the reaction.

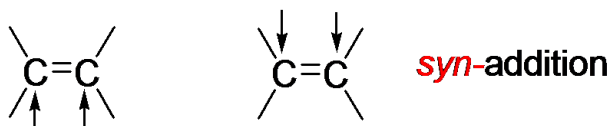
i) Stereochemistry of addition of halogens to alkenes: syn and anti addition.

Addition Reaction:

Addition can be of two types as Syn- and Anti- addition depending upon the approach of the reagent towards substrate.

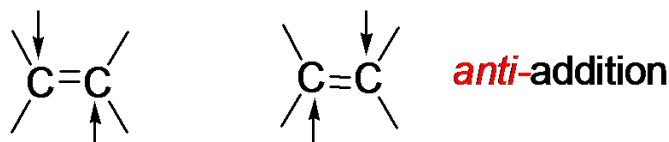
Syn-addition:

When both parts of the addendum approach the substrate from the same side/face of the molecular plane, the addition is called Syn-addition.



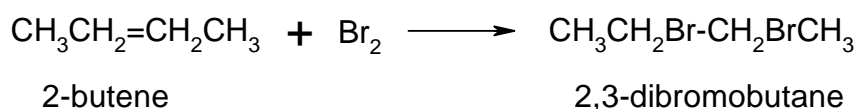
Anti-addition:

When the both parts of the addendum approach the substrate from the opposite side/face of the molecular plane, the addition is called Anti-addition.



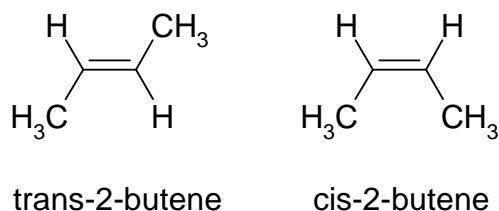
Example- Addition of bromine to 2-butene.

The addition of bromine to 2 butene can be represented as follows



Stereochemistry of reactants and products:

The reactant 2-butene exists as 2 geometric isomers as cis and trans 2-butene.



The product of addition of bromine 2,3-dibromobutane has two asymmetric carbon atoms. Hence the number of isomers possible are 2^2 , i.e.4 out of which third and fourth isomers are one and the same hence there are in all 3 isomers possible as shown in Fig. 24 as d and l and meso isomers. These are also named as (S,S)-,(R,R)-,and(R,S) forms in R & S nomenclature system as shown in Fig. 25

Note 6: R and S system of nomenclature for optical isomers: Step I. Assign the priority to the groups attached to asymmetric carbon atom as per the Cahn Ingold Prelog rules Step II: Assigning the configuration: Arrange the molecule in such a way that the group with highest priority goes to the top and the group with lowest priority goes back and the two groups with mid priority come forth on both sides. Now moving the eyes from group number 1 to 3 in decreasing order of priority, if the eyes move in clockwise direction, the molecule is assigned the configuration R otherwise it is S. In above example, (R,R) or (S,S) or (R,S) indicates the R or S configuration of the two asymmetric carbon atoms in the order mentioned. R (for Rectus, Latin for right), S (for Sinister, Latin for left)

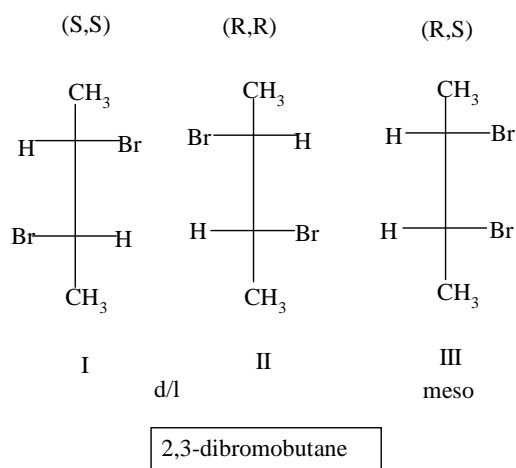
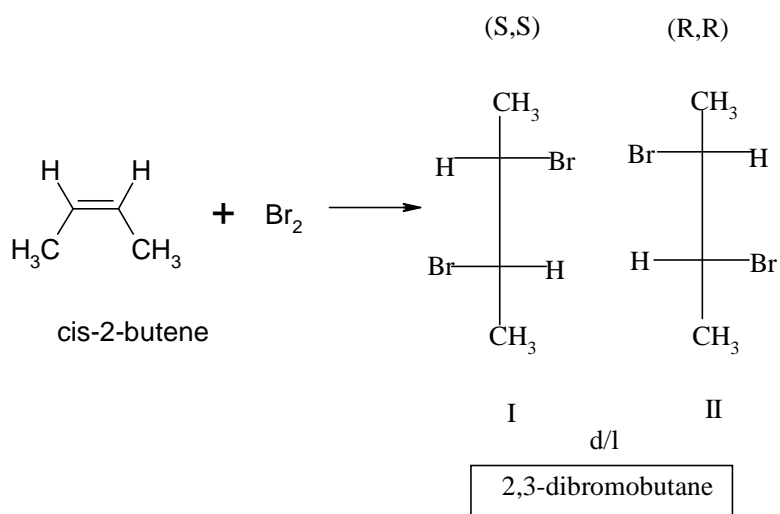
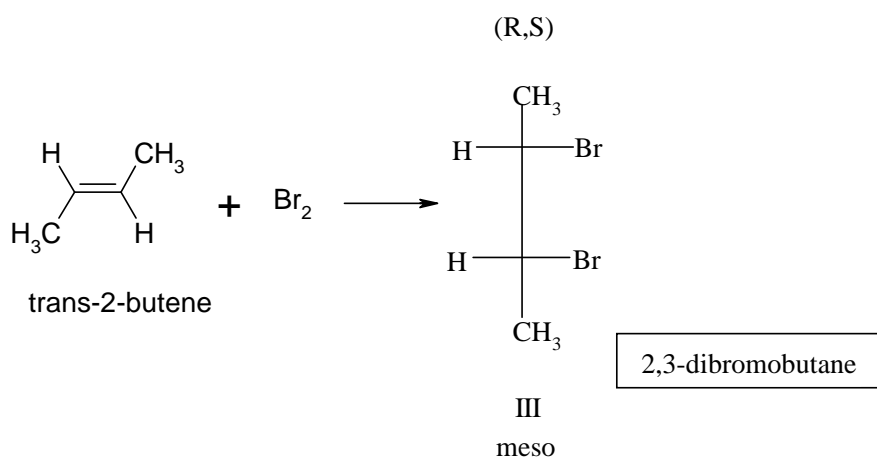


Fig.25: Possible isomers of 2,3-dibromobutane

Observations: If we start with cis-2-butene, on addition of bromine, we get the mixture of 2 products (S,S) and (R,R)-2,3-dibromobutane. As both the stereoisomers are formed this reaction is stereoselective.



Whereas the trans-2-butene gives rise to only meso- 2,3-dibromobutane as product. As only meso product is formed, the reaction is said to be stereospecific.



This is observed because the addition of bromine to 2-butene is Anti-addition. The reaction is initiated by electrophilic attack of the Br^+ on the double bond resulting into the formation of bromonium ion intermediate. Hence the attack of Br^- occurs from backside to form the C-Br bond. Hence from trans-2-butene, we get meso-2,3-dibromobutane. This can be understood well with the help of mechanism shown in Fig.26.

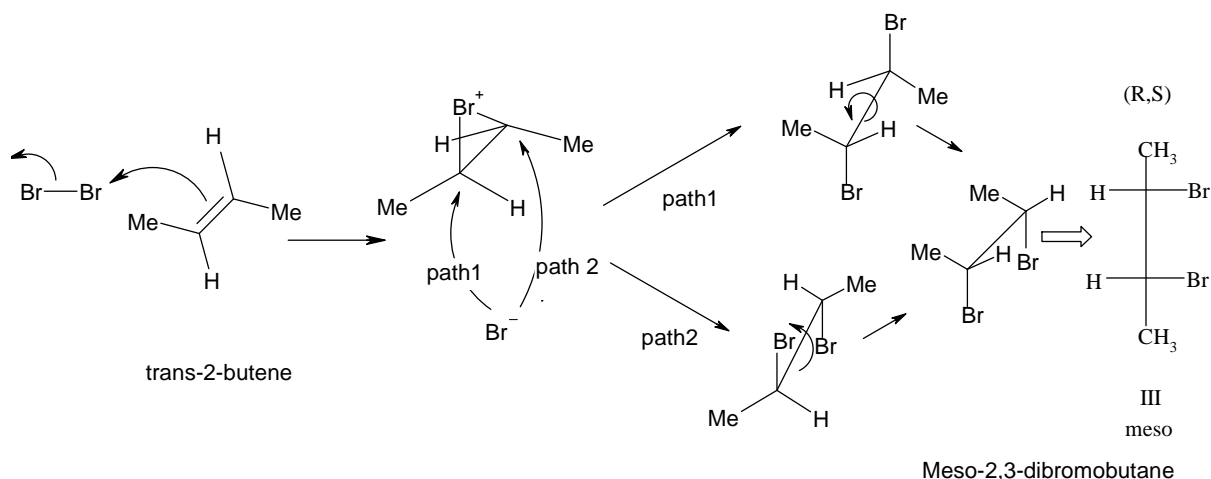


Fig. 26: mechanism of addition of bromine to trans-2-butene (Saw-Horse method)

The same can be understood with the help of Newman's projection formulae as shown in Fig.27.

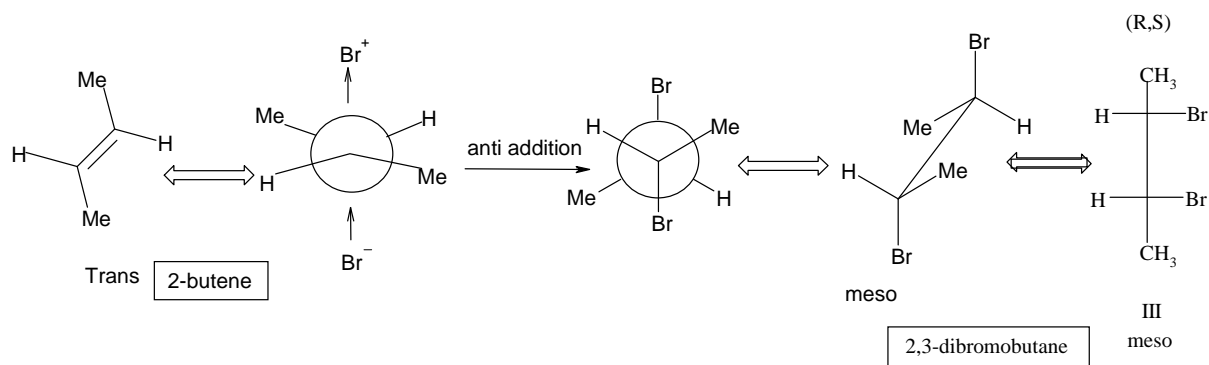


Fig.27: Mechanism of addition of bromine to trans-2-butene by Newman's projection formulae

Whereas, from cis -2-butene we get racemic mixture of *d*- and *l*- 2,3-dibromobutane.(Fig.28)

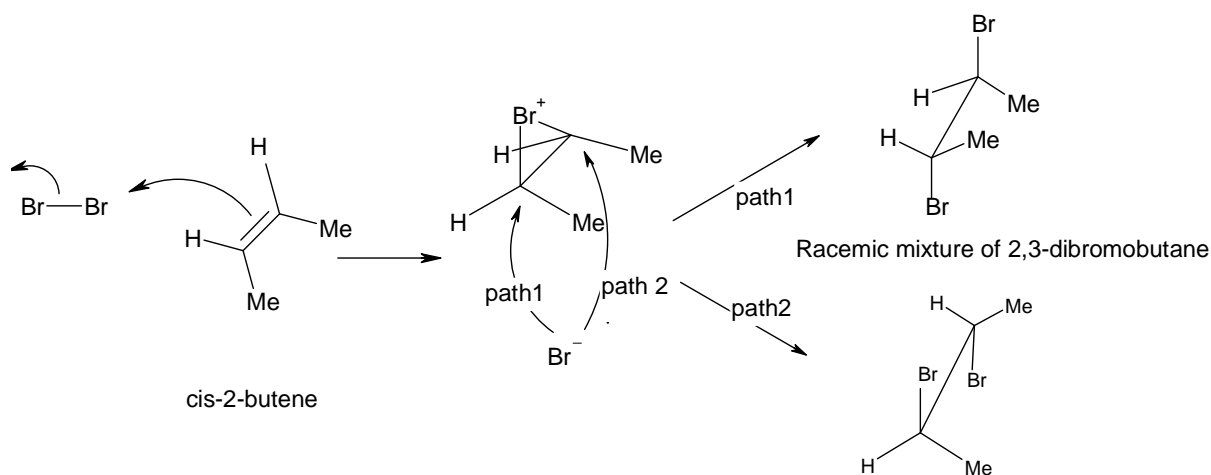


Fig. 28: mechanism of addition of bromine to cis-2-butene (Saw-Horse method)

The same can be understood with the help of Newman's projection formulae.(Fig.29)

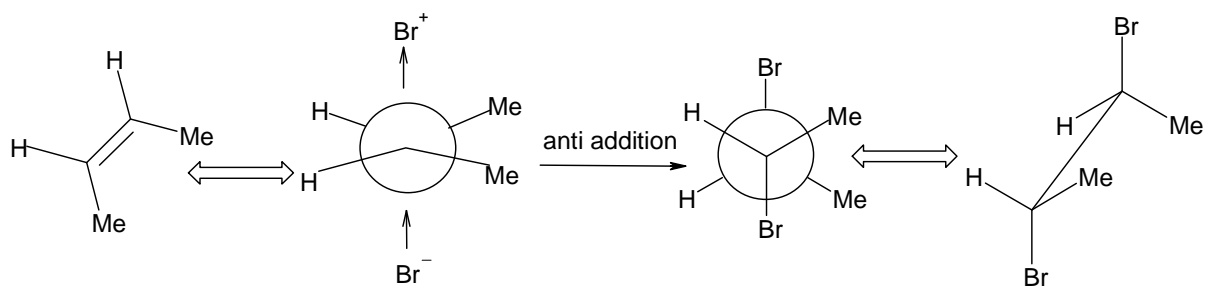


Fig.29: Mechanism of addition of bromine to cis-2-butene by Newman's projection formulae

ii) Stereochemistry of elimination reaction: syn and anti elimination.

Similar to addition reactions, the elimination reactions also can be syn and anti depending upon the direction of the two groups or atoms getting eliminated from the saturated compound to give unsaturated compound. As in unsaturated compounds, there is restricted rotation due to the newly created double bond, the products may show geometrical isomerism. The formation of the product as cis or trans isomer depends on the substrate and the mechanism.

Syn elimination:

The elimination reactions, where the groups are eliminated from the same face or direction of the molecule, is called Syn elimination. Syn elimination is less favorable than anti elimination because the molecule must be in a higher-energy eclipsed conformation for syn elimination to occur.(Fig.30)

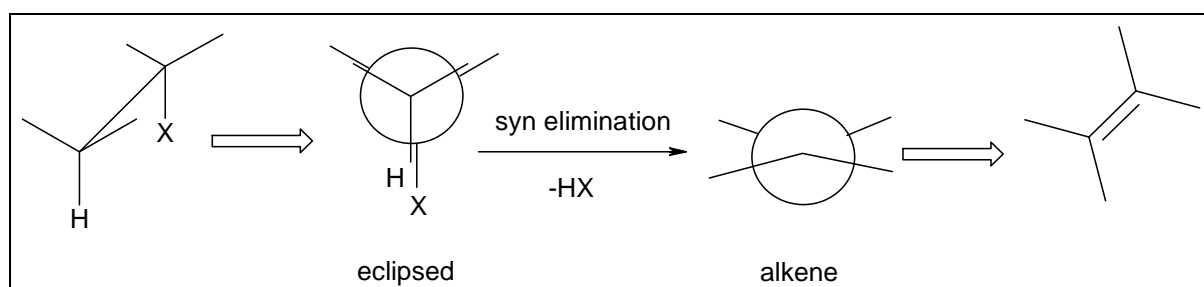


Fig.30: Syn elimination

Anti elimination:

The elimination reactions, where the groups are eliminated from the opposite face or direction of the molecule, is called Anti elimination. This is favourable as most of the saturated compounds are in their most stable staggered conformation where the groups getting eliminated are at the favourable angle of 180° . (Fig.31)

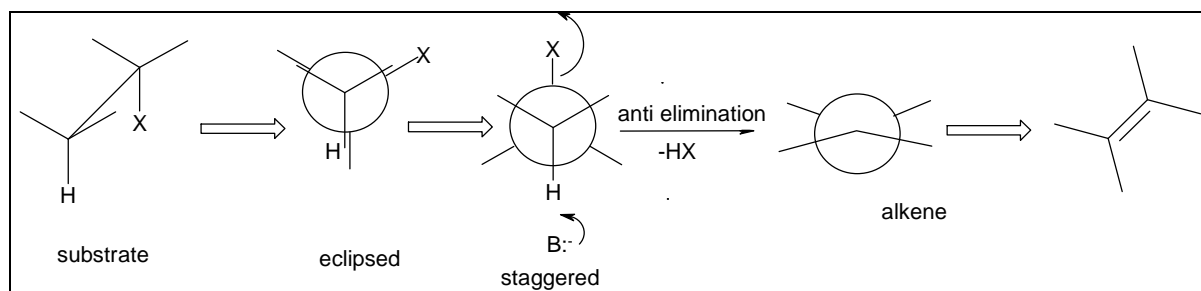


Fig.31: Anti elimination

Example-Dehydrohalogenation of 1-bromo-1,2-diphenylpropane. (mechanism not expected)

The reaction of dehydrohalogenation is a kind of anti elimination, where the proton and the halide are eliminated which are on the opposite side at 180° .

1-bromo-1,2-diphenylpropane has two asymmetric carbon atoms, hence four optical isomers are possible. All I,II,III and IV are optical isomers and the pairs (I & II) , (III & IV) are mirror images of each other, hence called 'enantiomers' named as *erythro* and *threo* as shown in Fig.32.

In isomers I and II, the like groups (both hydrogens) are on the same side, hence they are named as *erythro* isomers. Whereas, in III and IV, the like groups are on the opposite side, hence they are named as *threo* isomers.

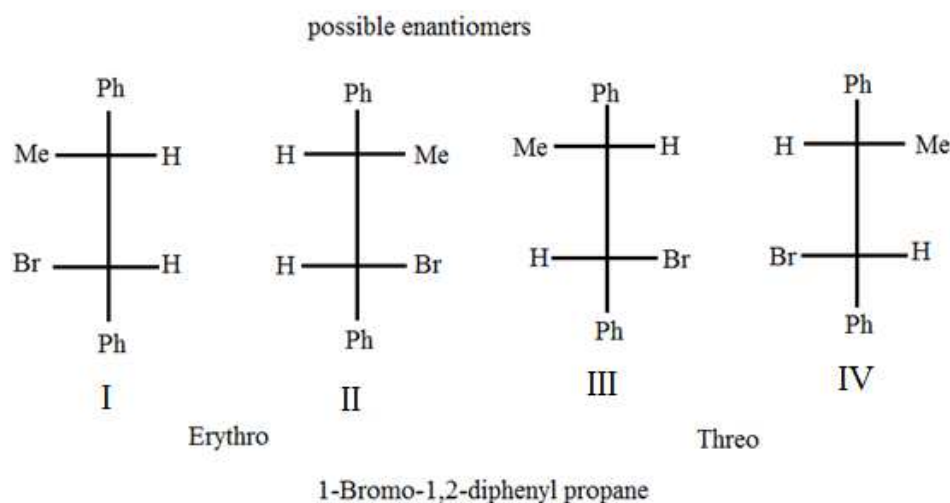
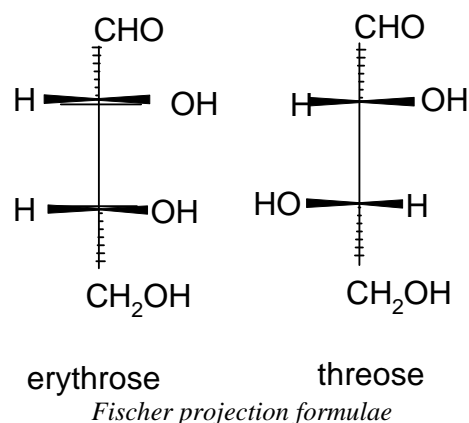


Fig. 32: Possible isomers of 1-bromo-,1,2-diphenyl propane

Note 6: draw the compound in a Fischer projection with the distinguishing groups on the top and bottom. In a Fischer projection, the horizontal lines represent bonds coming out of the plane of the paper, while the vertical lines represent bonds projecting behind the plane of the paper.

Erythro: when the two similar groups are on the same side, as in the sugar erythrose, the form is called erythro form.

Threo: when the two similar groups are on the opposite side as in the sugar threose, the form is called threo form.



In the dehydrohalogenation reaction, both the *erythro* and *threo* forms give rise to different products.

If we start with the *erythro* halide (I and II) where the two like groups (hydrogens) are on the same side of carbon chain as shown in Fischer's projection **A** (where all the dotted line and wedges are drawn as simple lines to avoid confusion); can be drawn as Saw Horse formula **B**, which can be better imagined as eclipsed form where two hydrogen atoms overlap each other. **C** (Fig. 33) Keeping the same configuration, if we try to draw the most stable staggered conformer of the molecule **D** such that the two leaving groups are on opposite sides at 180° angle from each other **D'**, we can see the anti elimination of the HBr causes formation of the cis or Z isomer of the product alkene as can be understood well with structures of alkene as **E** and **F**. Thus from erythro form, we obtain only the Cis or Z alkene (Fig.33)

If we start with the *threo* halide (III and IV) we obtain E alkene. The *threo* halide (III and IV) where the two like groups (hydrogens) are on the opposite side of carbon chain as shown in Fischers projection **A**; can be drawn as Saw Horse formula **B**, which can be better imagined as eclipsed form where two hydrogen atoms do not overlap each other. **C** (Fig.34) Keeping the same configuration, if we try to draw the most stable staggered conformer **D** of the molecule such that the two leaving groups are on opposite sides at 180° angle from each other **D'**, we can see the anti elimination of the HBr causes formation of the Trans or E isomer of the product alkene as can be understood well with structures of alkene as **E** and **F**. Thus from *threo* form, we obtain only the Trans or E alkene. (Fig.34)

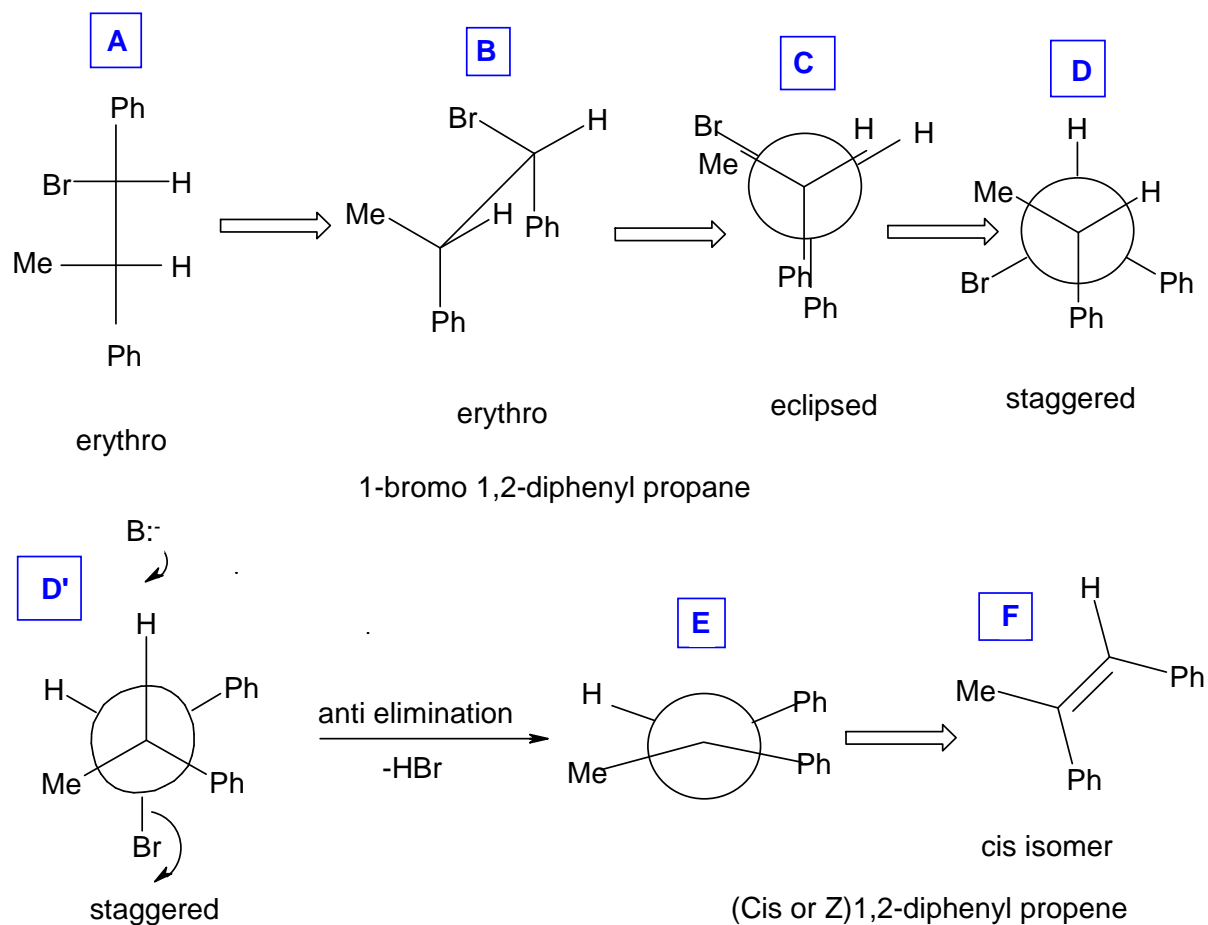


Fig 33: Representation of different forms of the *erythro* halide to understand the formation of Cis alkene on anti elimination of HBr

Note 7: E-Z system: Assign the priority to the groups attached to doubly bonded carbon atoms separately as per the Cahn Ingold Prelog rules i.e. in decreasing order of atomic number. If the two high priority groups or atoms lie on the same side of the double bond, the system is Z (zusammen); if they are on opposite sides, the system is E (entgegen).

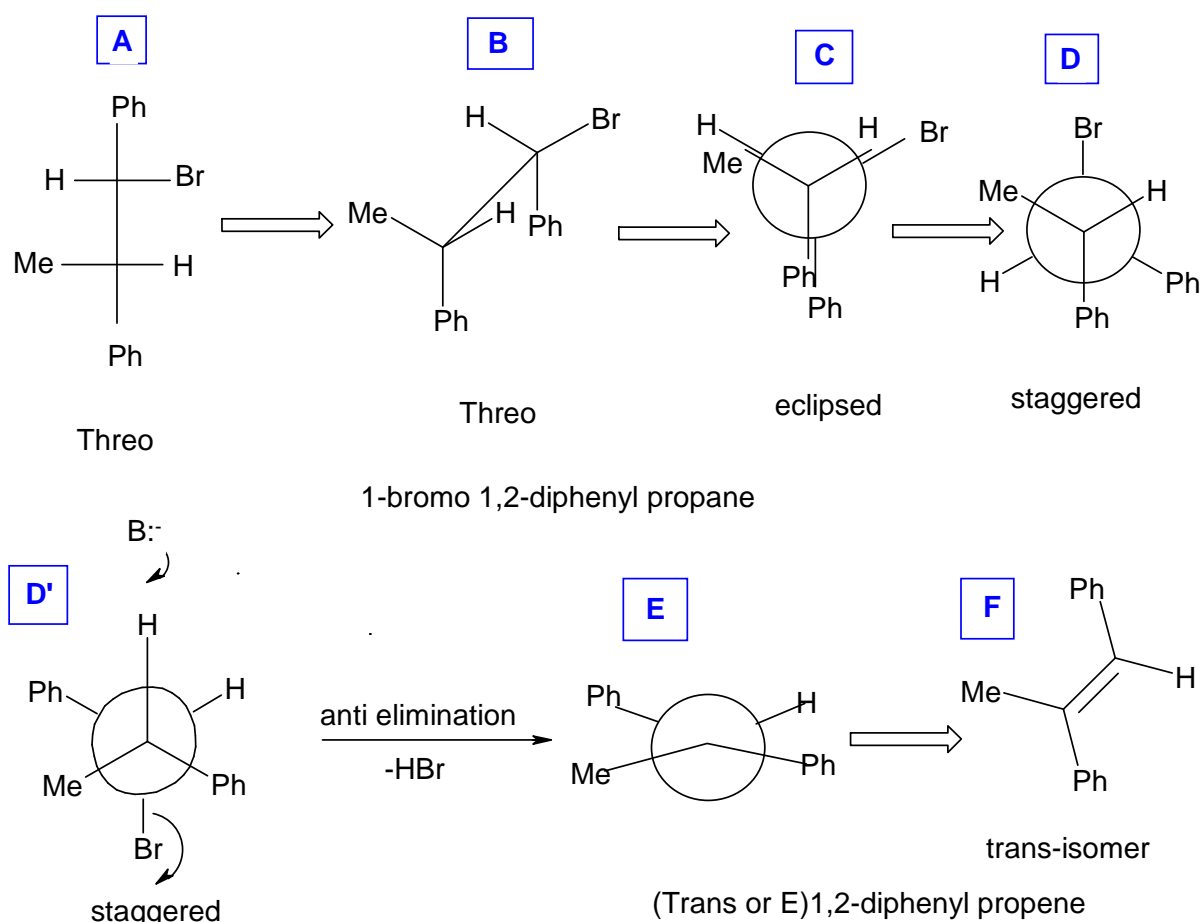


Fig 34: Representation of different forms of the *threo* halide to understand the formation of Trans alkene on anti elimination of HBr

Summary: (points to remember):

- Stereoisomerism is the phenomenon where, the isomers have identical molecular and structural formula but differ only in the spatial arrangement of groups or atoms (or configuration).
- There are two main types of the stereoisomerism as follows.
- Type 1: Configurational Isomerism: Eg. Optical and Geometrical isomerism
- Type 2: Conformational isomerism: different forms of same compound due to free rotation about single bond.
- Types of conformers: Staggered or anti, Skew or gauche, Eclipsed
- Methods of representation of conformers: Saw-Horse, Dotted line and wedge formulae, Newman's projection formulae.
- Conformational analysis of ethane: Staggered conformer is stable than skew and eclipsed.
- Conformational analysis of butane: Staggered conformer is most stable than Skew which are more stable than partially eclipsed which are more stable than fully eclipsed forms.

- Cyclohexane is present in the puckered forms as Chair, half boat, Boat and twist boat forms. Chair form is most stable.
- There are two kinds of bonds in chair: Axial and Equatorial
- In cyclohexane, the two chair conformations are same.
- In monosubstituted cyclohexanes, substituents at Equatorial position are more favoured than Axial ones in the most stable chair forms.
- The reactions which produce one of the two isomers (diastereoisomer or distereoisomeric pair) in majority over the other, are called stereoselective reactions.
- The reactions in which stereoisomerically different starting material react differently and give rise to stereoisomerically different product are called stereospecific reactions.
- Addition can be of two types as Syn- and Anti- addition .
- Addition of bromine to 2-butene is anti addition.
- cis-2-butene, on addition of bromine , gives mixture of 2 products (S,S) and (R,R)-2,3-dibromobutane.
- trans-2-butene on addition of bromine , gives only meso- 2,3-dibromobutane as product.
- Elimination reactions also can be syn and anti depending upon the direction of the two groups or atoms getting eliminated.
- Dehydrohalogenation of 1-bromo-1,2-diphenylpropane is anti elimination. Such that from erythro form, we obtain only the Cis or Z alkene, and from *threo* form, we obtain only the Trans or E alkene.

Exercises

[A] OBJECTIVE TYPE QUESTIONS

I] Select the most correct alternative from among those given below.

1. Isomers, where molecules have the same molecular formula but different connectivity between the atoms are calledisomers.
 - a) configurational
 - b) constitutional
 - c) conformational
 - d) stereochemical
2. An isomerism where the configuration is different and the isomers cannot be interconverted without breaking a bond is calledisomerism.
 - a) configurational
 - b) constitutional
 - c) conformational
 - d) stereochemical
3. Optical and Geometrical isomerism are the two types ofisomerism.
 - a) functional
 - b) constitutional
 - c) conformational
 - d) configurational
4. The isomerism where the isomers are interconvertible by rotations about single bonds is calledisomerism.
 - a) constitutional
 - b) configurational
 - c) conformational
 - d) cis-trans

5. The term is used to denote any of the infinite number of momentary arrangements of the atoms in space resulting from the free rotation about single bonds.
 - a) Conformers b) Rotamers c) conformations d) all of these
6. The conformational isomer when the two groups on the two atoms are as far away as possible is named as conformer.
 - a) Skew b) Gauche c) Staggered d) Eclipsed
7. The conformational isomer when the two groups on the two atoms are as near to each other as possible is named as conformer.
 - a) Skew b) Gauche c) Staggered d) Eclipsed
8. In dotted line wedge method, the bonds in the same plane are represented by
 - a) simple lines b) dotted lines c) points d) wedges or solid lines
9. In dotted line wedge method, the bonds going back to the plane of the paper are shown by
 - a) simple lines b) dotted lines c) points d) wedges or solid lines
10. In dotted line wedge method, the bonds are represented by wedges or solid lines.
 - a) in the plane of the paper b) coming towards the viewer c) going out of plane of paper d) none of these
11. The Gauche or Skew forms can be shown effectively by method.
 - a) Fischer's projection formulae b) Newman's projection formulae c) dotted line and wedge formulae d) Saw-Horse
12. Every conformer is associated with some potential energy due to the in the molecule.
 - a) dis symmetry b) free rotation c) hindrance d) torsional strain
13. In the staggered conformer the dihedral angle is, such that the C-H bond electrons remain away from each other as far as possible.
 - a) 60° b) 0° c) 120° d) 240°
14. The potential energy of the molecule is at the minimum for the conformation.
 - a) Skew b) Gauche c) Staggered d) Eclipsed
15. The potential energy of the molecule increases with rotation and reaches maximum at the conformation.
 - a) Skew b) Gauche c) Staggered d) Eclipsed
16. The variation of energy associated with different conformers of the compound w.r.t. the angle of rotation is called analysis.
 - a) spectral b) physical c) conformational d) constitutional

17. When the rotational angle is 0° , 120° , 240° and 360° , ethane molecule is in theconformation.
 a) Gauche b) eclipsed c) Staggered d) stable
18. The eclipsed conformers of ethane are associated with potential energy of
 a) 12 KJ per mole. b) 3 KJ/Mole c) 12 Kcal/Mole d) 0 KJ/Mole
19. The conformers, where the methyl group of one carbon and methyl of the other are overlapping each other; are calledconformers.
 a) fully eclipsed b) Staggered c) Gauche d) Partially eclipsed
20. At 25°C , 99.99% of all molecules in a cyclohexane solution will be in aconformation.
 a) half boat b) Twisted boat c) Boat d) chair
21. In cyclohexane, the two possible chair forms haveenergy.
 a) same b) different c) more d) higher
22. Boat conformation is least stable due to the..... bonds which are very much close to each other.
 a) equatorial b) axial c) C-C d) flag pole
23. Theconformer of the cyclohexane is highly unstable and has high potential energy of about 10-11 Kcal/mole.
 a) half boat b) Twisted boat c) Boat d) chair
24. It is the bowsprit-flagpole interaction, due to which the form is considerably less stable than the chair.
 a) half boat b) Twisted boat c) Boat d) half chair
25. 'E' form is more stable than A form of monosubstituted cyclohexane, as there is nointeraction.
 a) bowsprit-flagpole b) torsional c) butane gauche d) intramolecular
26. On addition of bromine, trans-2-butene gives rise to..... - 2,3-dibromobutane as product.
 a) only meso b) d/l- c) racemic d) meso and d/l
27. If we start with....., on addition of bromine, we get the mixture of 2 products (S,S) and (R,R)-2,3-dibromobutane.
 a) trans-2-butene b) cis-2-butene c) both of these d) none of these
28. The elimination reactions, where the groups are eliminated from the same face or direction of the molecule, is called elimination.
 a) cis b) symmetric c) syn d) anti

29. Dehydrohalogenation of 1-bromo-1,2-diphenylpropane is an example ofelimination.
a) cis b) symmetric c) syn d) anti
30. During the dehydrohalogenation of 1-bromo-1,2-diphenylpropane erythro form gives only thealkene.
a) Cis or Z b) Trans or E c) Anti d) unsymmetrical

Answers:

1. b)Constitutional 2. a) configurational 3. d) configurational 4. c) conformational
5. d)all of these 6. c)Staggered 7. d) Eclipsed 8. a) simple lines 9. b)dotted lines 10 .
b) coming towards the viewer 11 b) Newman's projection formulae 12. d) torsional
strain 13. a) 60° 14. c)Staggered 15. d) Eclipsed 16. c)conformational 17.
b)eclipsed 18. a) 12 KJ per mole. 19. a) fully eclipsed 20. d) chair 21. a) same
22. d) flag pole 23. a) half boat 24. c) Boat 25. c) butane gauche 26. a) only meso 27. b)
cis-2-butene 28. c) syn 29. d) anti 30. a) Cis or Z

[B] LONG AND SHORT ANSWER TYPE QUESTIONS:

1. What is stereochemistry? Explain different types of stereoisomerism.
2. Discuss the conformational analysis of ethane (OR Butane).
3. What is most stable form of the cyclohexane? Explain.
4. How will you show that E form is more stable than A form in monosubstituted cyclohexane ?
5. Discuss in detail the conformational isomerism in cyclohexane.
6. Explain conformational analysis of butane with Newman's projection formulae.
7. Write Short notes on:
 - i) Baeyer strain theory
 - ii) Stereoselective and stereospecific reactions
 - iii) Syn and Anti addition reaction
 - iv) Types of elimination reactions
 - v) Significance of stereochemistry
 - vi) Addition of bromine to 2-butene
 - vii) Dehydrobromination of 1-bromo-1,2-diphenylpropane
 - viii) Locking of conformation in t-butyl cyclohexane.

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2. Organic Chemistry Vol.2-Stereochemistry and the Chemistry of Natural Products by I.L.Finar 5th Edition. Sec. 2.4, 4.5, 4.11. ages- 76 to 79, 167 to 180, 187 to 190.
3. Stereochemistry of carbon compounds by Eliel. Relevant pages.
4. Stereochemistry of Organic Compounds by D. Nasipuri. Sec. 1.5,9.1,9.2,10.2,10.3,13.1. Pages- 8,9,193,196 to 198, 230 to 232, 236 to 241, 383,384.