**MODULE -2 LEARNING MATERIAL**

**Learning Material**

**Course: B. Pharmacy 4th Sem**

**MODULE-2: GEOMETRICAL ISOMERISM**

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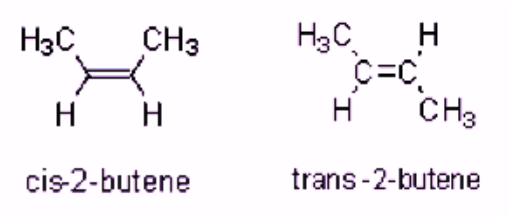
## GEOMETRICAL ISOMERISM

Geometrical Isomerism:- The isomers which are having same structural formula but are differing in spatial arrangement of the groups or atoms around the double bond are termed as geometrical isomers and the phenomenon is termed as geometrical isomerism.

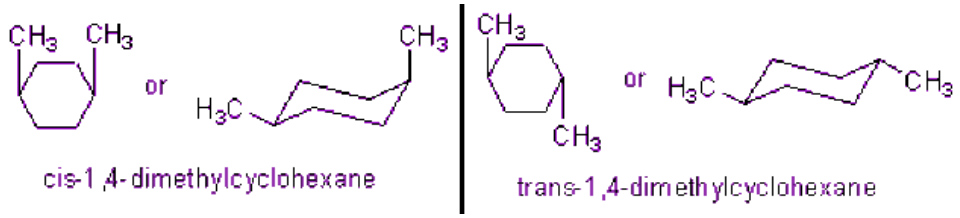
**Example 1:**

- Two different spatial arrangements of methyl groups about a double bond in **2-butene** give rise to the following geometrical isomers.
- Two forms are not inter convertible due to restricted rotation of double bond. In the cis isomer, the two methyl groups are arranged on the same side of a double bond. Whereas in the Trans isomer, they are on the opposite side.




**Example 2:**

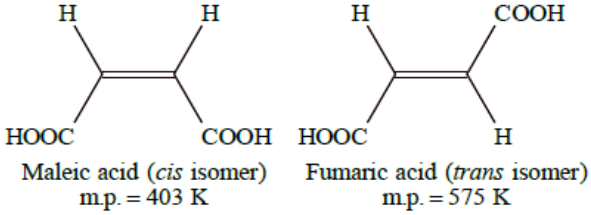
- There are two geometrical isomers (cis & trans) possible in case of 1,4–dimethylcyclohexane.
- Here the methyl groups are arranged differently about the plane of the cyclohexane ring. These isomers are not inter convertible since it is not possible to rotate the bonds in the cyclohexane ring.



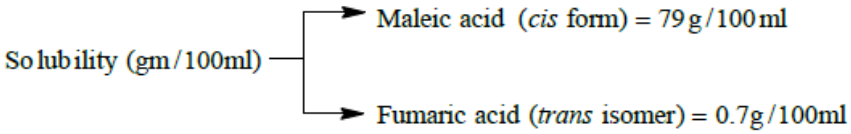

**Methods of determination of configuration of geometrical isomers:-**

**Melting point:**

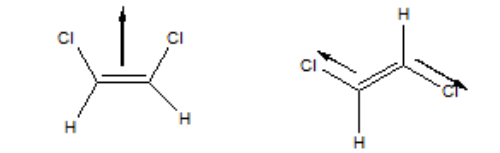
- In general, the melting point of a ***trans*** **isomer** is higher than that of the corresponding ***cis*** **isomer**. This is due to the reason that the molecules of a *trans* isomer are more symmetrical and hence fit more closely in the crystal lattice as compared to the molecules of a *cis* isomer.
- In order for the intermolecular forces to work well, the molecules must be able to pack together efficiently in the solid. Trans isomers pack better than cis isomers. The **"U"** shape of the **cis isomer** doesn't pack as well as the straighter shape of the **trans isomer**. The poorer packing in the cis isomers means that the intermolecular forces aren't as effective as they should be and so less energy is needed to melt the molecule a lower melting point.



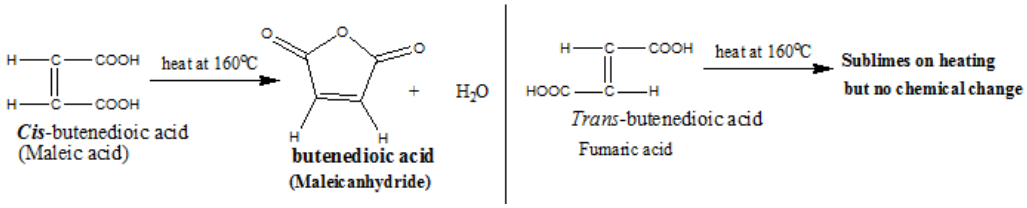
**Solubility:** In general, solubility of a ***cis isomer*** is higher than that of the corresponding ***trans isomer***. This is due to the reason that the molecules of a ***cis isomer*** are less tightly held in the crystal lattice.



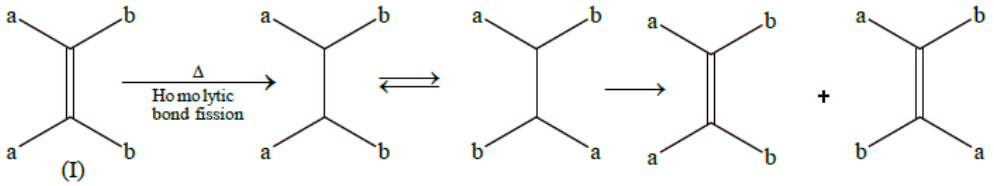

**Dipole moment:** The **cis isomer** has higher dipole moment than the corresponding **trans isomer**.




**Stability:** The **trans isomer** is more stable than cis isomer due to **steric hindrance**. Intermolecular reactions occur easily when reacting groups are close together. Hence, the **cis isomer** will form **cyclic deriv**atives more readily as against **trans derivatives**. But this reaction will take place in only those cis isomers in which the substituent's on two double bonded carbons are capable of intramolecular reaction with each other.




**Action of heat:** On strong heating cis and trans isomers are interconvertible. This interconversion takes place as follows:




**Thus cis isomer** ⇌ **Trans isomer**

## 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.*

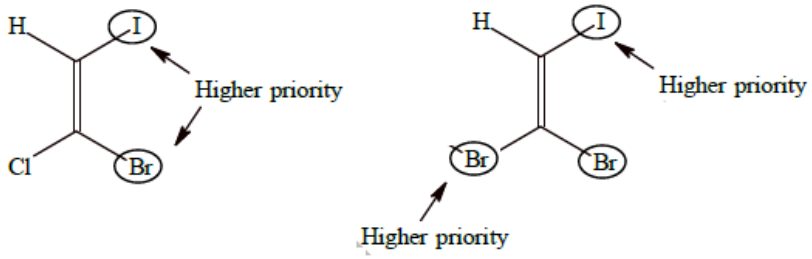
 First determine the higher priority group on each end of the double bond.

 If the higher priority groups are on the opposite sides of double bond, the isomer is denoted by the **descriptor, E**.

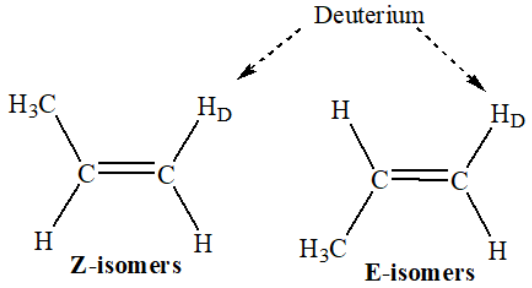
 Otherwise if they are on the same side of double bond, the **Z descriptor** must be used.

 ***The priorities are assigned by following Cahn-Ingold-Prelog sequence rules***:

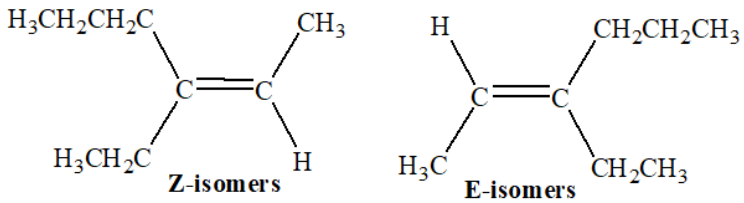
**- Rule 1:** Rank the atoms directly attached to the olefinic carbon according to their **atomic number**. **High priority** is given to the atom with **higher atomic number**.

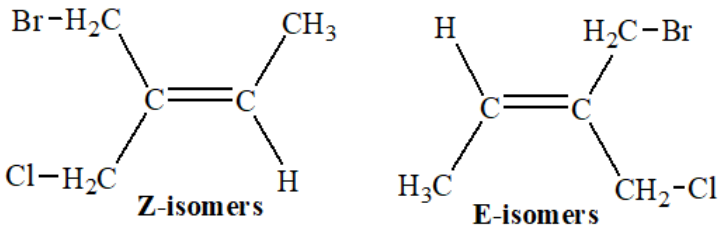



**Rule 2:** If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass. **E.g.** the Deuterium isotope (**$H_2$** or **D**) has more priority than protium (**$H_1$** or **H**). The **$C_{13}$** isotope has more priority than **$C_{12}$**.




**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 or sequence of atoms in the group 'X'.
e.g. for typing groupings in organic molecules where **X** is more than one atom ....
**X** = $-CH_2CH_2CH_3$ > $-CH_2CH_3$ > $-CH_3$ > -H i.e. the longer the hydrocarbon carbon chain the higher its priority,





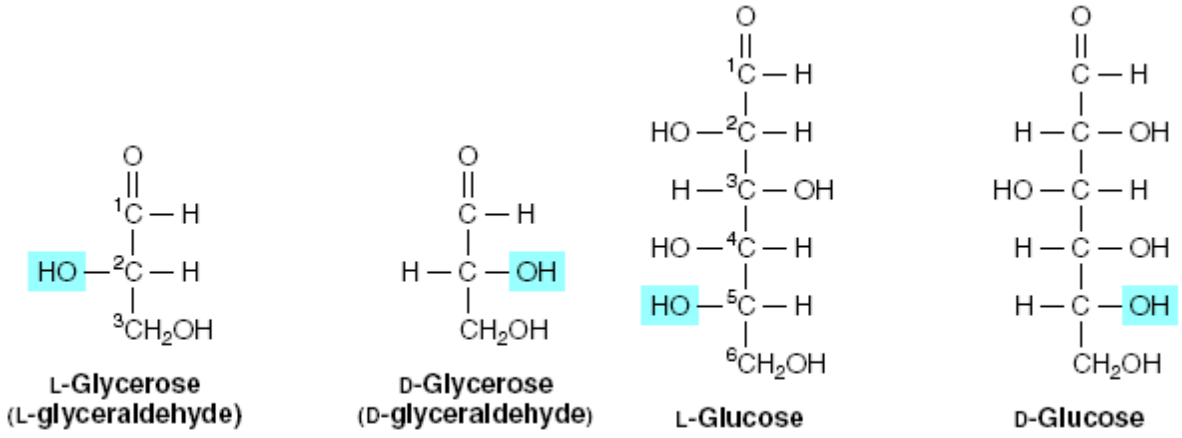

## D & L-System

- The **D** & **L** convention, not to be confused with the **d** (**dextro**) and **l** (**levo**) descriptors used to designate the direction of specific rotation of chiral compounds, is a convention used to distinguish between enantiomers of chiral monosaccharides and chiral alpha-amino acids, based on the molecule drawn as a ***Fischer projection*** in a specific orientation.

- The **L** and **D** forms of the sugar depends on the orientation of the **-H** and **-OH** groups around the carbon atom adjacent to the **terminal primary alcohol carbon** (carbon 5 in glucose) determines whether the sugar belongs to the **D** or **L** series.

- The **D-** and **L- notation** is based on **glyceraldehyde**.

- When the **-OH** group on this carbon is on the **right**, then sugar is the ***D-isomer***; when it is on the **left**, then it is the ***L-isomer***.



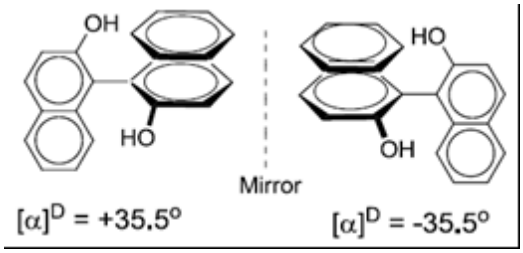

***D- and L-isomerism of glycerose and glucose***

**ATROPISOMERISM**

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

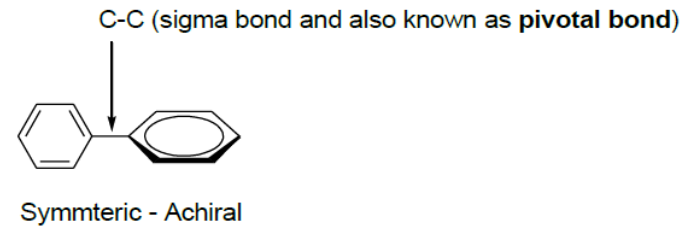
In unsubstituted **biphenyl**, there is sufficient amount of freedom of rotation around the central single bond to allow for free interconversion between the various conformers or rotamers so that the various rotamers cannot exist independently.

- 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**.



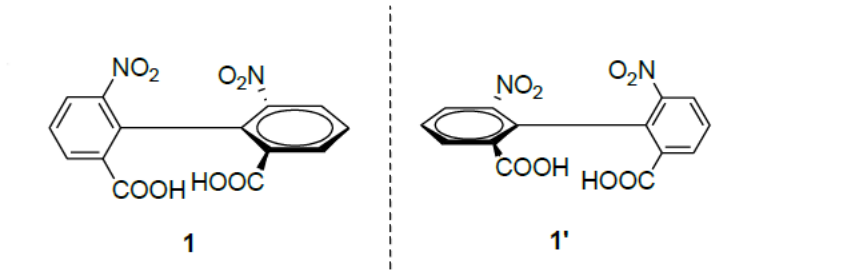

Atropisomerism are stereoisomers as a result of restricted rotation about a single bond.

- 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**.




Structure of biphenyl

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.



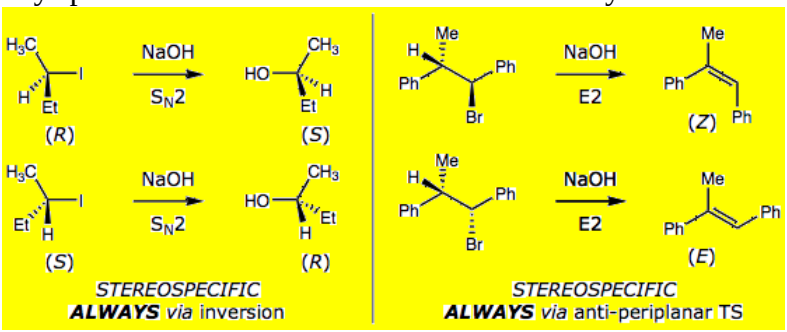

Enantiomers of the 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid

**Stereospecific and Stereoselective Reactions**

## ▯ STEREOSPECIFIC REACTIONS

- A stereospecific reaction is one which, when carried out with stereoisomeric starting materials, gives a product from one reactant that is a stereoisomer of the product from the other.

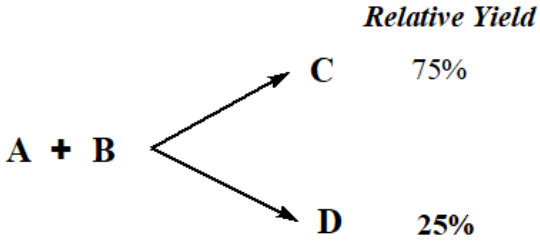
- '***Stereospecific***' relates to the mechanism of a reaction, the best-known example being the **SN2** reaction, which always proceeds with inversion of stereochemistry at the reacting centre.




## ▯ STEREOSELECTIVE REACTIONS

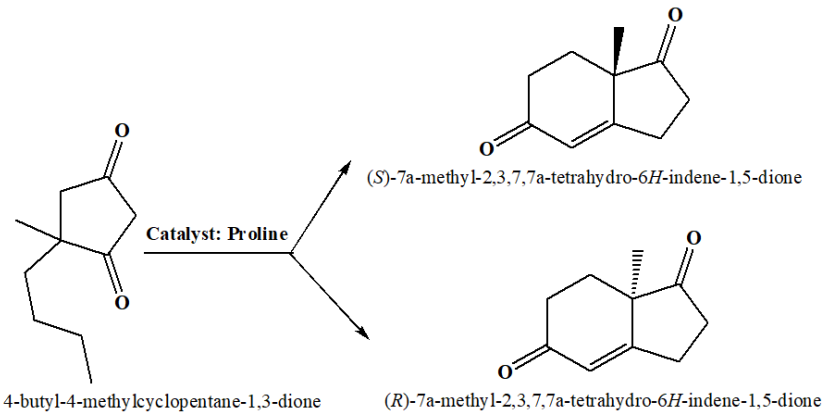
- A stereoselective process is one in which one stereoisomer predominates over another when two or more may be formed.

- 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**.

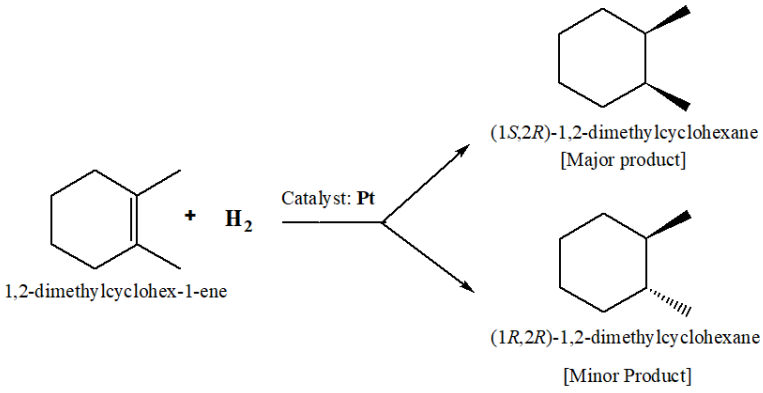


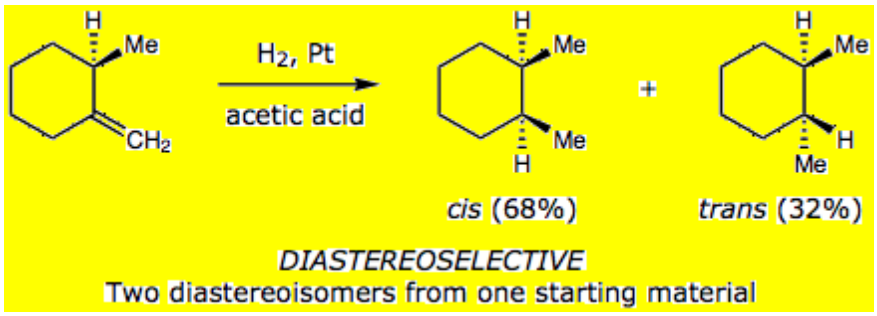

***The overall reaction between A and B is stereoselective.***

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**.



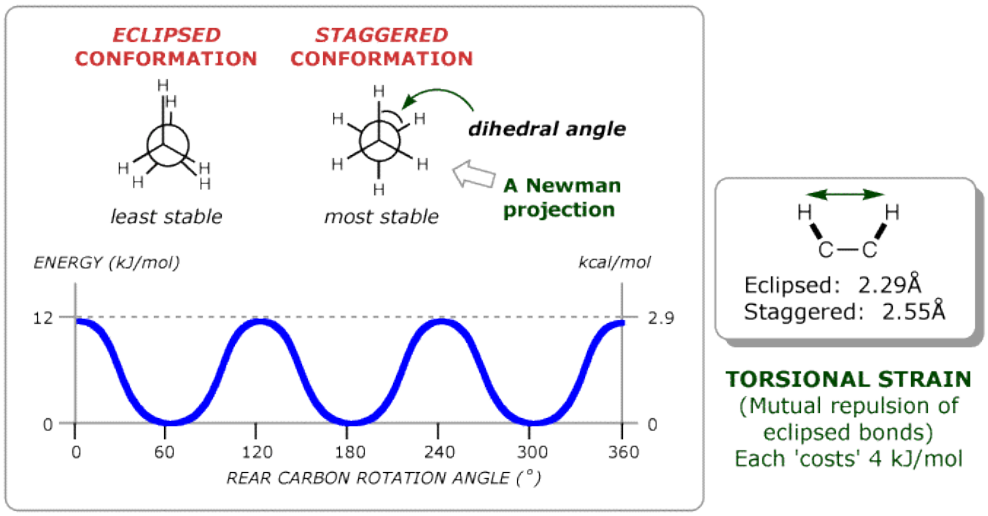

| | ***Stereospecific Reactions*** | ***Stereoselective Reactions*** |
|---|---|---|
| Definition | A stereospecific reaction is a reaction in which the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option. | A stereoselective reaction is a 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. |

**Conformational Isomerism:** The different arrangements of the atoms in space that result from the rotation of group about C-C bond axis called conformation. Conformations represent conforms which are readily interconvertible and thus nonseparable.

**Conformations of Ethane:-** There is a 12 kJ/mol (2.9 kcal/mol) barrier to rotation in ethane. The most stable (low energy) conformation is the one in which all six C–H bonds are as far away

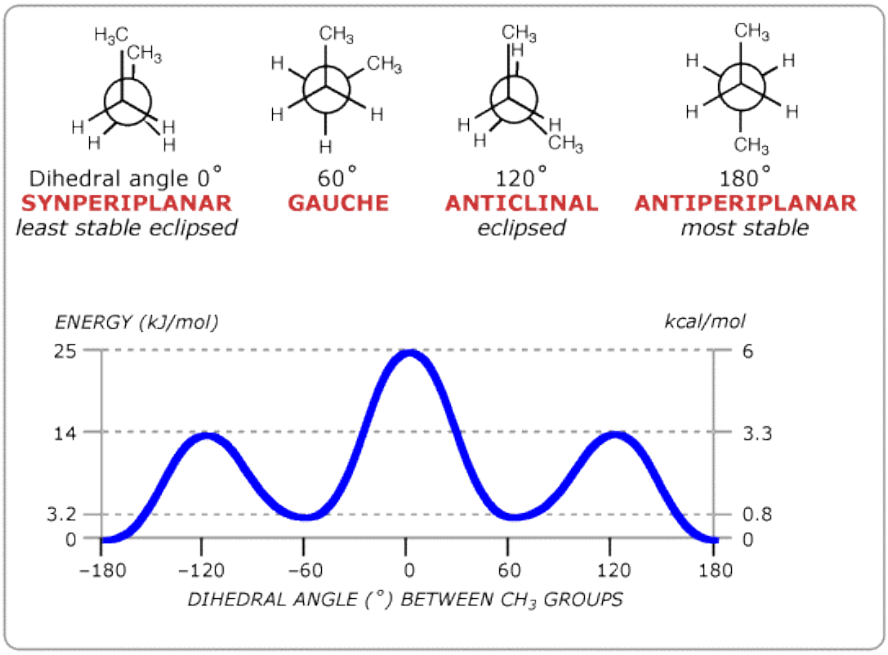
from each other as possible (***staggered*** when viewed end-on in a Newman projection). The least stable (high energy) conformation is the one in which the six carbon–hydrogen bonds are as close as possible (***eclipsed*** in a Newman projection). All other conformations lie between these two limits. The barrier to rotation is the result of three equal C–H bond-eclipsing interactions, so we can assign a value of about 4.0 kJ/mol (1.0 kcal/mol) to each of these interactions. The corresponding energy in propane is 14 kJ/mol (3.4 kcal/mol).

The 12 kJ/mol of extra energy in the eclipsed conformation of ethane is called ***torsional strain***. The barrier to rotation that results from this strain can be represented in a graph of potential energy versus degree of rotation in which the angle between C–H bonds on C-1 and C-2 (the ***dihedral angle***) completes one revolution. Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations. The torsional strain is thought to be due to the **slight repulsion between electron clouds in the eclipsed bonds**.




We can represent conformational isomers in one of two ways. ***Sawhorse*** representations view the carbon–carbon bond at an angle so as to show the spatial orientation of all C–H bonds. In a ***Newman projection*** the carbon–carbon bond is viewed along its axis and the two carbon atoms are repesented by a circle. The bonds attached to the front carbon are represented by lines going to the centre of the circle, and bonds attached to the rear carbon are represented by lines going to the edge of the circle. The advantages of Newman projections are that they are easy to draw and they clearly show the relationships among substituents on the different carbon atoms.

Conformation of n-butane:- The conformational possibilities increase as alkanes become larger. A plot of potential energy against rotation about the C(2)–C(3) bond in **butane** is shown below. The lowest-energy arrangement, called the ***antiperiplanar*** (or *anti*) conformation, is the one in which the two large methyl groups are as far apart as possible. As rotation around the C(2)–C(3) bond occurs, another eclipsed conformation (***anticlinal***) is reached in which there are two Me–H interactions and one H–H interaction. If we assign the energy value (4 kJ/mol) for H–H eclipsing interactions that was previously derived from ethane, we can predict that each Me–H interaction in the anticlinal conformation costs about 5 kJ/mol.




***synperiplanar*** has **two** different types of strain:

**TORSIONAL STRAIN**
Three eclipsed pairs of bonds (total cost about 12 kJ/mol)

**STERIC STRAIN**
Eclipsed [$CH_3$–$CH_3$] (costs about 13 kJ/mol)

***gauche*** is less stable than ***anti***:

**STERIC STRAIN**
Gauche [$CH_3$–$CH_3$] costs 3.2 kJ/mol

As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are 60° apart (a ***gauche*** relationship). This lies 3.2 kJ/mol higher in energy than the *anti* conformation even though it has no eclipsing interactions. This energy difference is due to the fact that the hydrogen atoms of the methyl groups are near each other in the *gauche* conformation, resulting in ***steric strain***, which is the repulsive interaction that occurs when atoms would otherwise tend to occupy the same space.

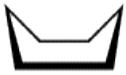
As the dihedral angle between the methyl groups approaches 0°, an energy maximum is reached. The methyl groups are forced even closer together than in the *gauche* conformation, and both ***torsional*** strain and ***steric*** strain are present. A total strain energy of 25 kJ/mol has been estimated for this conformation, allowing us to calculate a value of 17 kJ/mol for the Me–Me eclipsing interaction.

Completing the 360° rotation after the *synperiplanar* point produces the mirror images of what we've already seen; another ***gauche*** conformation, another eclipsed conformation and finally a return to the ***anti*** conformation.

Cyclohexane is not planar but *puckered* into a 3-D conformation that relieves all strain. Its most stable arrangement is referred to as the **chair** conformation. The different chair conformations of cyclohexane can interconvert or 'flip' very easily: the activation barrier is 45 kJ/mol.

**CHAIR**

C—C—C angles 111° (no angle strain)
All bonds staggered (no torsional strain)
Predominant conformation (>99.8%)



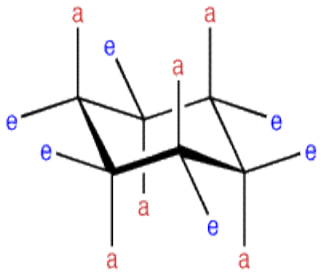
**BOAT**

High steric strain (short 1,4 distance)
Torsional strain (eclipsing of C–H bonds)
27 kJ/mol less stable than chair

**TWIST BOAT**

Less steric strain than boat (1,4 distance larger)
Less torsional strain than boat (less eclipsing)
6 kJ/mol more stable than boat

**CHAIR CYCLOHEXANE**




a = axial; e = equatorial