Module 8 Stereochemistry

Lecture 20 Stereochemistry I

Stereochemistry is the study of the relative arrangement of atoms or groups in a molecule in three dimensional space. Stereochemical isomers are molecules, which have the same chemical formula and bond connectivity but different relative arrangement in three-dimensional space. In contrast, constitutional isomers have same molecular formula but different bond connectivity. Thus, n-butane and isobutane are structural isomers while the isomers of limonene, the compound which gives different taste to lemon and orange are examples of stereochemical isomers (Figure 1).

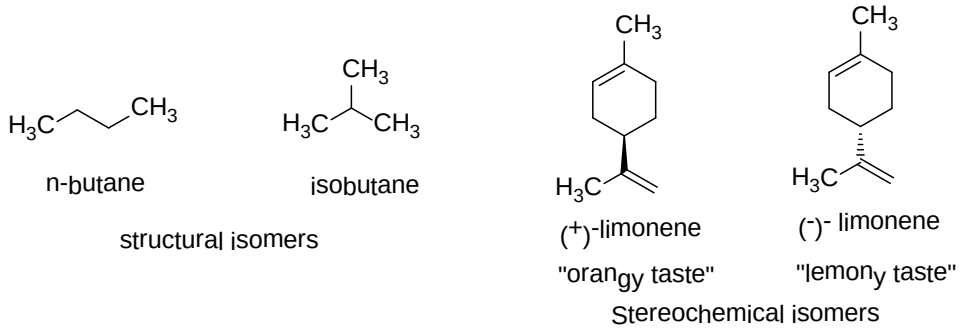


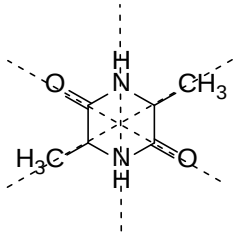
Figure 1

To understand the difference between the two isomers of limonene, introduction to some new terms and concepts are required. The most important being the concept of chirality.

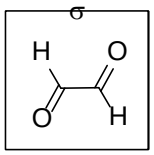
A chiral object is one that cannot be superposed on its mirror image. The term originates from the greek term for “hand”. As it is with human hands, the left hand cannot be superimposed on the right hand. It is the same with chiral molecules. They are non-superimposable mirror images of each other. Achiral objects, on the other hand, are easily superimposable on each other. A tennis racquet and a spoon are examples of achiral objects.

The next question that comes to the mind is how to determine whether a molecule is chiral or achiral. At times, it becomes extremely difficult to determine with increasing molecular complexity, to determine the non superimposibity of a compound with its mirror image. Thus, a mathemathical concept known as group theory can be applied to determine the symmetry elements in a molecule. There are four symmetry elements which needs to be considered for this purpose:

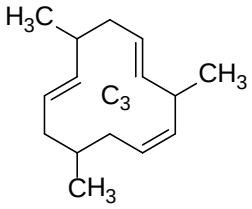
- Centre of symmetry(*i*): The center of symmetry *i* is a point in space such that if a line is drawn from any part (atom) of the molecule to that point and extended an equal distance beyond it, an analogous part (atom) will be encountered. Thus the molecule 3,6-dimethylpiperazine-2,5-dione has centre of symmetry (sometimes referred to as centre of inversion) running through the centre of the molecule.



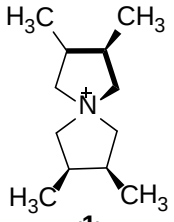
- Plane of symmetry (σ): A plane of symmetry is a reflection plane which brings into coincidence one point of the molecule with another one through the mirror reflection. Thus, glyoxal has a plane of symmetry running through the molecular plane.



- Axis of symmetry (C_n): Symmetry axis C_n, also called n-fold axis, is an axis which rotates the object (molecule) around by 360°/n, such that the new position of an object is superimposable with the original one. For example, (1Z,4E,8E)-3,7,11-trimethylcyclo-dodeca-1,4,8-triene has 3-fold rotation axis.



- Rotary reflection axis (S_n): Rotary reflection axis is an axis which rotates the object (molecule) around by 360°/n, followed by rotation in a plane perpendicular to the axis, such that the new position of an object is superimposable with the original one. All odd values of S_n are identical with C_n. Thus, in **1,** there is a 4-fold rotary reflection axis.



(**1**)

If a molecule has only either centre of symmetry or plane of symmetry then it is achiral. However, in most cases, molecules have more than one element of symmetry. In such cases, it becomes important to know the point group to which the molecule belongs. A point group reflects the combination of symmetry elements present in the structure. The point group of a molecule can be determined by following the algorithm given below. The point groups C_1, C_n and D_n are chiral groups and they contain chiral molecules while all other groups are achiral (Figure 2).

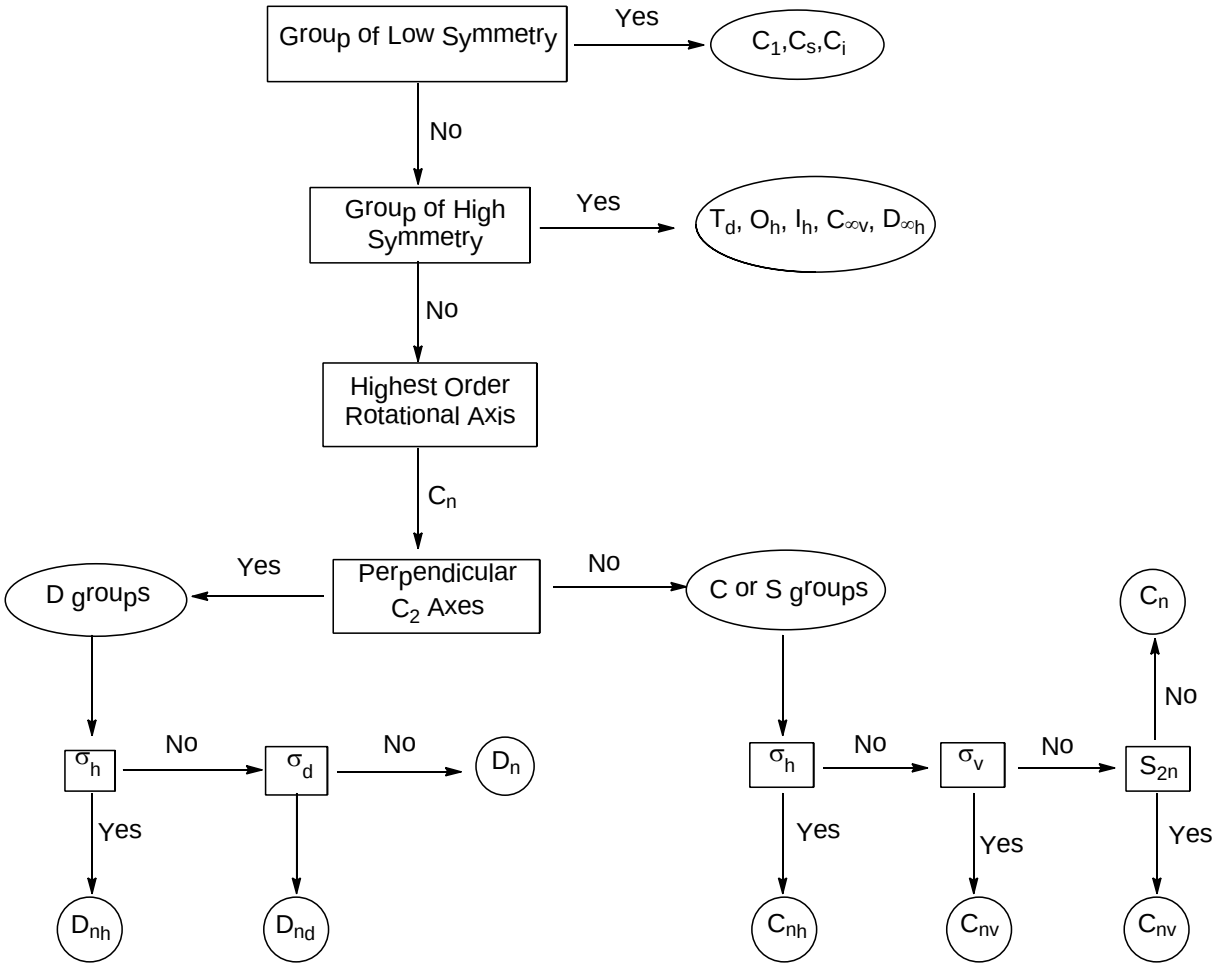


Figure 2

Enantiomers

If a molecule is non-superimposable on its mirror image, then the molecule is said to have enantiomeric relationship with its mirror image molecule. For example, in 2-chloropropane, the molecule is superimposable with its mirror image, so they are identical molecules, but in 2-chlobutane, the molecule is not superimposable with its mirror image and the two molecules are called enantiomers (Figure 3). Thus, enantiomers are stereoisomers since they differ only in the relative arrangement of the different groups in space but not in bond connectivity. Enantiomers are identical in all physical properties (except optical rotation) and chemical properties and reactivity compared to an achiral reagent in reactivity

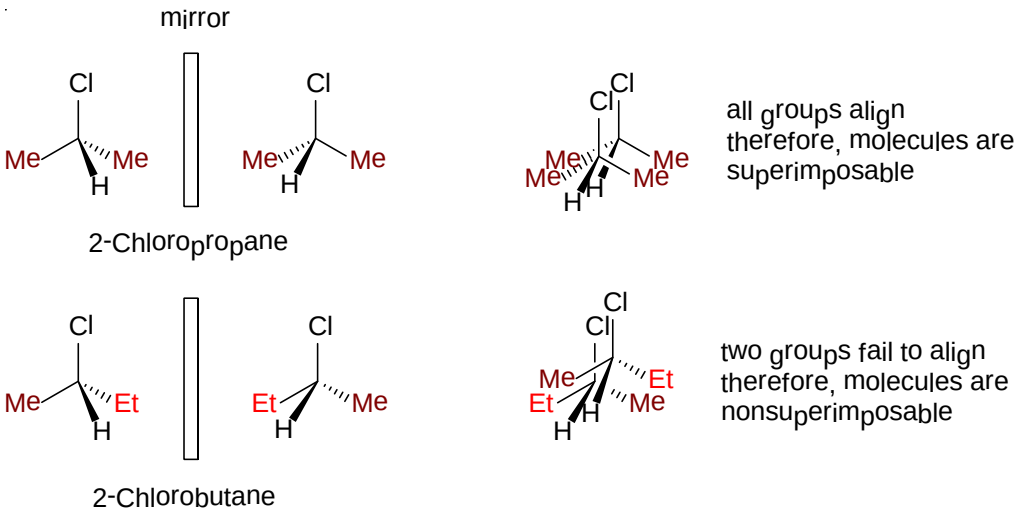


Figure 3

Obviously, the next issue is how to detect and analyse the enantiomers physically. In this respect, in 1801, Haüy, a French mineralogist observed that some quartz crystals rotate polarized light clockwise, while other crystals rotate polarized light to the left. Haüy also noticed that quartz crystals exhibit the phenomenon of hemihedrism (externally, some crystals are non-identical mirror images of other crystals). This is referred to as optical activity. Followed by this, J. B. Biot observed the optical activity in certain organic compounds and was able to conclude that it is a molecular property. In 1884, Louis Pasteur in an ingenius experiment crystallized and physically separated two types of crystals of tartaric acid –one of which was hemihedral to the left while the other was

hemihedral to the right. When he dissolved the two forms separately and measured their optical rotation, he observed that the crystals having the hemihedral to the left rotated the plane of polarized light to the left and vice-versa. Louis Pasteur thus proposed that the two forms of tartaric acid are mirror image of each other (enantiomers).

The optical activity of a compound was found to be proportional to

- The concentration of the compound in solution (c)
- The length through light traverses through the solution (*l*)
- The wavelength used for the measurement (λ) and the temperature at which the measurement is made (t). Usually, the sodium D-line is used for polarimetric measurement.

  Mathematically,

$$\alpha = [\alpha]_D lc \text{ at temperature t}$$

where [α] is the constant of proportionality

The constant of proportionality [α] is called specific rotation and is defined as the optical rotation in degrees of the plane of polarization of a ray of monochromatic light that passes through a tube 1 decimeter long containing the substance in solution at a concentration of 1 gram per millimeter in a polarimeter.

An enantiomer will thus rotate the plane of polarized light either clockwise or anticlockwise. The clockwise rotation is usually denoted by either of the prefix dextro or (+). Similarly anticlockwise rotation is denoted by laevo or (-). Thus, an equimolar mixture will not give any optical rotation at all. Such a mixture is referred to as a racemic mixture.

Whether a particular sample consists of a single enantiomer or a mixture of enantiomers can be determined by its *observed specific rotation*. For example, an **enantiomerically pure** sample-meaning only one enantiomer is present-of (*S*)-(+)-2-bromobutane will have an *observed specific rotation* of +23.1° because the *specific rotation* of (*S*)-(+)-2-bromobutane is +23.1°. If, however, the sample of 2-bromobutane has an observed specific rotation of 0°, we will know that the compound is a racemic mixture. If the observed specific rotation is positive but less than +23.1°, we will know that we have a

mixture of enantiomers and the mixture contains more of the enantiomer with the *S* configuration than the enantiomer with the *R* configuration. From the observed specific rotation, we can calculate the **optical purity** of the mixture.

$$\text{optical purity} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

For example, if a sample of 2-bromobutane has an observed specific rotation of +9.2°, its optical purity is 0.40. In other words, it is 40% optically pure-40% of the mixture consists of an excess of a single enantiomer.

$$\text{optical purity} = \frac{+9.2°}{+23.1°} \times 100 = 40\%$$

Because the observed specific rotation is positive, we know that the solution contains excess (*S*)-(+)-2-bromobutane. The **enantiomeric excess** (**ee**) tells us how much excess (*S*)-(+)-2-bromobutane is in the mixture. As long as the compound is chemically pure, enantiomeric excess and optical purity will be the same.

$$\text{enantiomeric excess} = \frac{\text{excess of a single enantiomer}}{\text{entire mixture}} \times 100\%$$

$$= \frac{40\%}{100\%} \times 100\% = 40\%$$

If the mixture has a 40% enantiomeric excess, 40% of the mixture is excess *S* enantiomer and 60% is a racemic mixture. Half of the racemic mixture plus the amount of excess *S* enantiomer equals the amount of the *S* enantiomer present in the mixture. Thus, 70% of the mixture is the *S* enantiomer and 30% is the *R* enantiomer.

Another class of stereoisomers is the so called diastereomers which have different chemical and physical properties. Such compounds may include geometrical isomers- the *cis* and *trans* isomers (Figutre 4).

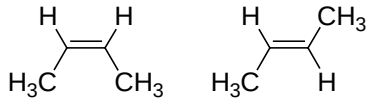


Figure 4

A different type of isomerism may exist in disubstituted cyclic compounds. Thus, in 4-tert-butylcyclohexanol, two isomers-*cis* and *trans* exist (Fig 5).

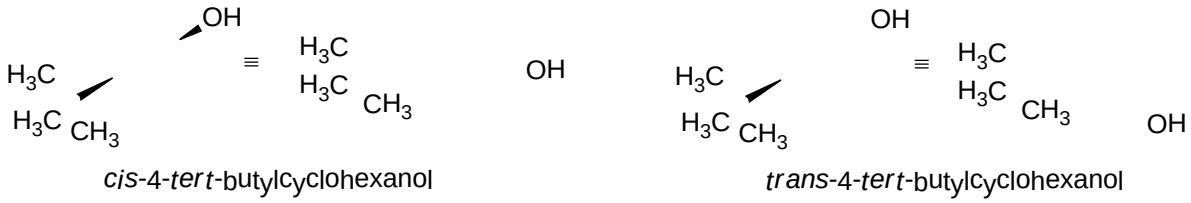


Figure 5

Diastereomeric compounds may or may not be chiral. The above two examples are both achiral, each having a plane running through them. However, when *cis* and *trans* epoxides are compared, it can be easily seen that they may be chiral compounds. As an example, the comparison of *cis* and *trans* isomers of 2,3-dimethyloxirane, the *cis*-isomer is achiral having a plane of symmetry in the molecule. However, the *trans* isomer does not have any plane of symmetry through the molecule and as such it is a chiral molecule (Figure 6).

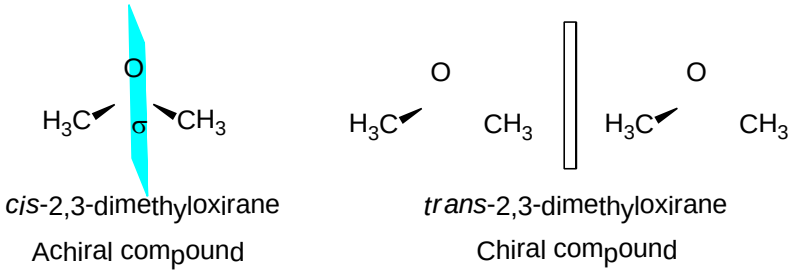
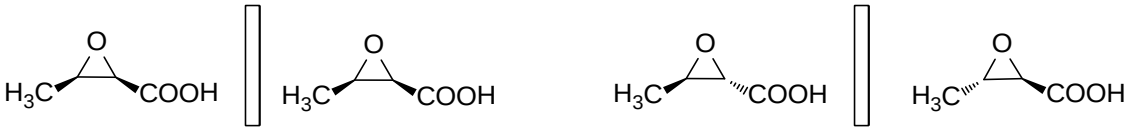


Figure 6

A similar observation can be made for 3-methyloxirane-2-carboxylic acid but here both the *cis* and *trans* isomers are chiral compounds each of which exist as a pair of enantiomers (Figure 7).



cis-3-methyloxirane-2-carboxylic acid *trans*-3-methyloxirane-2-carboxylic acid

Figure 7

The term chiral centre used so far is actually a subset of the term stereogenic centre. A stereogenic centre is defined as an element where the interchange of two substituents will lead to a stereoisomer. Not all stereogenic centres are chiral centres and even achiral molecules may have stereogenic centres.

The actual arrangement of the atoms or groups in a molecule about a stereocentre is called absolute configuration. It is mostly determined by X-ray crystallography or by inference based on chemical reactions of specific stereochemistry involving a compound whose absolute configuration is known, whereas the relative configuration is defined as the correlation between the different stereogenic centres within the molecule.

Though, here, the enantiomers are represented in the flying wedge form where two of the groups around the chiral centre are depicted in the plane of the paper and groups towards us in bold bonds and groups away from us in broken bonds, there are other forms of depictions of chiral compounds. These are discussed below.

- ***Fischer projection formula***. It is a representation of a 3D molecule as a flat structure where a tetrahedral carbon is represented as two crossed lines. The two vertical bonds about the stereocentre are above the plane of paper (towards the viewer) while the horizontal bonds are below the plane of the paper (away from the viewer) (Figure 8).

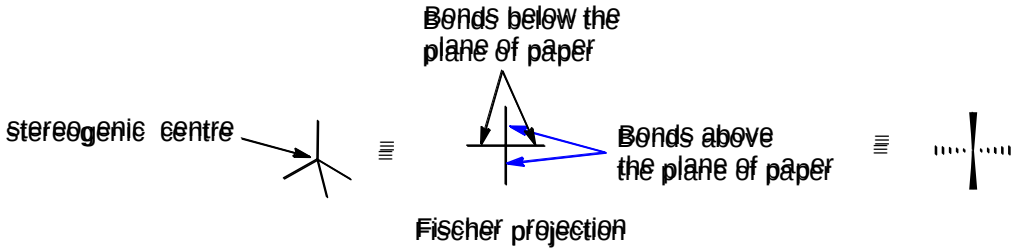


Figure 8

A few examples of depiction of molecules in Fischer projection formula is given below. It must be noted that when bonds are rotated by 180°, they result in the same identical molecule (Figure 9).

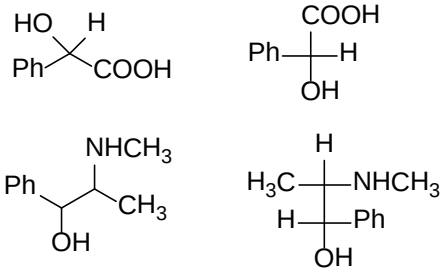


Figure 9

- ***Sawhorse projection formula***. Sawhorse projection formulas are used to denote two principal stereocentres. It is a view of a molecule down a particular carbon-carbon bond, with the groups connected to both the front and back carbons are drawn using sticks at 120° angles. Sawhorse Projections can also be drawn so that the groups on the front carbon are staggered (60 ° apart) or eclipsed (directly overlapping) with the groups on the back carbon. The overall representation is given below (Figure 10).

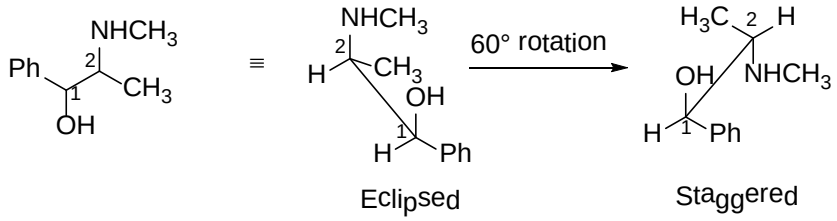


Figure 10

- ***Newmann projection formula***. In this notion, the molecule is again viewed by looking down a particular carbon-carbon bond. The front carbon of this bond is represented by a dot, and the back carbon is represented by a large circle. The three remaining bonds are drawn as sticks coming off the dot (or circle), separated by one another by 120°. Just like Sawhorse projection formula, Newman Projection can be drawn such that the groups on the front carbon are staggered (60 ° apart) or eclipsed (directly overlapping) with the groups on the back carbon (Fig 11).

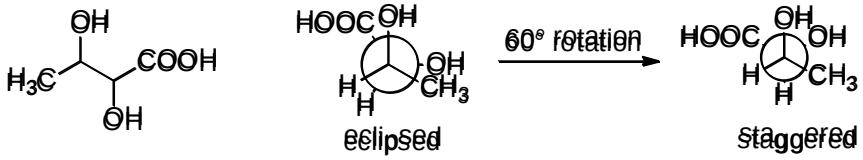


Figure 11

Module 8 Stereochemistry
Lecture 21 Stereochemistry II

Keywords: Enantiomer, Configuration, Racemic, Diastereisomer, Purification

In order to convert from one depiction to another certain rules have to be followed. Firstly, it must be noted that Fischer projection always depicts the molecule in eclipsed form. Thus, whenever, a Fischer projection is converted to Newman or Sawhorse projection, it results in an eclipsed form of the molecule which is then converted to the more stable staggered form. Similarly, while converting a Newmann or a Sawhorse projection to Fischer projection, the molecule must be first depicted in eclipsed form before conversion.

For example, to convert a flying wedge projection to Fischer projection, firstly, the bonds which are supposed to be on the plane are to be decided which must be two bonds, one vertical and horizontal connected to a carbon (Figure 1). If the vertical bond to the right is choosen, and the other horizontal bond is bent to the right, the remaining vertical bond group is depicted above the plane.

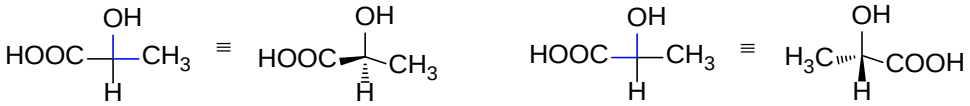


Figure 1

If on the other hand, if the vertical bond to the left is choosen, and the other horizontal bond is bent to the right, the remaining vertical bond group is depicted below the plane (Figure 2).

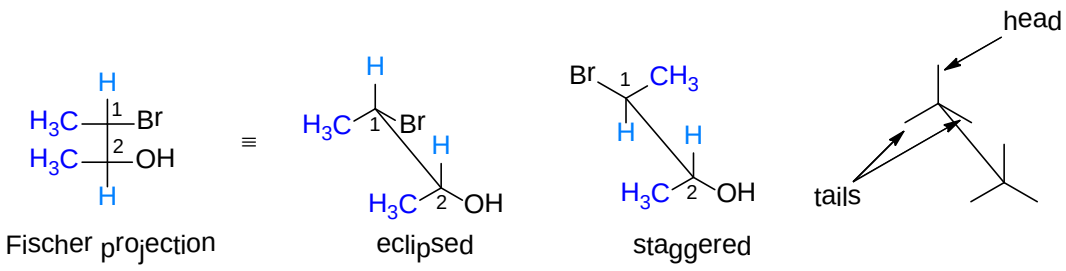


Figure 2

Step1: Put the groups at the vertical bonds on the tails of the "Y" of sawhorse projection.

Step 2: Put the other groups on the head of "Y".

In other words, imagine that C_1-C_2 bond is in plane of the paper and look across the C_1-C_2 bond, the groups which are coming out of the plane of paper form the tails of "Y" while the groups below the plane of the paper form the heads of "Y".

In order to convert a molecule from Fischer projection to sawhorse projection, the molecule has to be first depicted in eclipsed form. Then the steps outlined above are to be carried out in a reverse manner (Figure 3).

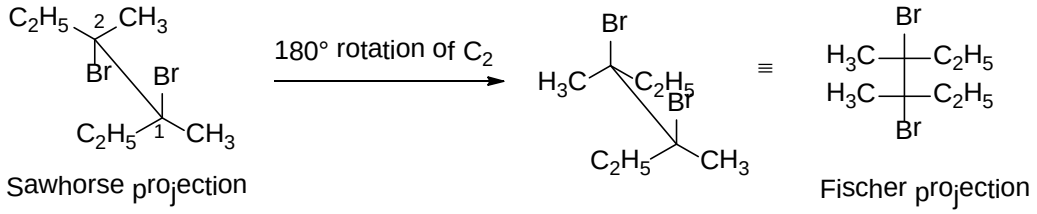


Figure 3

In other words, again look along the C_1-C_2 bond as being the plane of paper, then the groups lying above the paper form the vertical line while the groups below the paper form the horizontal bonds in Fischer projection.

To convert a Sawhorse projection to Newmann projection look along the C_1-C_2 bond through C_1 such that C_2 is not visible. Now the groups on C_1 are same for both sawhorse and Newmann projection. The C_2 carbon is replaced by a circle and the bonds emanating from C_2 being retained in their actual spatial location (Figure 3).

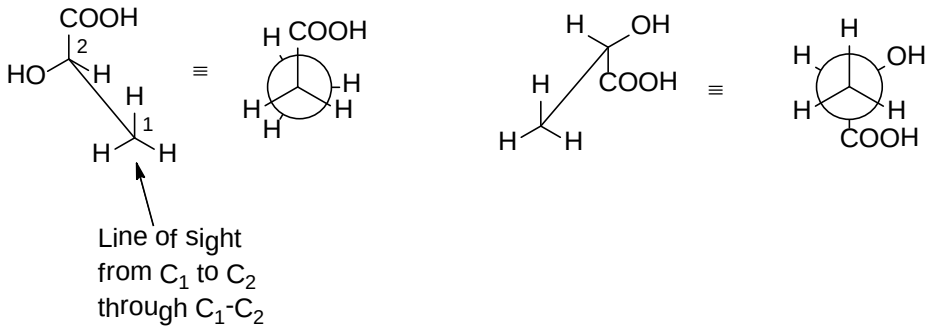


Figure 3

Now coming back to the issue to assign the relative configurations of a stereocentre, several approaches were used. The first one being the stereochemical descriptor D/L which relies on the chemical correlation of the configuration of the chiral center to D-glyceraldehyde. The compounds which can be correlated without inverting the chiral center are named D, those correlated to its enantiomer are designated as L. It is worth a while to note that though D-glyceraldehyde is dextrorotatory (rotates the plane of polarized light to the right), the compounds correlated to D-glyceraldehyde do not have to be dextrorotatory and vice versa (Figure 4).

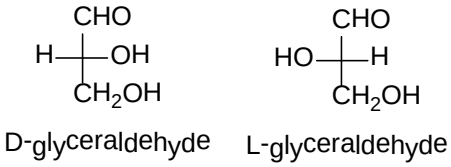


Figure 4

This system is not much in use today. However, traditionally it is still used for sugars and amino acids. In cases of carbohydrates, only the carbon at the end of carbon chain is considered for assigning D/L after writing the molecule in Fischer projection with the anomeric carbon on the top. Now if the carbon at the end of chain (farthest from anomeric carbon) has a hydroxyl group to the left, it is denoted as an L-sugar and it has a hydroxyl group to the right, it is called a D-sugar (Figure 19).

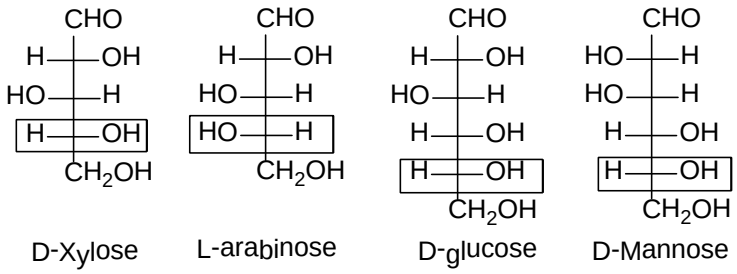


Figure 5

All naturally occurring amino acids are L-amino acids since they can be correlated with L-glyceraldehyde with the most oxidized group at the top and amino group at left in Fischer projection (Figure 6).

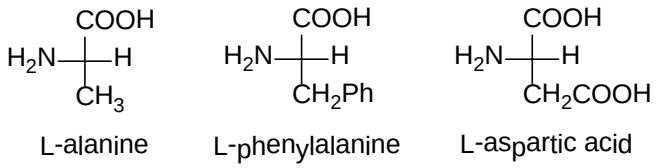


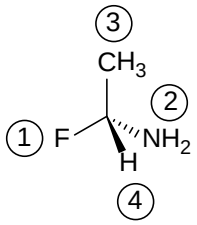
Figure 6

The Cahn-Ingold-Prelog convention is the most widely accepted system for naming the configurations of chirality centers. Each asymmetric carbon atom is assigned a letter (*R*) or (*S*) based on its three-dimensional configuration. To determine the name, we follow a two-step procedure that assigns "priorities" to the four substituents and then assigns the name based on the relative positions of these substituents. The procedure follows:

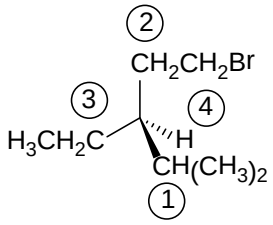
- Rank the groups (or atoms) bonded to the asymmetric carbon in order of priority. The atomic numbers of the atoms directly attached to the asymmetric carbon determine the relative priorities. The higher the atomic number, the higher the priority.

  Examples of priority for atoms bonded to an asymmetric carbon:

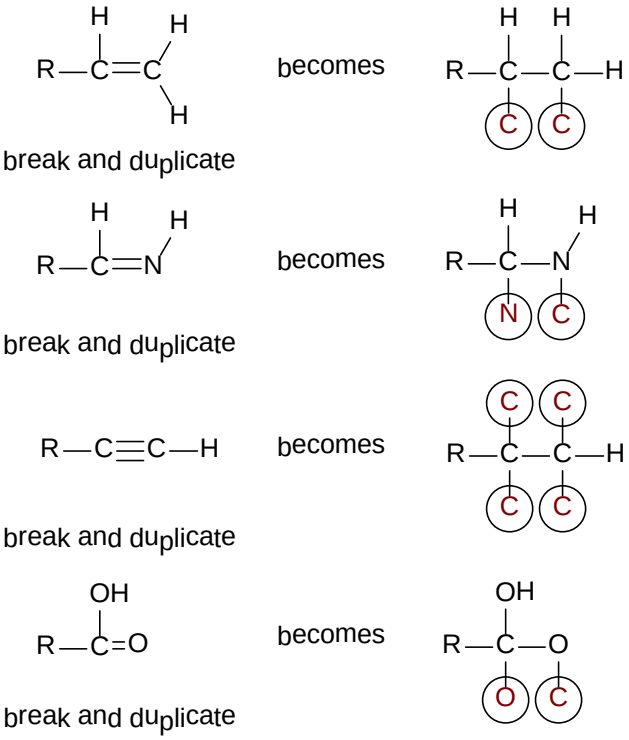
  $I > Br > Cl > S > F > O > N > {}^{13}C > {}^{12}C > Li > {}^{3}H > {}^{2}H > {}^{1}H$



- In case of ties, use the next atoms along the chain of each group as tiebreakers. For example, we assign a higher priority to isopropyl -$CH(CH_3)_2$ than to ethyl -CH_2CH_3 or bromoethyl -CH_2CH_2Br. The first carbon in the isopropyl group is bonded to two carbons, while the first carbon in the ethyl group (or the bromoethyl group) is bonded to only one carbon. An ethyl group and a -CH_2CH_2Br have identical first atoms and second atoms, but the bromine atom in the third position gives -CH_2CH_2Br a higher priority than -CH_2CH_3. One high-priority atom takes priority over any number of lower-priority atoms.

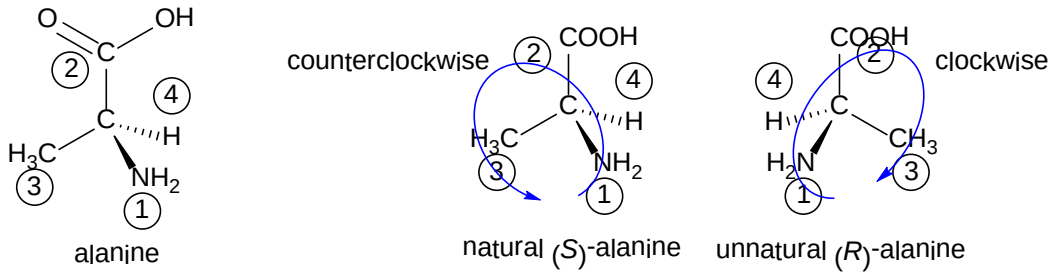


- Treat double and triple bonds as if each were a bond to a separate atom. For this method, imagine that each pi bond is broken and the atoms at bothends duplicated. Note that when you break a bond, you always add two imaginary atoms. (Imaginary atoms are circled below.)



- Using a three-dimensional drawing or a model, put the fourth-priority group away from you and view the molecule along the bond from the asymmetric carbon to the fourth-priority group. Draw an arrow from the first-priority group, through the second, to the third. If the arrow points clockwise, the asymmetric carbon atom is called (*R*). If the arrow points counter-clockwise, the chiral carbon carbon atom is called (*S*).

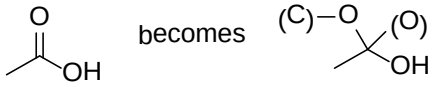
A few examples are given to clarify the assignment of priority and configuration.



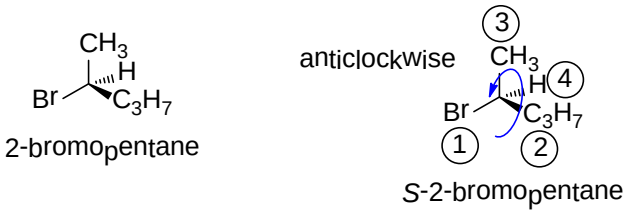
Here, the order of priority is assigned as follows:

Following rule 1, amino group gets first priority.

Following rule 3, carboxylate group gets second priority as shown below.



Following rule 2, methyl group gets third priority over hydrogen.

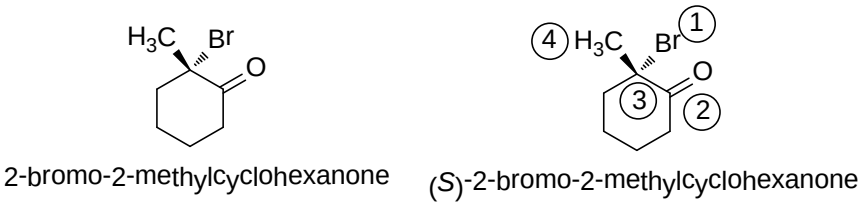


Here, the order of priority is assigned as follows:

Following rule 1, bromo group gets first priority.

Following rule 2, propyl group gets second priority ahead of methyl group.

Following rule 2, methyl group gets priority over hydrogen.

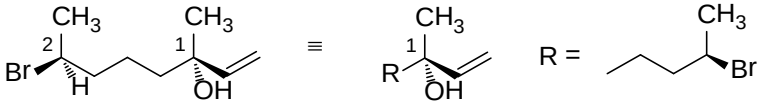


Here, the order of priority is assigned as follows:

Following rule 1, bromo group gets first priority.

Following rule 3, carbonyl group gets second priority.

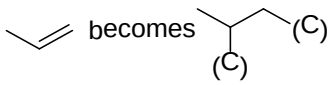
Following rule 2,  group gets third priority over methyl.



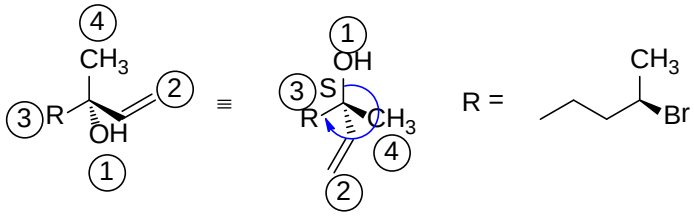
Here, for C_1, the priority order is set to be as follows.

Following rule 1, hydroxyl group gets first priority.

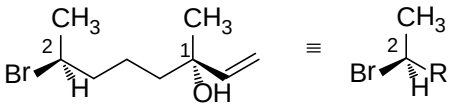
Following rule 3, ethenyl group gets second priority ahead of R and methyl groups.



Following rule 2, R group gets priority over methyl.



Since, in this case, the lowest priority group is on the plane and not below it, so, it is converted to an identical form by keeping one of the groups on plane constant and rotating the other 3 groups clockwise. Now, it can be seen that the configuration is S.

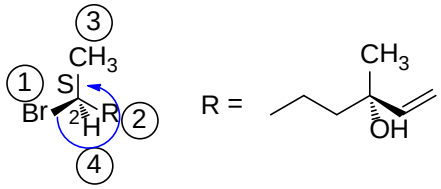


Here, the priority order is decided as follows:

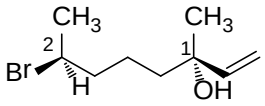
Following rule 1 bromo gets first priority

Following rule 2, R gets second priority

Following rule 2, methyl gets third priority.



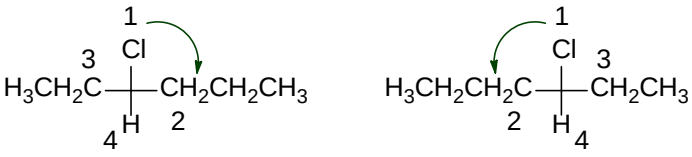
Hence the molecule is



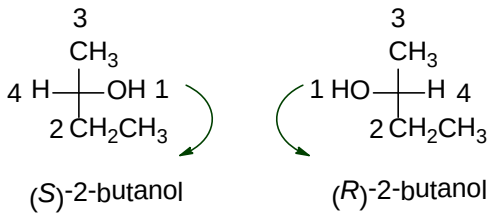
(3*S*,7*S*)-7-bromo-3-methyloct-1-en-3-ol

Sometimes, the determination of configuration of a compound drawn as a Fischer projection is necessary. The rules are given below.

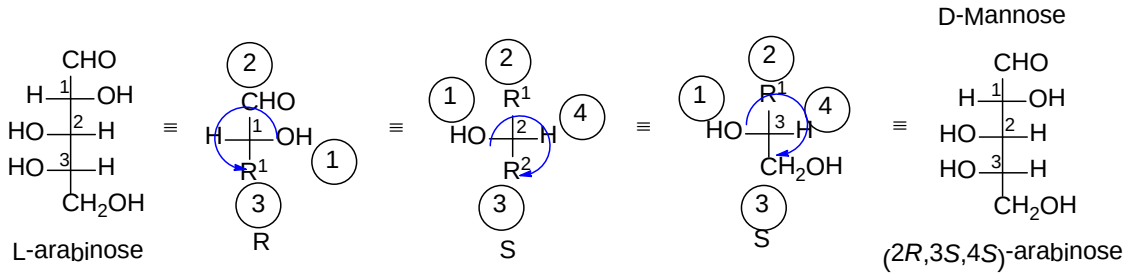
- Rank the groups (or atoms) that are bonded to the asymmetric carbon in order of priority.
- Draw an arrow from the group (or atom) with the highest priority (1) to the group (or atom) with the next highest priority (2). If the arrow points clockwise, the enantiomer has the *R* configuration; if it points anti-clockwise, the enantiomer has the *S* configuration, provided that the group with the lowest priority (4) is on a vertical bond.



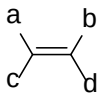
- If the group (or atom) with the lowest priority is on *a horizontal* bond, the answer you get from the direction of the arrow will be the opposite of the correct answer. For example, if the arrow points clockwise, suggesting that the asymmetric carbon has the *R* configuration, it actually has the *S* configuration; if the arrow points counter clockwise, suggesting that the asymmetric carbon has the *S* configuration, it actually has the *R* configuration. In the following example, the group with the lowest priority is on a horizontal bond, so clockwise signifies the *S* configuration, not the *R* configuration.



An example for finding configuration of a compound using Fischer projection formal is provided below.

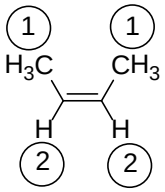


In case of nomenclature of unsaturated diastereomeric compounds which are geometric isomers, a different nomenclature is allowed. However, the CIP rules for determining priority are still used. Then the groups on each carbon of the double bond are marked according to priority. Now if the groups having higher priority are on the same side, then the group is labelled Z (*Zusamenn*- german for together) while if the groups of higher priority are not on the same side of the double bond then the compound is labelled as E (Entgegen –german for opposite)This system may be understood from the examples below.



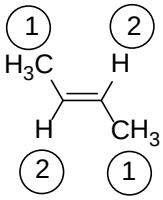
If priority order is a>b, c>d then compound is Z-compound

If priority order is a>b, c<d then compound is E-compound



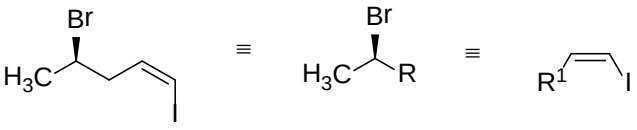
cis-butane

(Z)-but-2-ene



trans-butane

(E)-but-2-ene



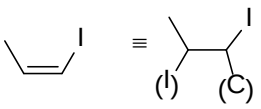
4-bromo-1-iodopent-1-ene

For the chiral centre,

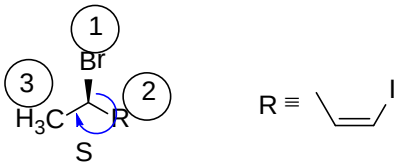
Following rule 1, bromo group gets first priority

Following rule 3, 

group gets second priority.



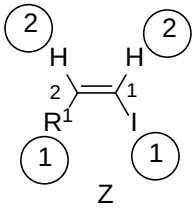
Following rule 2, methyl group gets third priority.

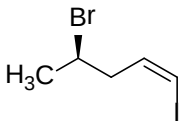


For the alkene part, priority order is as follows.

Following rule 1, iodo group gets first priority on C_1.

Following rule 3, R^1 gets first priority on C_2.





(*R*,*Z*)-4-bromo-1-iodopent-1-ene

The discussion so far concerns the enantiomers only on paper, but to separate them experimentally is altogether new ball game. The process of separating a racemic mixture into its component enantiomers is called resolution. Historically, Louis Pasteur had resolved tartaric acid by crystallization and then separating the enantiomers by tweezers on the basis of hemihedral faces. However, as Pasteur said “Chance favours the prepared mind”, he was indeed fortuitous in this case. As it happened, he prepared the solution of racemic tartaric acid below 23 °C. Had the temperature been any higher, he would have got crystals having both the enantiomers i.e.; racemic crystals. If the enantiomers in racemic mixture crystallize out of solution as pure enantiomers, then the enantiomers are said to form a conglomerate. It is usually rare and also depends on temperature and therefore the process is mainly of historical interest only. Sometimes seeding by the optically pure crystals of one enantiomer causes it to preferentially come out of solution.

A method that can be used practically is the based on the fact that enantiomers same physical and chemical properties but not diastereomers. This process involves the conversion of an enantiomer to a diastereomer by treating with a chiral reagent. The diastereomers are then separated by the usual methods. The separated diastereomers are then treated with appropriate reagents to regenerate the original enantiomers. An example of this method is the resolution of a racemic mixture of chiral acids by treatment with an optically pure base (Figure 7).

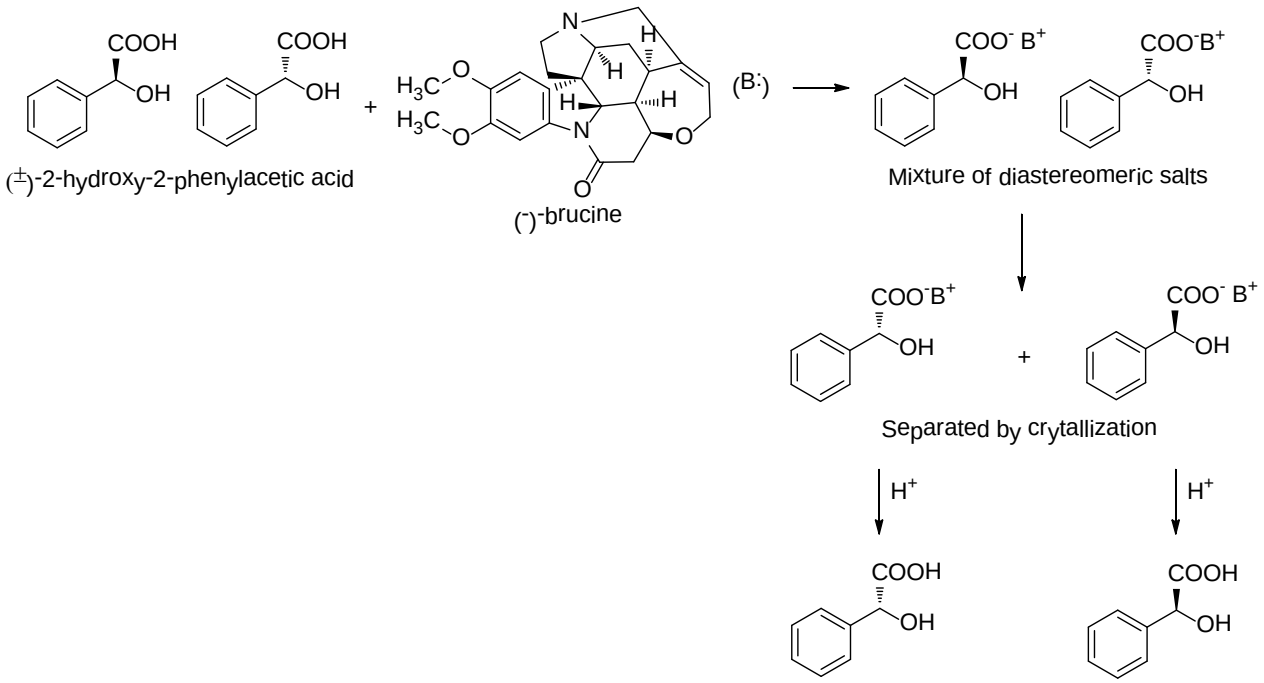


Figure 7

Module 8 Stereochemistry
Lecture 22 Stereochemistry III

Beside the formation of diastereomeric salts, enantiomers can be separated by resolution. Here, enantiomers react with chiral inclusion hosts to form diastereomeric inclusion complexes. This is called chiral recognition. So, if a particular host is employed, only one enantiomer forms inclusion complex while other remains in solution. However, mostly, both of the enantiomers form complexes but vary in the rate of formation of inclusion complexes. An example of this technique is the use of crown ether for the resolution of 1-phenylethanaminium hexafluorophosphate in chloroform (Figure 1).

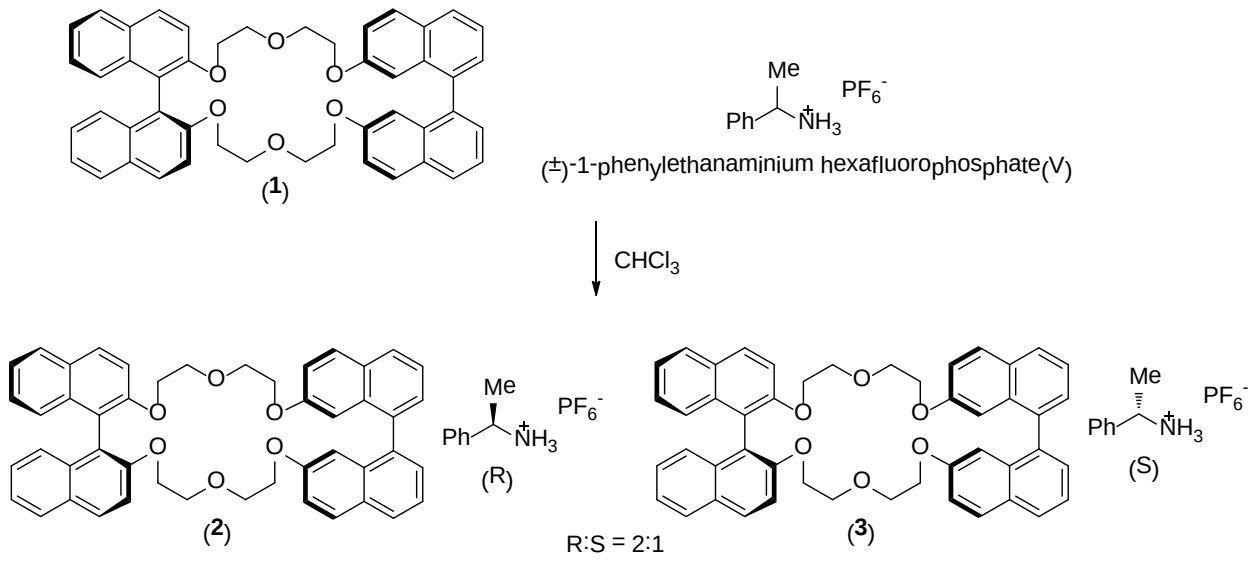


Figure 1

Similarly, enantiomers react at the same rate only with achiral reagents, but react differently with chiral reagents can be used to separate the enantiomers in a process called Kinetic Resolution. An example of application of this technique is the resolution of allylic alcohols with an enantiomer of chiral epoxidizing agent. In this case, only the (R) enantiomer was converted to the epoxide while the (S) isomer was unaffected. However, this method is sacrificial in nature as the recovery of one enantiomer often leads to the destruction of the other (Figure 2).

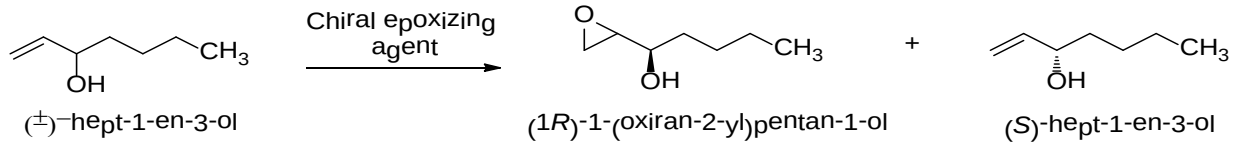


Figure 2

A variation of the sacrificial method for the resolution of a racemate involves treating it with some bacteria which contains a chiral enzyme that reacts at different rate with the different enantiomers. Since enzymes are very specific in their response to enantiomers, only one enantiomers is degraded and the other enantiomer is obtained with a very high purity (ee). This method however has only limited scope as the availability of such organisms or enzymes cannot be met easily. Thus, the enzyme emulsion from bitter almonds acts upon (±)-mandelonitrile to hydrolyze the (+)-form more rapidly.

With the advent of technology, column chromatography, the definitive tool for separation of organic compounds can also be applied for separation of enantiomers. The principle for the separation remains the same-differential adsorption-one enantiomer binds with the chiral stationary phase more strongly than the other thereby causing them to have different retention time in the column. Chiral stationary phase can consist of starch, which for instance allows almost complete resolution of mandelic acid (2-hydroxy-2-pheylethanoic acid), PhCH(OH)COOH. Synthetic stationary phases such as **A**, derived from the enantiomerically pure amino acid alanine, and **B**, likewise from valine, are effective in resolution of alcohols, amines and amino acids (both α and β) (Figure 3).

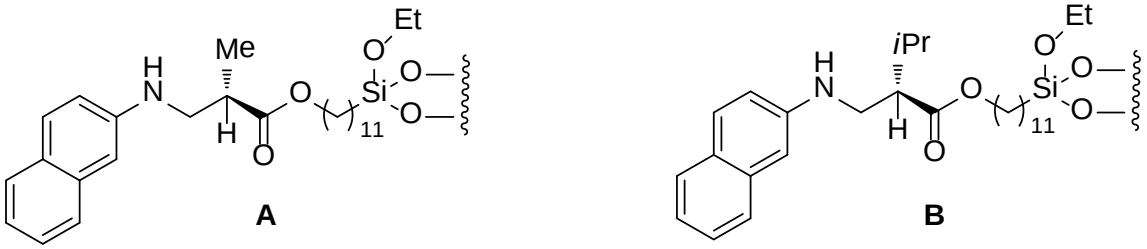


Figure 3

So far, all stereoisomers discussed differ in configuration but a separate class of stereoisomers also exist which are called conformational isomers. The difference between them being that in a set of conformational isomers, the isomers can be converted from one isomer to the other by mere rotation of bonds. On the other hand, configurational isomers cannot be achieved in this fashion. A bond needs to be broken and reconnected at the same stereocentre in a different spatial arrangement to obtain a configurational isomer from another.

As an example, the molecule of ethane is to be considered. Now, it cannot possibly have any configurational isomers since none of the carbons are dissymmetric. However, it may have conformational isomers. The atoms remain connected in the same order during conformational change. If the C_1-C_2-bond is considered in ethane, then it is possible to draw two structures, one in which the hydrogen atoms on one of carbon atoms eclipse the other and another where they are as far away from each other as possible. There is a difference in energy between the two structures. The eclipsed form has a higher potential energy than the staggered form (12 kJ mol^{-1}) (Figure 4).

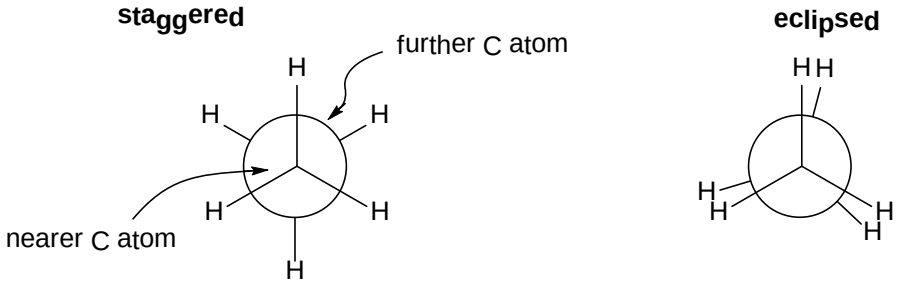


Figure 4

The rotational barrier in this case is said to be 12 kJ mol^{-1}. This is the energy required to convert the stable staggered form to the unstable eclipsed form (Figure 5). The change in energy on going from staggered form to eclipsed form and vice versa is plotted in with respect to the dihedral angle. The angle between two intersecting planes on a third plane normal to the intersection of the two planes is called dihedral angle. In this case the dihedral angle is angle between the planes containing the atoms **1** and **2** and the plane containing the atoms **3** and **4**.

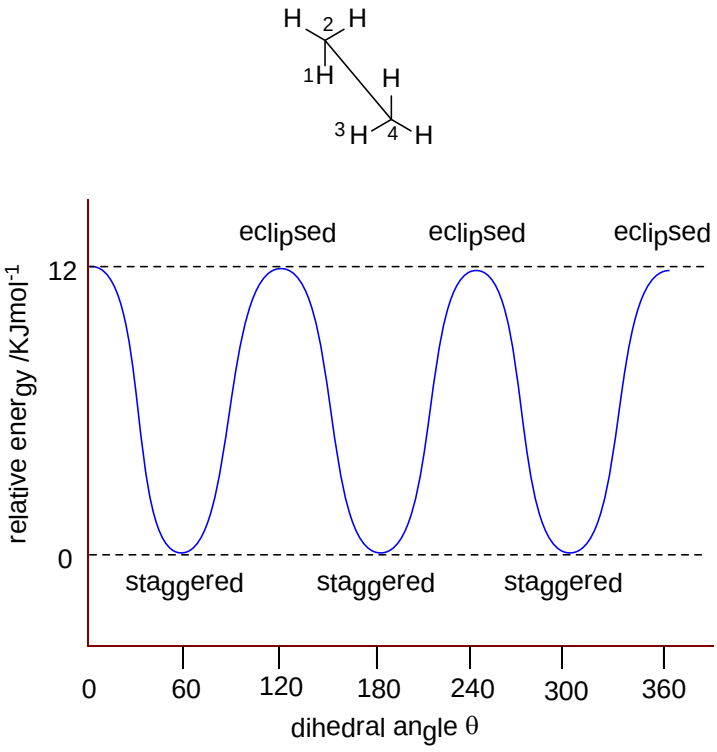


Figure 5

The conformational analysis of ethane is given below. Thus, between these two extremes, there are lots of other conformations and energy change is gradual is nature. However, this does not mean that the ethane spends equal time in all conformations. In fact it mostly stays at the bottom of the potential well (staggered conformation). Obviously, it comes to mind whether the hydrogen atoms are bulky enough to cause a change in the energy states of the eclipsed and staggered conformation. As a matter of fact, this occurs due to the fact that the electrons in the bonds repel each other and this repulsion is at a maximum in the eclipsed conformation. There

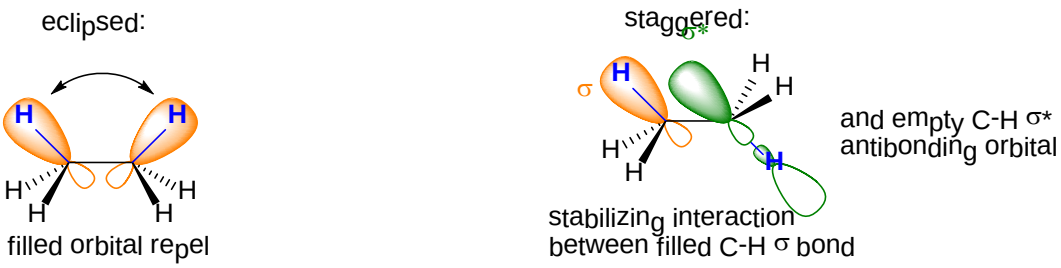


Figure 6

may be some stabilizing interaction between the C–H σ-bonding orbital on one carbon and the C-H σ* anti-bonding orbital on the other carbon, which is greatest when the two orbitals are exactly parallel: this only happens in the staggered conformation (Figure 6).

As the hydrocarbon chain size increases, more complex effects seem to effect the energy considerations of the conformations (Figure 7). In the conformational study of propane, the conformational analysis can be done either along the C_1-C_2 bond or the C_2-C_3 bond-both being identical. In this case, the rotational barrier being 14 $kJmol^{-1}$ is only slightly more than that of ethane. Thus the conformational analysis diagram is almost similar to ethane.

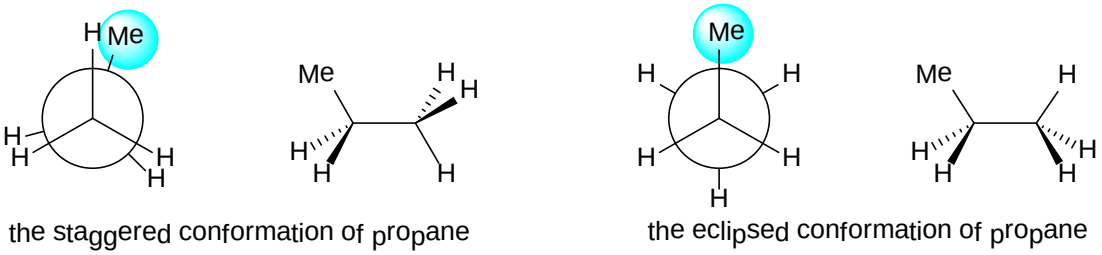


Figure 7

With butane, there are two methyl groups if we consider the C_2-C_3 bond as the pivotal bond for rotation. Here, the two methyl groups could eclipse each other in a conformation and since the steric hindrance due to this should be significant enough, so the potential energy will be highest for this conformation. The other eclipsed conformations will have a methyl group eclipsed by hydrogen which will be lower in energy than the former. Similarly, for the staggered conformations, there will two types of staggered conformations differing in energy. Hence the terms eclipsed and staggered are insufficient to describe the conformations.

A new system of naming the conformational isomers is thus devised (Figure 8). The term torsion angle is defined as the angle (having an absolute value between 0° and 180°) between bonds to two specified groups, one from the atom nearer (proximal) to the observer and the other from the further (distal) atom in a Newman projection. The torsion angle between groups A and D is then considered to be positive if the bond A-B is rotated in a clockwise direction through less than 180° in order that it may eclipse the bond C-D: a negative torsion angle requires rotation in the opposite sense. Stereochemical arrangements corresponding to torsion angles between 0° and ±90° are called syn (s), those corresponding to torsion angles between ±90° and 180° anti (a). Similarly, the arrangements corresponding to torsion angles between 30° and 150° or between -30° and -150° are called clinal (c) and those between 0° and 30° or 150° and 180° are called periplanar (p). The two types of terms can be combined so as to define four ranges of torsion angle; 0° to 30° synperiplanar (sp); 30° to 90° and -30° to -90° synclinal (sc); 90° to 150°, and -90° to -150° anticlinal (ac); ±150° to 180° antiperiplanar (ap). The synperiplanar conformation is also known as the *syn*- or *cis*-conformation; antiperiplanar as anti or *trans* and synclinal as gauche or skew.

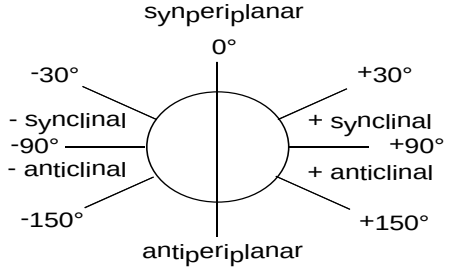
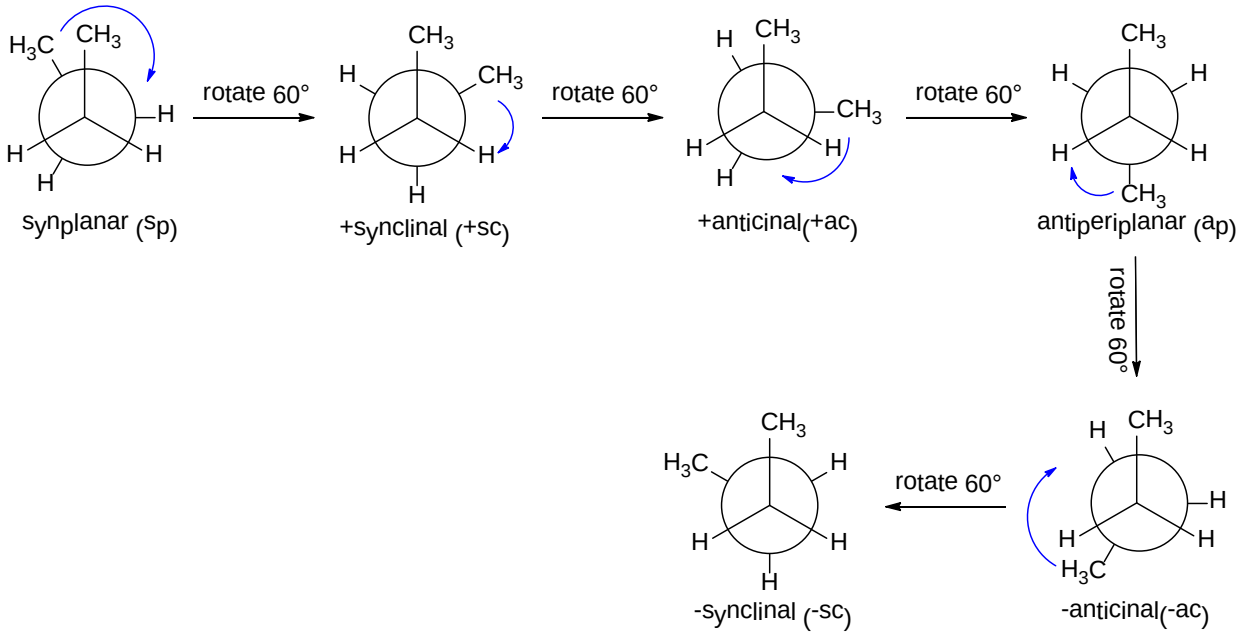


Figure 8

According to this system, the conformational isomers of butane due to rotation about the C2-C3 bond may be named as:



Thus, the conformational analysis diagram of the different conformational isomers of n-butane due to rotation about C_2-C_3 bond as a function of dihedral angle is given below (Figure 10). As expected the synperiplanar conformer having methyl groups eclipsed with each other has the highest energy and is least stable. The other eclipsed conformations have lower energy than the synperiplanar conformer. These are the two anticlinal conformations. The staggered conformers also show a similar pattern. Thus, there are two synclinal conformers (also called gauche conformers) where the two methyl groups are at an angle of 60° to each other. If we consider angle of torsion the then the two anticlinal conformers may be differentiated according to the sense of rotation of the angle of torsion. Thus they may be termed as +anticlinal (P-gauche) for a positive angle of torsion or –anticlinal (M-gauche) for a negative angle of torsion. The anticlinal conformations may also be prefixed with + or – to denote the angle of torsion.

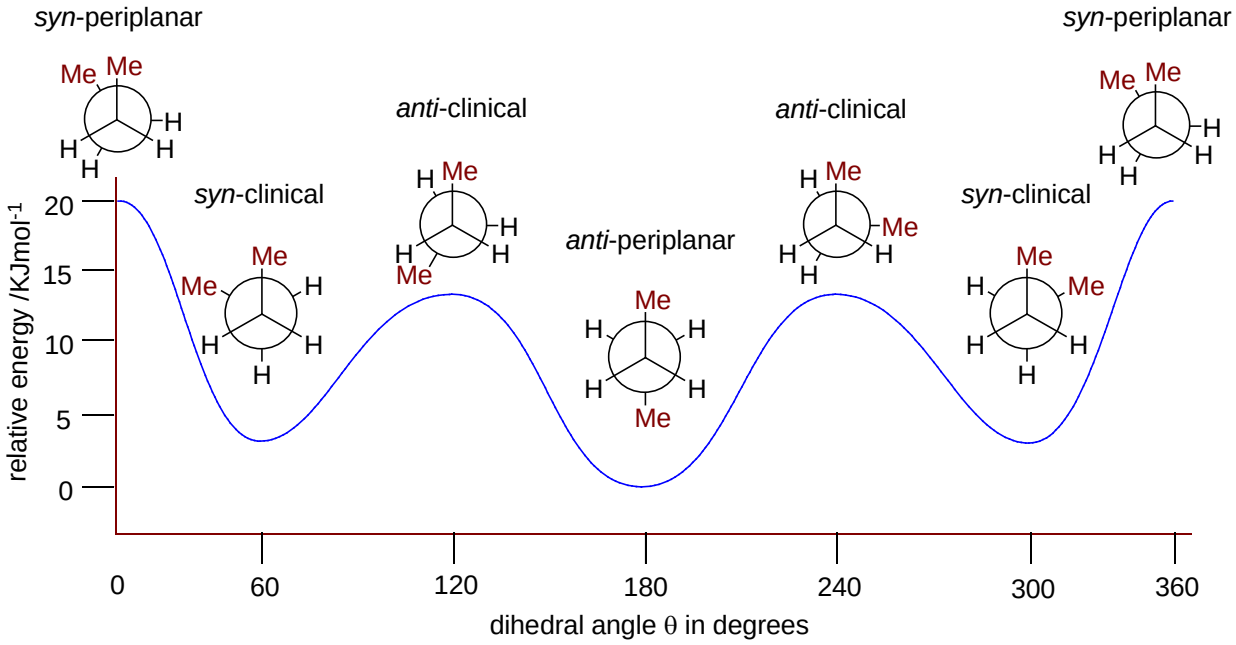


Figure 9

The compounds considered so far are linear compounds and thus rotation about carbon-carbon bond is easily possible. However, it is expected that this rotation will be hindered in cyclic compounds. Also, the hindrance will large in small rings compared to large rings. This brings to a new concept- Bayer's ring strain.

In a alicyclic compounds, all the carbons are sp^3 hybridized and thus the bond angle should be 109° ideally. But in a small planar ring, like that of cyclopropane it is not possible to achieve this bond angle. As such the actual bond angle in cyclopropane is 60° instead of 109°. This thus introduces a strain in the molecule known as ring strain. According to Bayer, this strain would increase as rings grow larger and smaller than cyclopentane, they should show increasing angular strain and increasing strain energy.

In reality, a different scenario emerges as it is observed that, the cyclopropane ring is highly strained, the ring strain decreases with ring size and reaches a minimum for cyclohexane and not cyclopropane. The ring strain then increases but not as rapidly as is expected by Bayer's theory and reaches a maximum at cyclononane and then decreases again. As the number of ring carbons increase beyond 14, the ring strain remains roughly constant.

This apparent deviation between theory and observed fact could be explained by the erroneous assumption that the rings are planar. In 1890 Hermann Sachse argued that, cyclohexane exist as non-planar chair and boat conformations which could rapidly interconvert into one other. This was experimentally observed by O. Hassel and D. Barton, who using X-ray crystallography one half of the twelve bonds of cyclohexane in the chair conformation of cyclohexane were arranged parallel to 3-fold rotational axis (C_3 axis) while the remaining half were close to the imaginary equator plane of the ring system. The former group of hydrogens are called axial hydrogen while the later are called equatorial hydrogens (Figure 10).

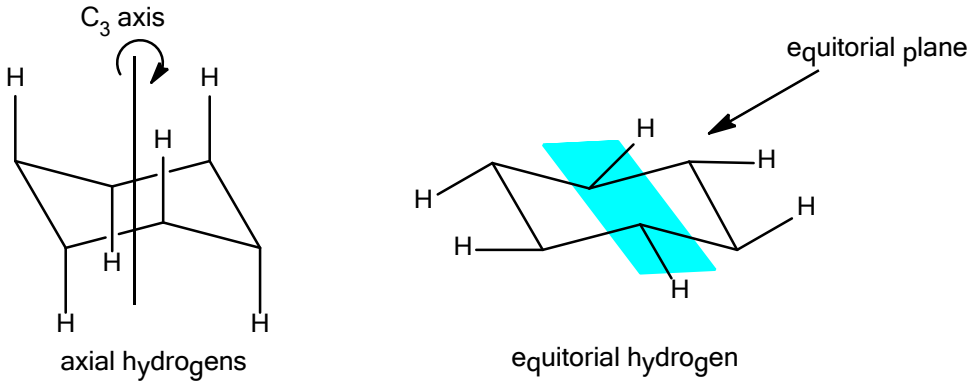


Figure 10

In the chair conformation, all the bond angles are 109° and hence there is no angle strain. The same may be said of the boat conformation, where all the angles are also 109°. However, it will be seen later that this conformation is higher potential energy than the chair form. In this case, the different groups of hydrogens are shown below (Figure 11).

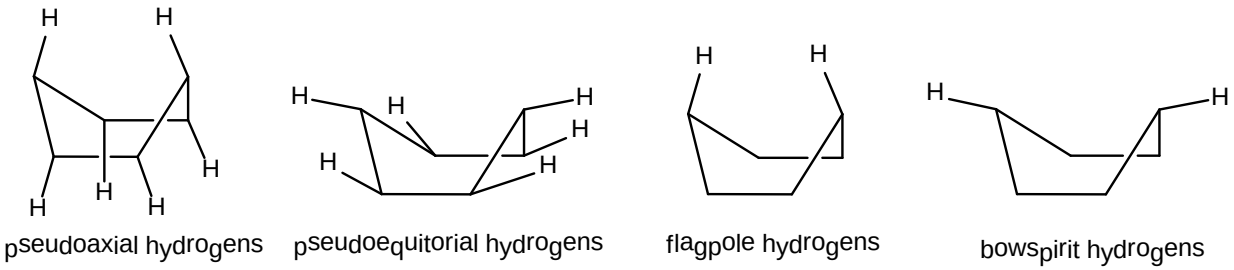


Figure 11

To understand why the boat conformation has higher energy than the chair conformation, they need to be drawn in the Newmann projection. As can be seen from the Newmann conformational formula, in chair conformation, there is no eclipsing of the C-H bonds. However, in boat conformations, there are several eclipsing interactions. Besides these, there is also an interaction between the two flagstaff hydrogen atoms. These interactions cause the boat conformation to have 25 kJ mol^{-1} higher energy than the chair conformation (Figure 12).

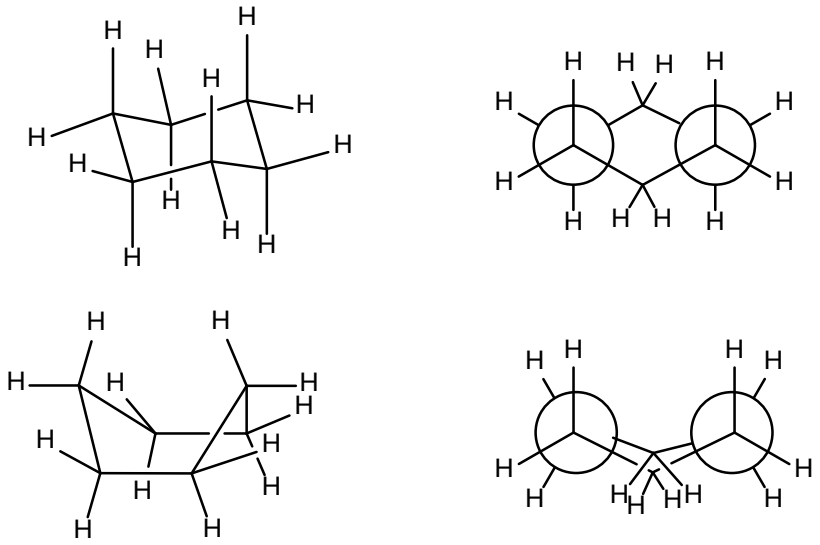
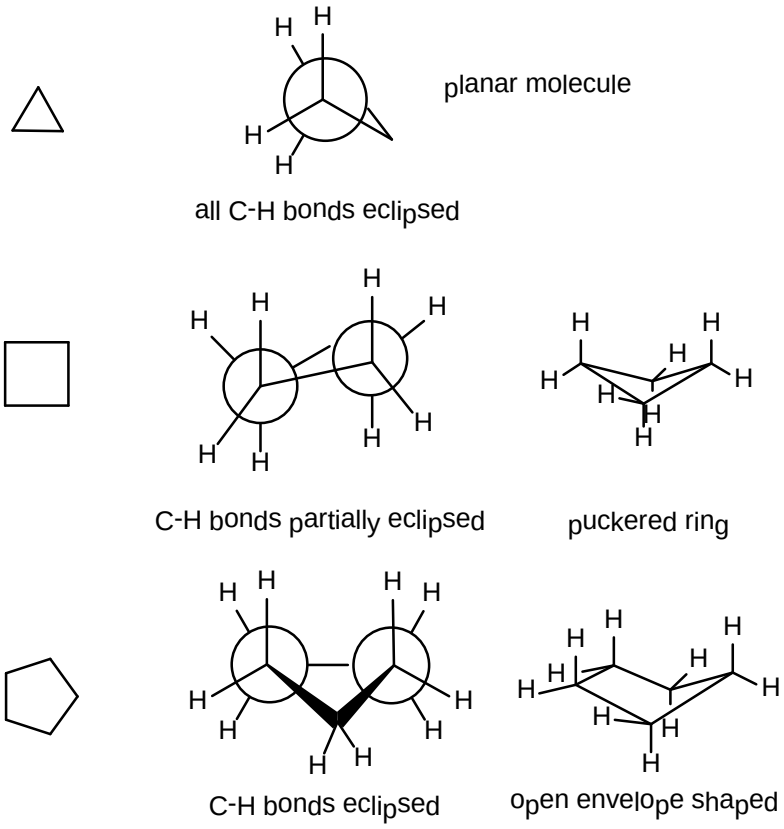


Figure 12

Thus the non-planarity of the cyclohexane ring causes the ring strain to decrease. Thus, it may be expected that the phenomena may be occurring in other smaller ring system to

relieve the ring strain (Scheme 13). In fact, the cyclobutane and cyclopropane rings are not planar as well. But, non-planarity alone cannot relieve ring strain because the smaller size of ring does not allow the freedom required to twist the C-C bonds out of plane without cleaving the ring. The high value of heat of combustion of cyclopropane is a clue to the ring strain due to deviation from the normal bond angle of a sp^3 hybridized carbon and also the result of eclipsing of all C-H bonds. In cyclobutane, the ring bends to adopt a so called "puckered ring" shape. This shape though alleviates the eclipsing of C-H bonds but decreases the bond angles to 88.5°, even further to increase the ring strain. Thus, it appears that the eclipsing effect is impotant. Thus, in cyclopentane, even when the bond angles (108°) are close to the ideal value, there is some strain in the molecule and this causes the cyclopentane to adopt an open enevelope form which in turn decreases bond angle and increases angle strain.



Scheme 13

Module 8 Stereochemistry
Lecture 23 Stereochemistry IV

So far, all the stereogenic centres discussed involve a carbon atom with 4 different substituents attached to it (asymmetric centre). However, in case of trivalent central atoms having a lone pair of electrons, the lone pair of electrons may be considered as a fourth substituent. Usually, in such cases, the enantiomers will undergo Walden inversion from one form to other. The Walden inversion may however be prevented by locking using bulky substituents. Here, while the trisubstituted aliphatic amines easily undergo inversion, the same is not possible for aziridines as it would require twisting of the 3-membered ring. Similarly, in Troger's base, the trivalent nitrogen is present on bridge head and cannot undergo inversion (Figure 1).

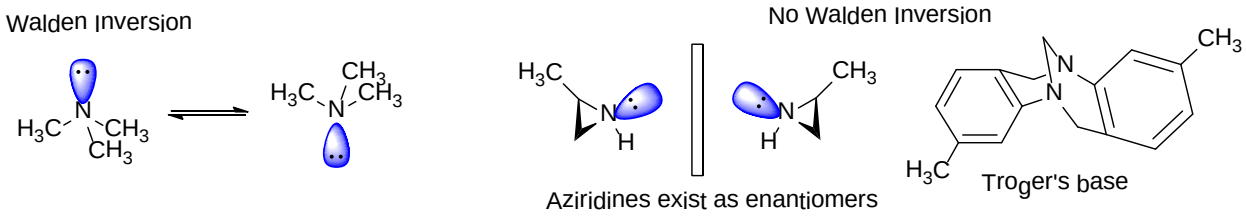


Figure 1

It is also to be remembered that for a compound to have enantiomers, it must be non-superimposable on its mirror image. This condition can also be satisfied by certain other compounds which do not have asymmetric centre. As an example, *cis*-octahedral complexes may exhibit enantiomers even though they lack an asymmetric centre (Figure 2).

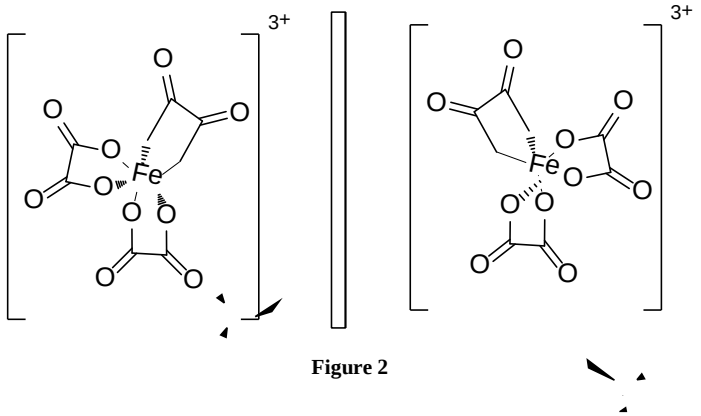


Figure 2

Some compounds which do not have asymmetrically substituted carbon atoms (no stereogenic centre) may still be chiral if they feature two perpendicular planes which are not symmetry planes. If these disymmetric (chiral) planes cannot freely rotate against each other, the corresponding compounds are chiral. Compounds of this type are said to be axially chiral. Some examples of this type involve unsymmetrically substituted allenes, biphenyl derivatives and spiro compounds (Figure 3).

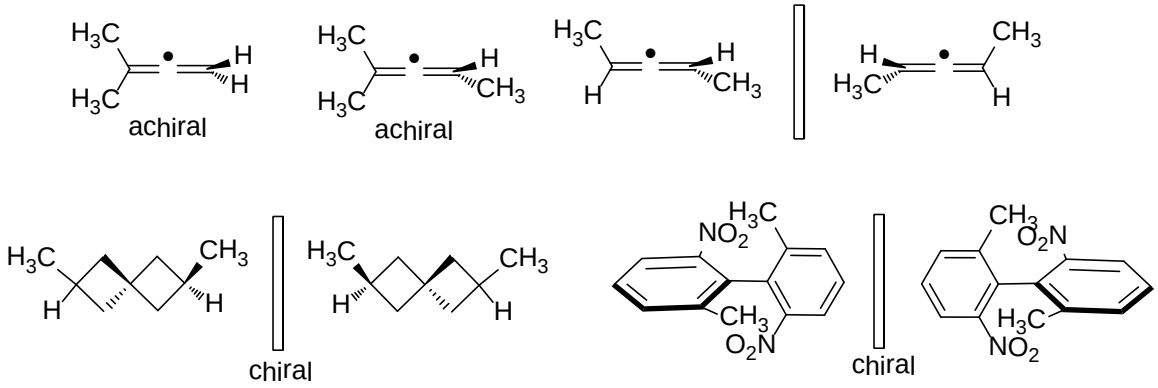
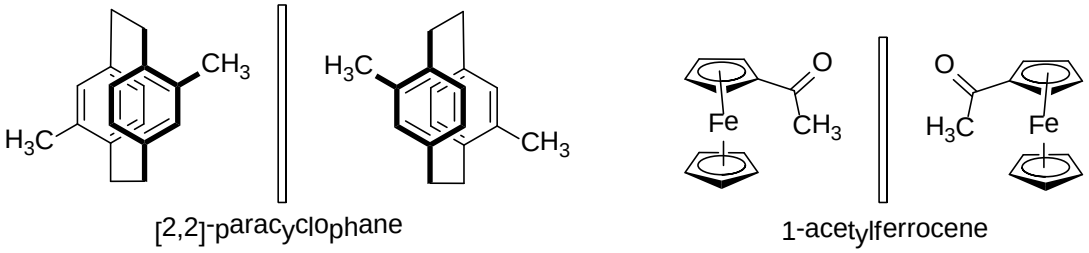


Figure 3

In case of biphenyl derivatives, if both aromatic ring systems are asymmetrically substituted, the compounds are chiral. As the chirality of these structures originates not from an asymmetrically substituted atom center, but from an asymmetric axis around which rotation is hindered, these enantiomers are also called atropisomers. In the biphenyls, the *ortho*-substitutents must be large enough to prevent rotation around the central single bond. Since only the hindered rotation about the central C-C single bond leads to the stereoisomerism of these compounds. Therefore, biphenyl- and binaphtyl-derivatives are conformational stereoisomers (not configurational stereoisomers).

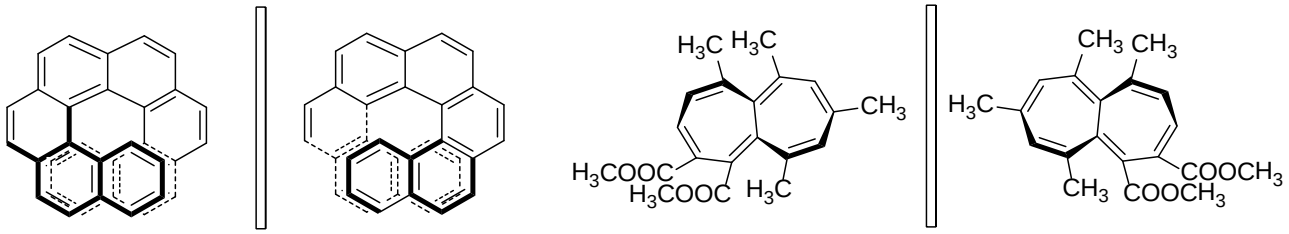
Planar chirality may arise if an appropriately substituted planar group of atoms or ring system is bridged by a linker-chain extending into the space above or below of this plane. Some common examples are the planar chirality of cyclophanes or alkenes as shown below (Figure 4).



[2,2]-paracyclophane 1-acetylferrocene

Figure 4

Helices are also chiral as they can exist in enantiomeric left- or right-handed forms. Typical examples for helical strutures are provided by the helicenes (benzologues of phenanthrene). With four or more rings, steric hinderance at both ends of these molecule prevents the formation of planar conformations, and helicenes rather adopt non-planar, but helical and enantiomeric structures with C_2 symmetry (Figure 5).



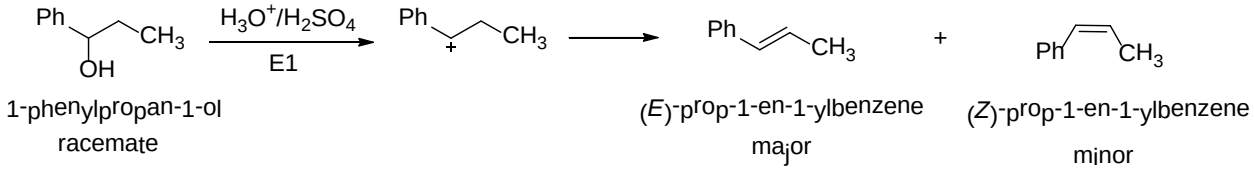
[8]-helicene enantiomers

dimethyl 5,6,8,10-tetramethylheptalene-1,2-dicarboxylate

Figure 5

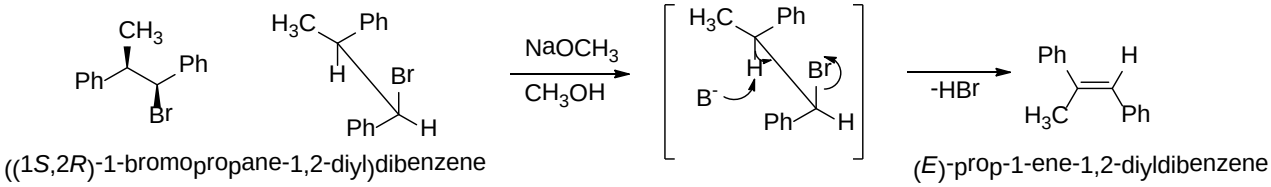
The stereochemistry of a substrate may have profound effect on the rate of a reaction or the composition of the products of a particular reaction. With respect to the composition of products obtained by a reaction two terms are important.

- Stereoselective reactions are those reactions which give one predominant product of the two or more products possible because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product (thermodynamic control). Thus, E1 dehydration of 1-phenylpropan-1-ol provides (E)-prop-1-enylbenzene as the major product (Scheme 1).



Scheme 1

- On the other hand, stereospecific reactions lead to the production of a single isomer as a direct result of the mechanism of the reaction and the stereochemistry of the starting material. There is no choice. The reaction gives a different diastereoisomer of the product from each stereoisomer of the starting material. In case of E2 elimination of ((1S,2R)-1-bromopropane-1,2-diyl)dibenzene, only the E-alkene is formed as the product (Scheme 2).

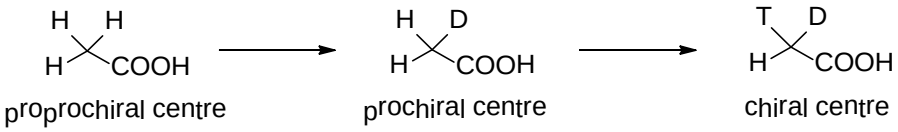


Scheme 2

These two classes of reactions may further be subdivided into enantioselective or diastereoselective reactions and enantiospecific or enantiospecific reactions based on the product formed.

In some reactions, an achiral centre may be converted to a chiral centre. Similarly, a double bond may be converted into chiral centres. To understand the relationship between an achirl substate and chiral product, two new terms need to be introduced.

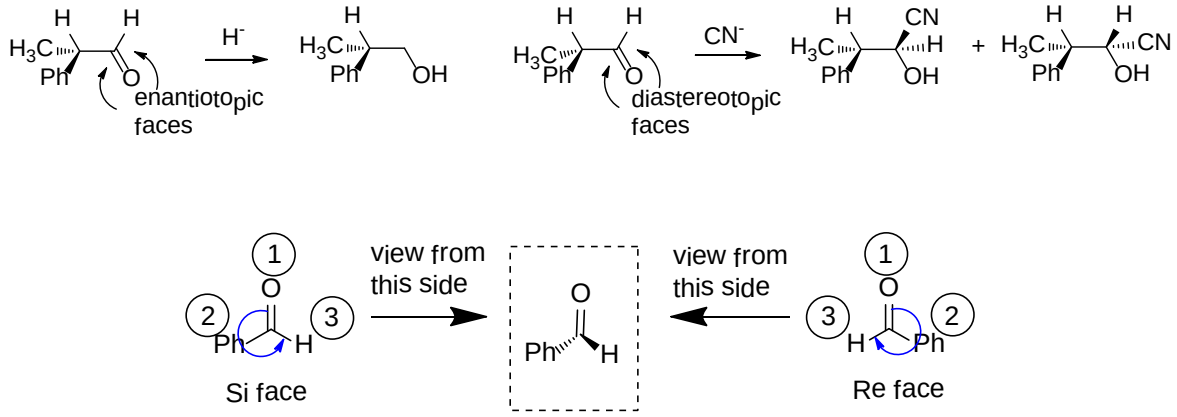
Prochirality is the geometric property of an achiral object (or spatial arrangement of points or atoms) which is capable of becoming chiral in a single desymmetrization step (Figure . An achiral molecular entity, or a part of it considered on its own, is thus called prochiral if it can be made chiral by the replacement of an existing atom (or achiral group) by a different one. An achiral object which is capable of becoming chiral in two desymmetrization steps is sometimes described as proprochiral (Scheme 3).



Scheme 3

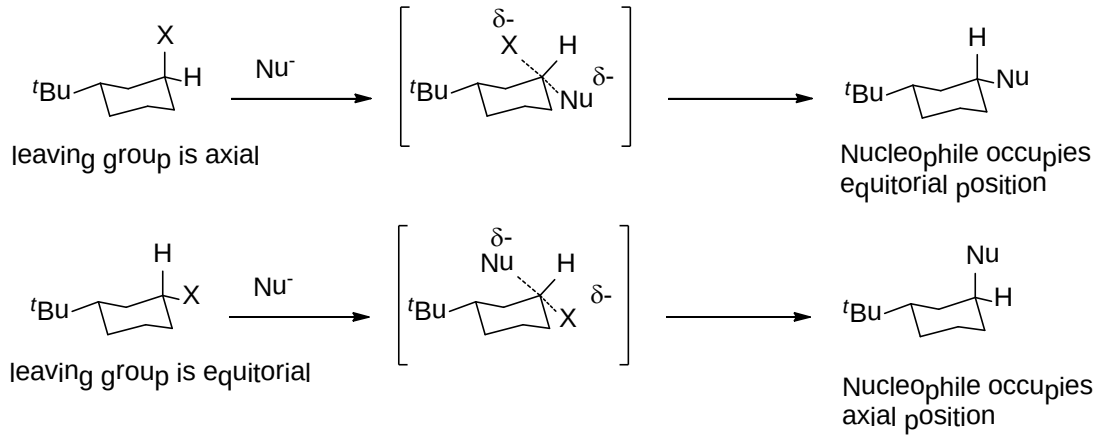
In the case of addition reactions, multiple bonds may be reduced to single bonds giving rise to chiral centres (Scheme 4). In these cases, there are no prochiral centres but rather prochiral faces. Thus, the term prochirality also applies to an achiral molecule or entity which contains a trigonal system and which can be made chiral by the addition to the trigonal system of a new atom or achiral group. The addition of hydrogen to one of the faces of the prochiral ketone methyl ethyl ketone gives one of the enantiomers of the chiral alcohol. Since the addition of hydrogen generates an enantiomer and not a diastereomeric alcohol, so the faces in this case are referred to as enantiotopic faces. However, the same faces may regarded as diastereotopic if the addition of a nucleophile generates a diastereomic species. Thus, addition of cyanide anion to one of the diastereotopic faces of the chiral aldehyde shown below converts it into one of the diastereoisomers of the cyanohydrin. The two faces of the trigonal system may be described as Re and Si. The allotment of the descriptor follows a rule similar to the allotment of R and descriptors. First, the substituents are assigned priority according to the CIP rules. Next, consider the molecule in the plane of paper. Then, looking from the top, an arrow from the first-priority group, through the second, to the third. If the arrow

points clockwise, the face is called (*Re*). If the arrow points counter-clockwise, the face is called (*Si*).



Scheme 4

In the next few pages, some of the reactions discussed in various chapters will be discussed from a perspective of stereochemistry (Scheme 5). S_N2 reactions of cyclohexane derivatives present a nice case. If the conformation of the molecule is fixed by a locking group, the inversion mechanism of the S_N2 reaction, means that, if the leaving group is axial, then the incoming nucleophile will end up equatorial and vice versa.



Scheme 5

It is, however, found that the substitution of an axial substituent proceeds faster than the substitution of an equatorial substituent. This is because, in the formation of the transition state, the nucleophile attacks the σ*-molecular orbital of the carbon-leaving group (C-X) bond. In the case of an axial attack, this line of attack is hindered by the axial groups at 3 and 5 positions. For an equatorial attack the direction of attack is parallel with the axial groups antiperiplanar to the leaving group and hence much less hindered (Figure 6).

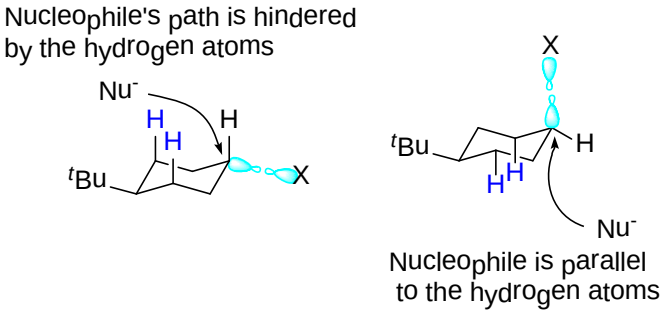
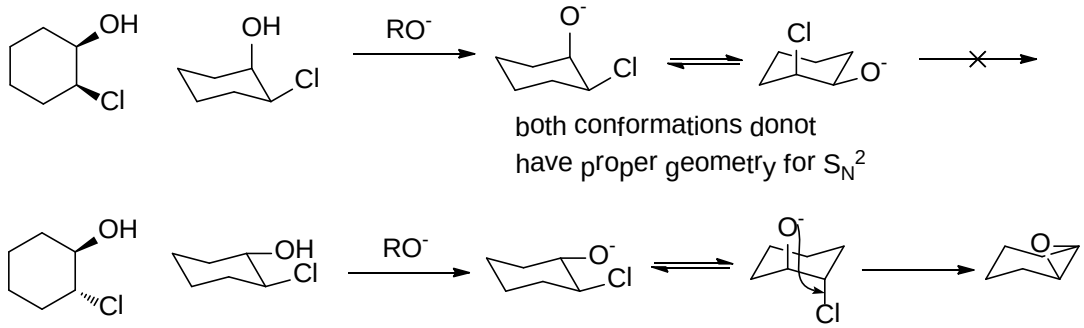


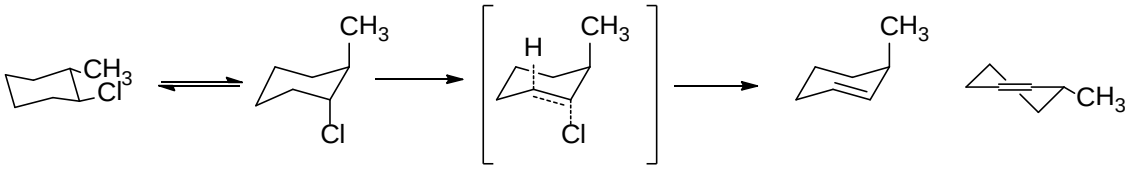
Figure 6

Similarly, the ring closing to form epoxides occurs only in the trans isomer. The *cis* isomer adopts a conformation where one of the groups is axial (less bulky one), while the other is equatorial. In this conformation the two groups are not antiperiplanar as required for a S_N2 reaction. The *trans* isomer, on the other hand adopts a conformation where both the groups are equatorial to each other. Though, it still seems not suited for a S_N2 attack but the attack can take place in the diaxial conformation which may be generated from the diequitorial conformation by ring flipping. Though the former is less stable than the latter, a small amount of the molecule in diaxial conformation may drive the reaction forward (Le Chatelier's principle) (Scheme 6).



Scheme 6

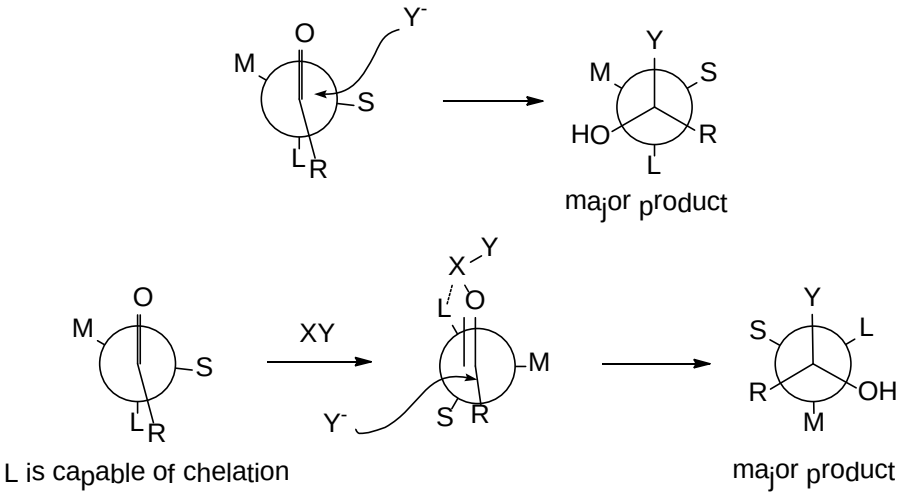
As with substitution, the elimination reaction in cyclohexane derivatives is also dependent on the conformation. Since E2 reactions can occur only through an antiperiplanar transition state so they must be stereospecific in nature. Thus, in the elimination of *trans*-1-chloro-2-methyl cyclohexane, the elimination takes place from the diaxial isomer (Scheme 7).



Scheme 7

One of the most profilic stereoselective reactions is the nucleophillic attack on carbonyl compounds. These compounds have two stereogenic faces and, thus, it is a question on which face will the attack preferentially take place. In this respect two empirical rules have been developed which predict the same result.

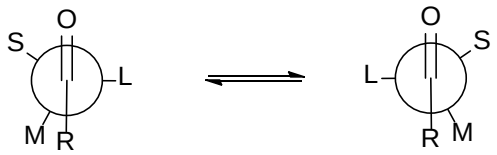
- Cram's rule: According to this rule, if the molecule is observed along the axis, (represented as shown below), where S, M and L stand for small, medium and large, respectively. The oxygen of the carbonyl orients itself between the small and the medium sized groups. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group (Scheme 8).



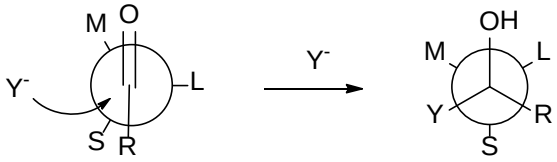
Scheme 8

But, when chelation may occur between the carbonyl oxygen and the counteraction of the incoming nucleophile, then the result of Cram's rule may be reversed. In this case the large group chelates counter cation of attacking nucleophile and carbonyl oxygen.

- Felkin Ahn model: The statement of the rule is same as that of Cram's rule but the objective is achieved by reasoning from a different angle. Assuming that there isn't an unusually electronegative atom on the carbon next to the carbonyl, the largest group (L) prefers a conformation where it is perpendicular to the carbonyl C=O. This gives two relatively competitive lowest energy conformations, with the medium (M) and smallest (S) groups differing in their proximity to the carbonyl oxygen.

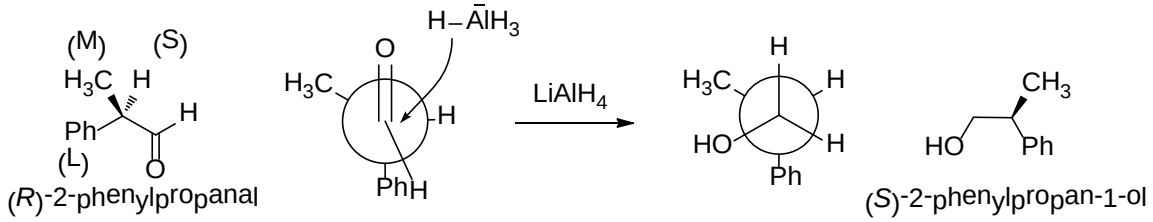


It is further determined that the nucleophile prefers to attack away from the large group at an angle of 107°. Thus, it attacks nearer to the small (S) group giving rise to only one diastereomer.



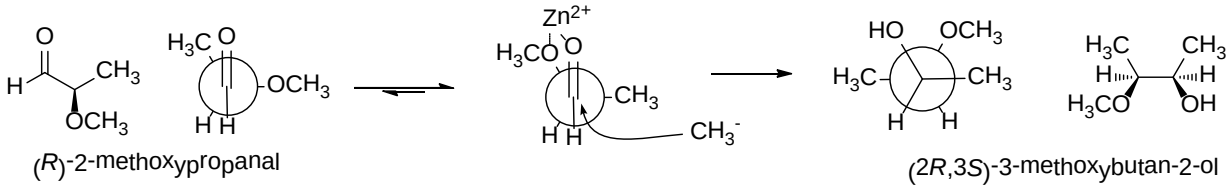
If, however, there is an electronegative atom or group at the site α- to the carbonyl, there is a slight change. This 'slight change' is that this electronegative group(X) becomes the equivalent of the 'large' group in the Felkin-Ahn model. The reason for this that the energy of the C-X σ* antibonding orbital is rather low, and so it overlaps with the π*of the carbonyl to make a new, lower energy LUMO (lowest unoccupied molecular orbital). This really means is that this conformational arrangement is more reactive than any other.

A few examples will clarify the case of application of these rules. The major product for reduction of (R)-2-phenylpropanal can be predicted according to the Cram's rule (Scheme 9).



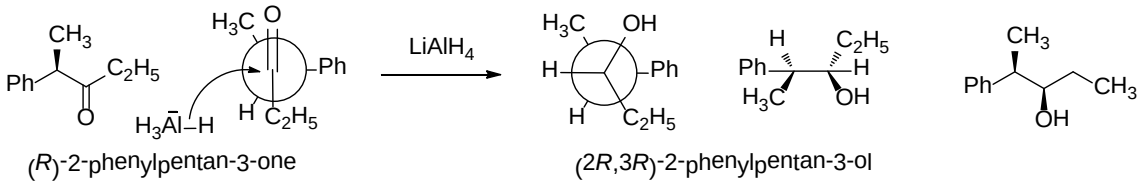
Scheme 9

However, to determine the configuration of the product of the reaction between (R)-2-methoxypropanal and dimethyl zinc, the Cram's chelate rule needs to be applied. In this case a chelate is formed between methoxy group's oxygen and carbonyl group with zinc (Scheme 10).



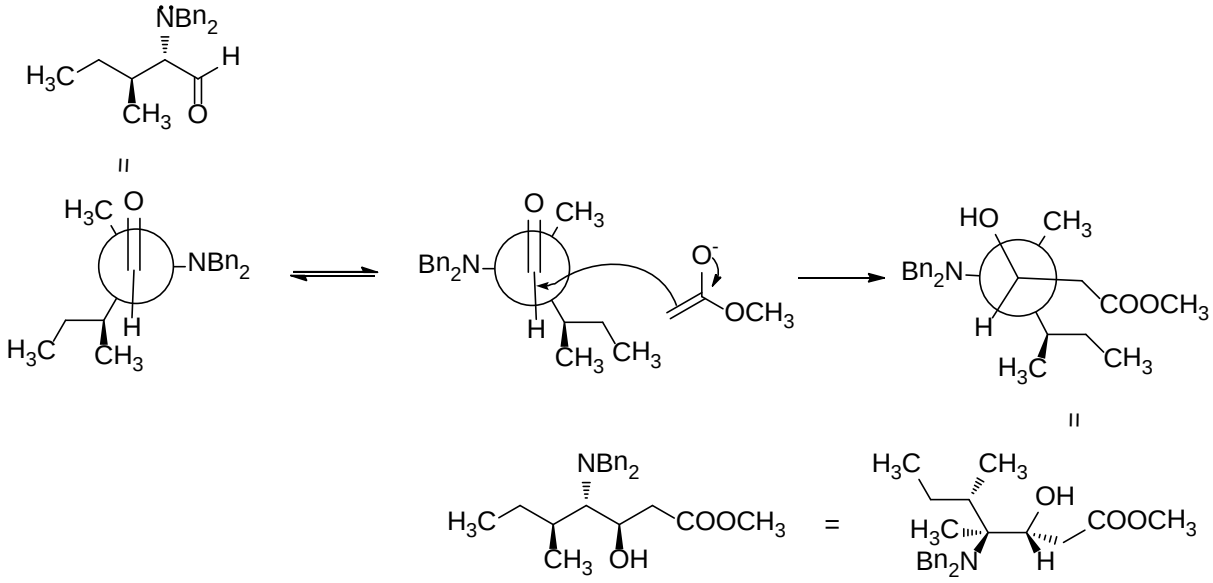
Scheme 10

Similarly Felkin Anh model is applied for the following example. Here, the large, medium and small groups are phenyl, ethyl and methyl groups, respectively. The attack of hydride (R)-2-phenylpentan-3-one takes from the side of the smallest group (Scheme 11).



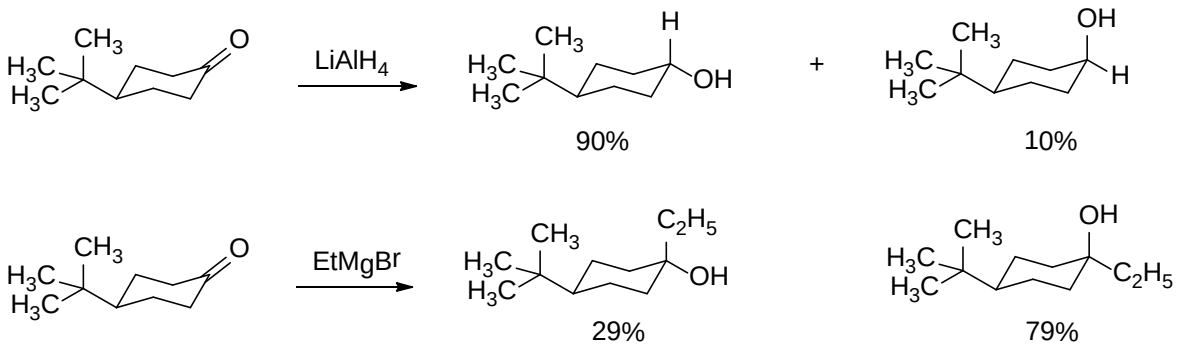
Scheme 11

In this case, there is an electronegative atom containing a lone pair of electrons. Here, also classification of the groups into large, medium and small group. As a result of the overlap between C-N σ* antibonding orbital π*of the carbonyl makes this conformation shown below even more important. This results in great increase in the degree of diastereoselectivity (Scheme 12).



Scheme 12

In case of cyclohexanone derivatives, a cyclic system, the addition of a nucleophile generates either a conformation with the nucleophile at an equatorial or an axial position. However, unless the molecule is locked in a particular conformation, it does not matter whether the nucleophile is attacking a line to the equatorial or axial position since a ring inversion can put the molecule in a favourable conformation. However, in 4-^{t}butylcyclohexanone, the t-butyl group always occupies equatorial conformation. Now, with the increase in steric bulk of the attacking nucleophile, there will be tendency to attack at the equatorial position as compared to the axial position. Thus, the reduction of 4-^{t}butylcyclohexanone with $LiAlH_4$ results in mostly in *trans* alcohol while Grignard addition of C_2H_5MgBr results in mostly *cis*-alcohol (Scheme 13).



Scheme 13

Steric hindrance often slows down a reaction. Similarly, sometimes steric assistance increases the rate of a reaction. The phenomena can be seen in the ester hydrolysis of conformationally locked cyclohexane deivatives. In the ester hydrolysis the rate limimting slow step is the formation of sp^3 hybrid intermediate by the nucleophilic addition on the trigonal carbonyl group. This imparts some steric bulk to the intermediate as well as decreases its degree of solvation as the species is now negatively charged. Thus, on going from the ester to the intermediate, the steric requirement of the ester group increases as it passes through the transition state. As a result, the difference in free energies of the axial and equatorial isomers is enhanced in the transition state than in the ground states and the axial isomer reacts at a slower rate. This is an example of steric hindrance. However, in the chromic acid oxidation of cyclohexyl alcohols a different scenario. This reaction is supposed to consist of two steps, the rapid formation of a chromate ester followed by its rate determining decomposition into a ketone. In this case

the axial alcohols are oxidized faster than their equatorial isomers. This occurs because the difference in free energies between the axial and the equatorial chromate esters in the ground state exceeds that between the respective transition states due to more ketone like structure of the latter.