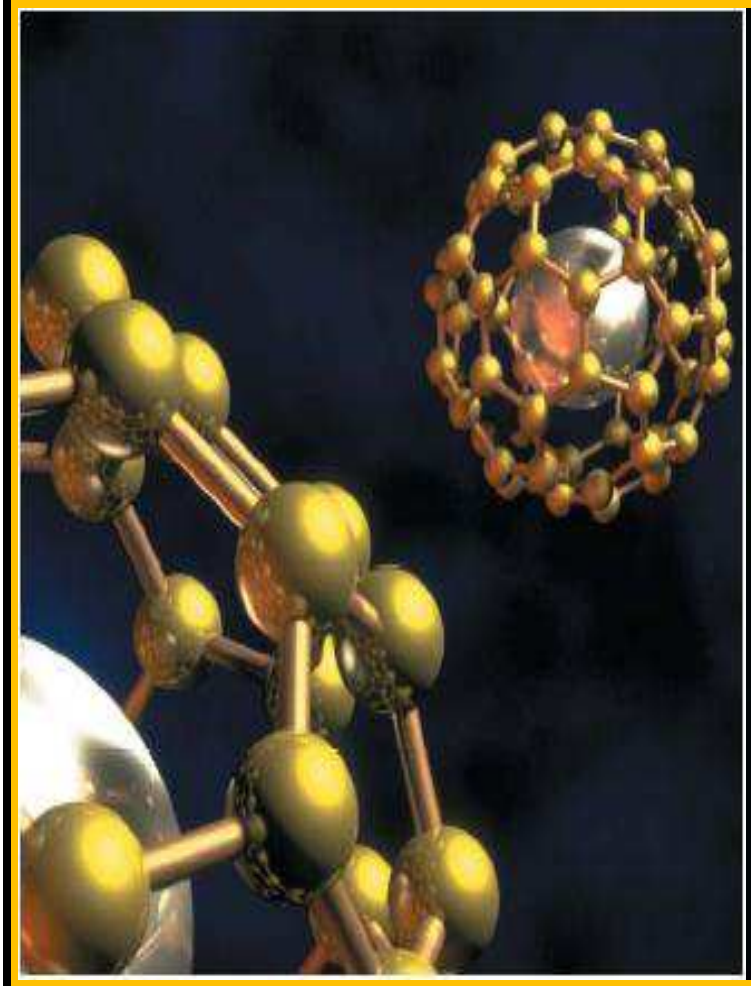
MSCCH-502

M. Sc. I Semester

ORGANIC CHEMISTRY-I



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DEPARTMENT OF CHEMISTRY
UTTARAKHAND OPEN UNIVERSITY

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UNIT 1: NATURE OF BONDING IN ORGANIC MOLECULES

CONTENTS

1.1 OBJECTIVE

- To describe localized and delocalized bonding
- To explain conjugation and related concepts
- To illustrate Hückel's rule and aromaticity
- To compare aromatic, non-aromatic and anti-aromatic compounds
- Introduction, synthesis and applications of crown ethers, cryptands, and inclusion compounds
- Synthesis and applications of catenanes, rotaxanes and ionic liquids

1.2 INTRODUCTION

Organic compounds have great importance in human's life. The carbon comes from a variety of sources like plants, animals and vegetables etc. What are these products? How they are formed? By the term "organic," we actually mean about the molecules that are created from the carbon element (C). Carbon shows striking flexibility in its ability to form various different bonding arrangements with other carbon atoms as well as with elements such as nitrogen (N), oxygen (O), sulfur (S), and phosphorus (P). As such, the presence of covalent bonds is the characteristic of organic (carbon) compounds. The linkages in carbon chemistry are called bonding which is chiefly responsible for the synthesis of various organic products.

1.3 DELOCALIZED CHEMICAL BONDING

In organic chemistry, it has been realized that the concept of having delocalized electrons is invoked repeatedly to explain the behavior as well as different properties of organic compounds. Indeed, the electronic delocalization is a very important concept. The electrons that are limited to

a particular region are generally called localized electrons. The localized electrons are confirmed between two atoms or belong to a single atom while some electrons are not confirmed to a single atom or bond. The electrons which neither belong to a single atom nor are limited to a bond between the two atoms, but are shared by three or more atoms are known as delocalized electrons. Thus, delocalization is a characteristic feature of π-electrons, where the π-electrons changes their locations (in between different sub-orbitals).

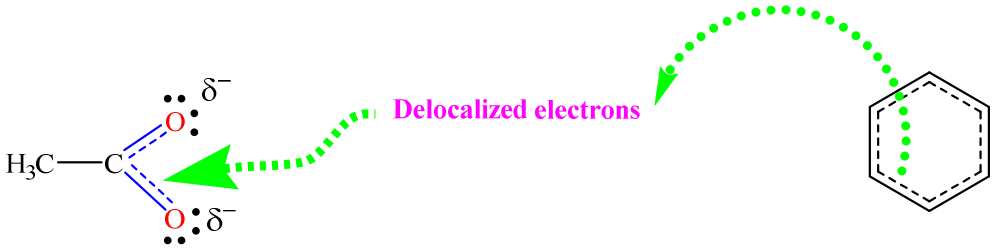


Figure 1 Structures of (left) the acetate ion and (right) benzene (resonance hybrid)

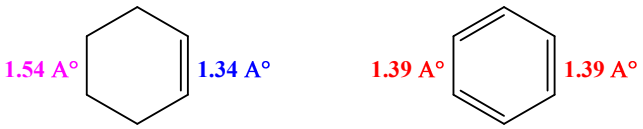
In Figure 1, have you noticed that the two electrons stand for a π-bond of the COO^-group are common between one carbon and two oxygen atoms? The dashed lines indicate that the two electrons are delocalized (shared) over three atoms. However, a drawback of using dashed lines to represent delocalized electron is that they do not tell us about how many π-electrons are there in the molecules. For example, the dashed lines inside the hexagon in the representation of benzene indicate that the π-electrons are shared uniformly by all the six carbon atoms and that all the carbon-carbon bonds have the same bond lengths, but they do not entail about the exact number of π-electrons in the benzene ring (Figure 1, right side). For this reason, chemists prefer to use structures with localized electrons to approximate the actual structure having delocalized electrons. The main factor which influences delocalization is the extra availability of sub-orbitals of about same energy than those of the number of electrons. The delocalization usually involves sp^2, sp^3, and other complex hybridizations. It chiefly occurs due to the presence of double and triple bonds which are the characteristics of hybridization.

1.3.1 Types of delocalization: The delocalization in chemical bonds can be carried out in different ways, and in different systems. Some of these systems are briefly discussed as follows.

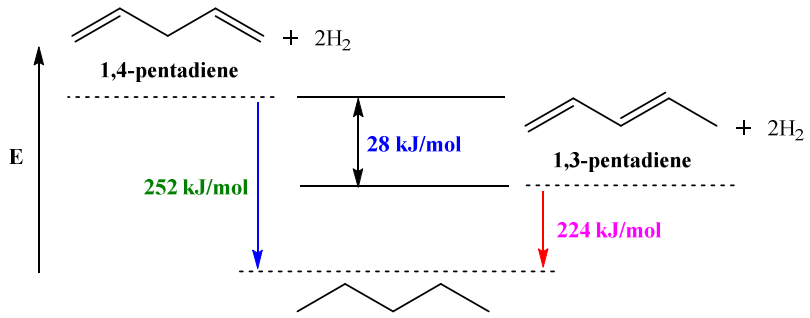
1. **Isolated systems:** The delocalization of electrons occurs in those compounds in which double bonds are separated by more than one single bond.
2. **Conjugated systems:** The systems in which alternate single and double bond exist. For example, benzene.
3. **Cumulated systems:** If double bonds are adjacent to each other as in 1,2-dipropene ($H_2C=C=CH_2$).The delocalization is carried out by forming a delocalized bond to uphold the stability of the molecule. Hyperconjugation is also the result of delocalization.

1.3.2 Consequences of electron delocalization:

a) Intermediate bond length: In simple molecules, C-C (alkanes) and C=C (alkenes) bond lengths are 1.54 and 1.34 Å, respectively but in case of benzene, all C-C bond lengths (single, double, and delocalized) are 1.39 Å (see below).



b) Stability of diene: Compounds having delocalized bonds are more stable than those of normal compounds. For instance, 1,3-pentadiene is more stable than 1,4-pentadiene by 28KJ/mol as shown below.



c) Acidity: Delocalization increases the acidity of compounds e.g. carboxylic acids (RCOOH) are much more acidic than those of alcohols (ROH).

d) Stability of carbonium ion: It contributes toward the stability of a carbocation intermediate. e.g. allylic and benzylic carbocations have delocalized electrons, and thus they are more stable than other primary carbocations.

e) **Dipole moment:** Dipole moment also increases due to the delocalization of electrons, which are involved in resonance.

1.3.3 Orbital picture of delocalization:

The orbital picture of delocalization can get somewhat complicated. We start by noting different varieties of sp^2-hybridized carbon atoms. The most important and common sp^2-hybridized carbons are neutral and positively-charged sp^2 carbons. Substances having neutral sp^2 carbons are regular alkenes. Species containing positively-charged sp^2 carbons are called carbonium ions. The central carbon in a carbocation has trigonal planar geometry with an unhybridized empty p orbital. These concepts can be best conveyed as shown in Figure 2.

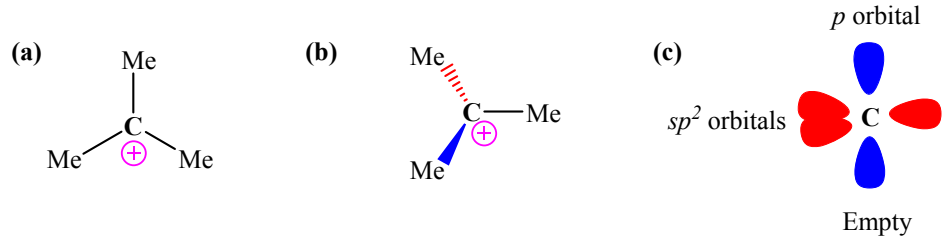
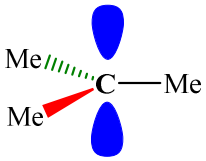
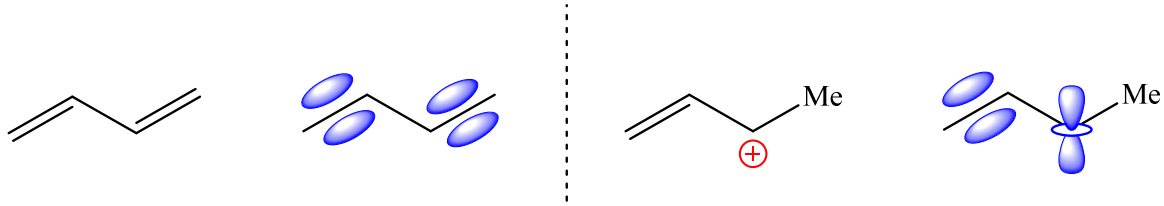


Figure 2 (a) top and (b) side view of a carbonium ion in Lewis and 3D representation while (c) is an orbital overview of a carbonium ion or carbocation

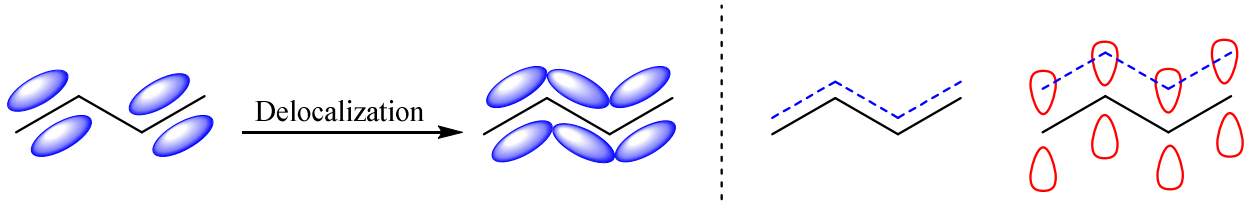
A combination of Lewis and orbital or 3D formula is a popular means of representing certain features that we may want to highlight. For example, if we omit sp^2 orbitals and just focus on the role of p orbitals, we can use the following notation.



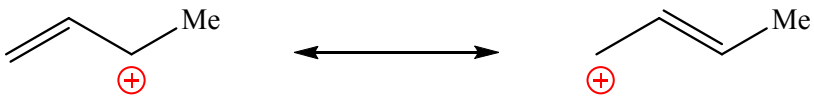
Let's now focus on two simple systems where the delocalization of π-electrons exists. In particular, one of these systems contain two π-bonds in conjugation while the other has a π-bond next to a positively-charged carbon atom. The line drawing along with the orbital picture of these systems can be presented as follows.



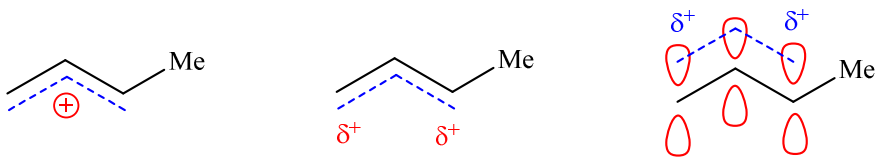
The two π-molecular orbitals shown in blue color on the left below are close enough to overlap. Indeed, the overlapping of orbitals is a good sign as it helps in the delocalization of the electrons and spreads them over a larger area, and thus imparts stability to the system. It is however time-consuming to draw orbitals all the time, and a delocalized system can be presented as shown on the right below. An analogous process applicable to the carbocation can lead to a similar picture.



It would be worthwhile to mention here that the resonance representation conveys the idea of delocalization of charge and electrons rather well (see below).



On a final note, the following representations are sometimes also used, but again, the simpler they are, the less accurately they represent the delocalization picture.



1.4 CONJUGATION AND CROSS-CONJUGATION

A system or molecule which has alternate single and double bonds simply serves as a conjugated system. Conjugation relies on the partial overlap of p-orbitals on adjacent double or triple bonds. A very familiar conjugated system is 1,3-dienes such as 1,3-butadiene. In a conjugated system, overlap of p-orbitals allows electrons to be delocalized over a larger portion of the molecule, thus lowering the energy of the molecule and making it more stable. The conjugation effect is at a maximum when the axes of the orbitals are aligned in a parallel style because this allows a maximum orbital overlap. The word "***conjugation***" is derived from a Latin word that means "to link together". Conjugation provides an electron highway for electrons to delocalize from one side of a molecule to another. Due to delocalization of electrons, a delocalized bond is formed by fluctuation of π-bonds resulting in different structures, which are known as resonance or contributing structures.

Notably, any atom that is capable of donating a p orbital can be the part of a conjugated system, and thus the atoms with lone pairs, radicals or carbonium ion may be the part of a conjugated system as shown in Figure 3.

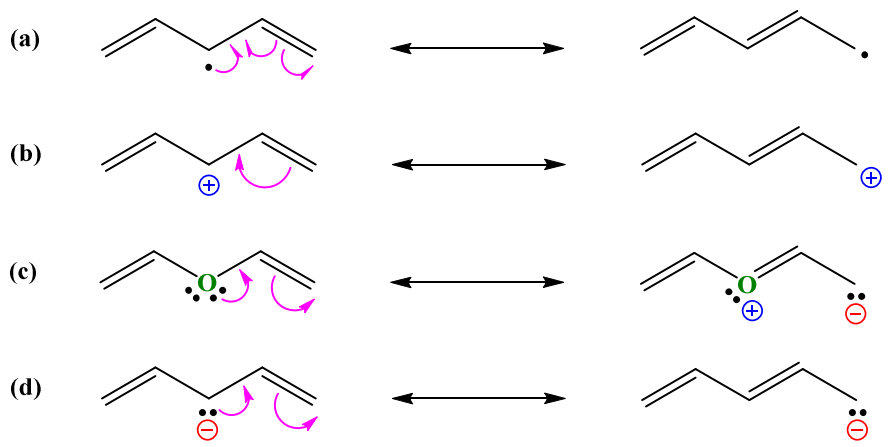


Figure 3 Representative conjugated systems: (a) radical; (b) carbocation; (c) an atom with a lone pair, and (d) carbanion

Aside from that, conjugated compounds may be linear, cyclic, and also of mixed types (Figure 4). Conjugation is broken completely by the introduction of saturated (sp^3-hybridized)

carbon atom. Systems containing conjugated double bonds are more stable than those containing non-conjugated double bonds, i.e. 3-Cyclohexenone is less stable than 2-Cyclohexenone.

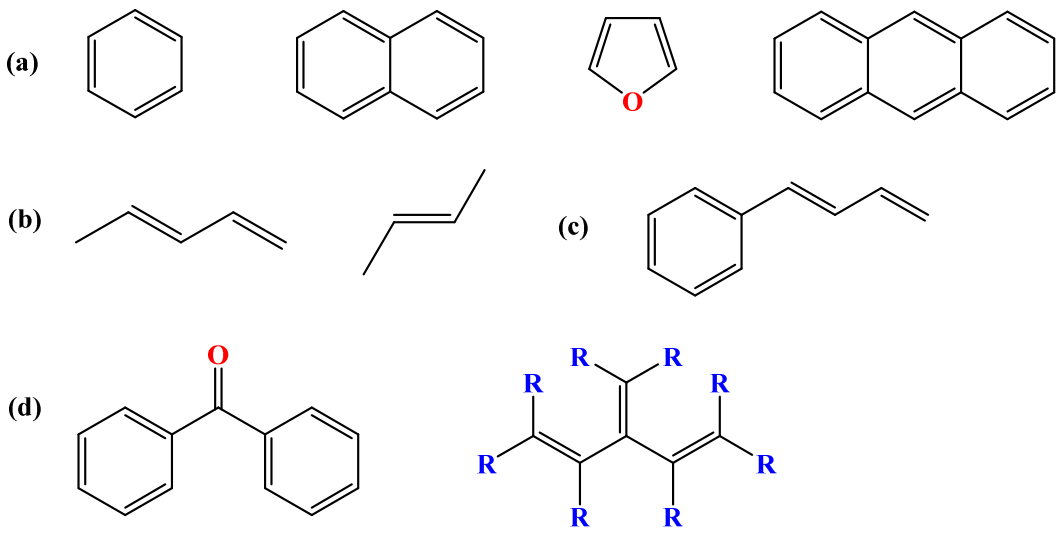
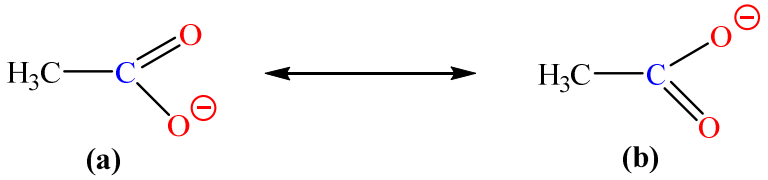


Figure 4 Examples of different conjugated systems; (a) cyclic, (b) linear, (c) mixed, and (d) cross-conjugated systems

Alongside of conjugation phenomenon, it would be worthwhile to know about cross-conjugation. Specifically, cross conjugation is a special type of conjugation in which three double bonds are present; out of which two double bonds are not conjugated with each other although each one is conjugated with the third double bond (Figure 4d). i.e interruption of the strict alteration of single and double bonds.

1.5 RESONANCE

Most of the organic covalent compounds have a single Lewis structure (dot structure).The Lewis structure explains the bonding in that molecule, but for many molecules, two or more dot structures are also possible. To explain the structure and physico-chemical properties of such covalent compounds that could not be represented by a single structure, Heisenberg introduced the phenomenon of resonance. Specifically, resonance is a situation in which more than one plausible structures can be written for a species but not the true structure at all. For example, the acetate ion can be represented by two equivalent structures, (a) and (b) as shown below:



Resonating structures (a) and (b) of an acetate anion

Of the above two structures, one structure cannot exactly describe all the properties of acetate ion, and thus each of these two structures can contribute to the true structure of the acetate ion. These types of different structures are called 'resonance or canonical structures'. The structure with localized electrons is called a resonance contributor, a resonance structure, or a contributing resonance structure while the actual structure with delocalized electrons is called a resonance hybrid as shown for benzene (Figure 5). The resonance structures are just alternate Lewis structures for a given ion or molecule. The stability of a real molecule is usually measured in terms of resonance energy or resonance stabilization energy. The resonance energy is defined as the energy difference between the most stable resonating structures and the resonance hybrid form. In benzene, the experimentally measured carbon-carbon bond length is 140 pm, which is intermediate of C-C (154 pm) and C=C (134 pm) bond lengths, suggesting that a resonance hybrid is a true representation.

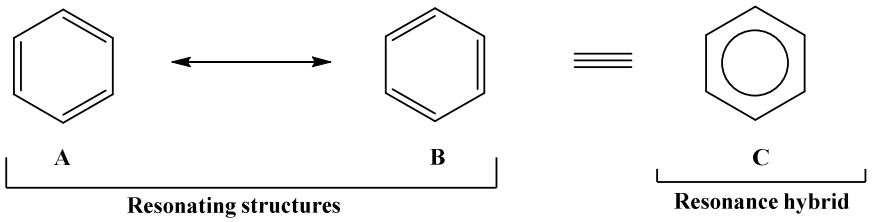


Figure 5 Resonating structures (A and B) and resonance hybrid form (C) of benzene

Resonance is very important and significant feature of many organic molecules. Resonance influences the structure, chemical reactions and physical properties of such molecules. In order to fully understand this phenomenon, one must be able to draw the contributing resonance structures as well as the resonance hybrid form.

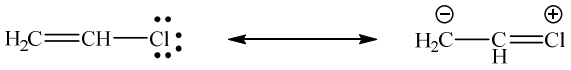
Characteristics of resonance/resonance structures

- All the atoms in the molecules taking part in resonance must be coplanar. This is essential for successful overlap of the p-orbitals.

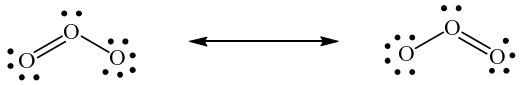
- The sp^3-hybridized atoms do not participate in resonance. They exist only in those parts of molecules that are composed of sp or sp^2 atoms; p-orbitals are an absolute requirement for resonance.
- While making a resonance structure, electrons (lone pairs/π-electrons/a negative charge or the unpaired electrons present on radicals) move only between the adjacent atoms. In particular, these electrons move to the 'resonance acceptor atom' from a 'resonance donor atom', which must be adjacent to the acceptor atom. An atom with a formal positive charge, can also be a resonance acceptor atom as long as the atom does not accept more electrons than it can normally accommodate.
- The resonance structures (or contributing structures) are only the imaginary structures. Thus, the resonance structures do not have a real existence as the individual species. These imaginary structures only proposed to explain the properties of a molecule, and none of these 'resonance structures' can be prepared in the laboratory.
- The resonance hybrid is the real structure. Due to the resonance conjugation fact, the bond lengths in resonating structures exhibit equal values.
- In different resonating structures, the position of the nuclei must be the same in all the structures and the total charge should also be constant.
- The resonance hybrid has lower energy and thus greater stability than any of the contributing structures.
- Greater the resonance energy, greater is the stability of the molecule.
- The structures with similar charges on adjacent atoms are irrelevant due to electrostatic repulsion, and consequently, show instability.
- Those structures have small contribution where negative charge (when separating charge giving rise to ions) is on the less electronegative elements.

For clarity, the resonating or canonical structures of some selected species are given below.

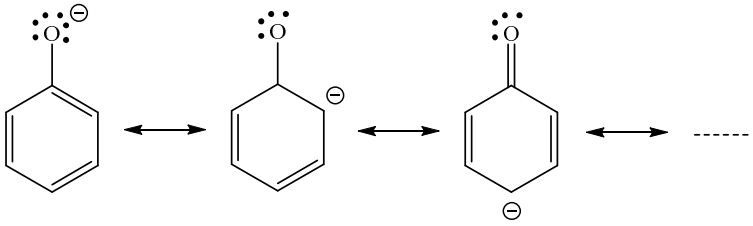
Vinyl Chloride



Ozone



Phenoxide ion



1.6 HYPERCONJUGATION

In an elegant work, Baker and Nathan suggested that alkyl groups with at least one α-hydrogen atom, when attached to an unsaturated carbon atom, are capable to release electrons by a mechanism similar to that of the electromeric effect. This effect is known as hyperconjugation or Baker-Nathan effect. Hyperconjugation is an unusual type of resonance in which delocalization of electrons takes place through the overlapping between the sigma (σ) bond orbital(usually C-H or C-C) with an adjacent empty or partially filled *p*-orbital or a π-orbital giving an extended molecular orbital that increases the stability of the system. The stabilization arises because the orbital interaction leads to the electrons being in a lower energy orbital (Figure 6a). Hyperconjugation occurs due to the partial overlap of sp^3-s σ bond orbital and the empty p-orbital or π-bond orbital of an adjacent carbon atom.

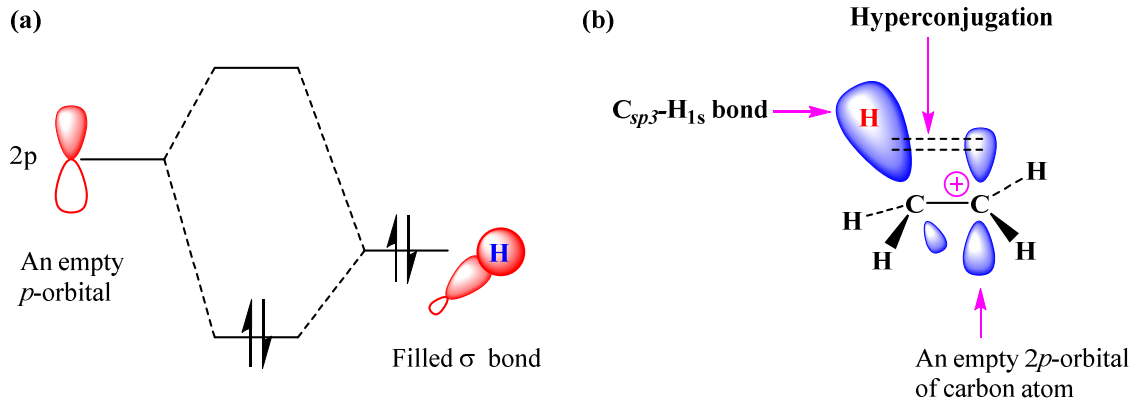


Figure 6 The orbital pictures of hyperconjugation

From figure 6b, we observe that one of the three C-H bonds of the methyl group can align in the plane of the empty *p*-orbital and the electrons constituting the C-H bond in a plane with this *p*-orbital can then be delocalized into the empty *p*-orbital. This results in the delocalization of π-electrons and increase the stability of molecule.

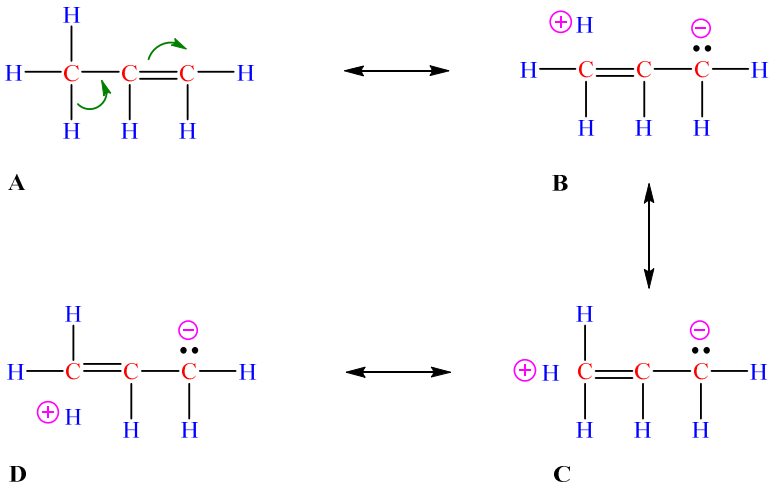


Figure 7 Resonating structures of propene exemplifying hyperconjugation effect

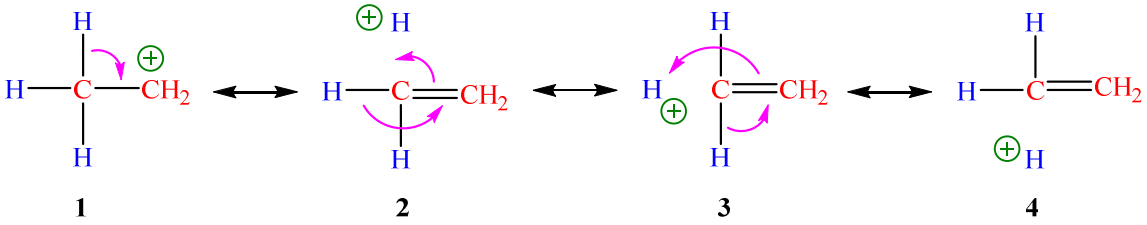
As can be seen in the resonating structures of propene (Figure 7), there is no bond between carbon and hydrogen ion, therefore, hyper conjugation is also called as no bond resonance. Based on the valence bond model of bonding, hyperconjugation can be described as "double bond-no bond resonance". This type of delocalization involves σ and π-orbitals, and thus it is also called as σ-π conjugation. Notably, Hyperconjugation effect is a permanent effect. What is the key difference between hyperconjugation and resonance? Hyperconjugation is a factor in explaining why increasing the number of alkyl substituents on a carbocation or radical centre leads to an increase in stability.

Examples of Hyperconjugation

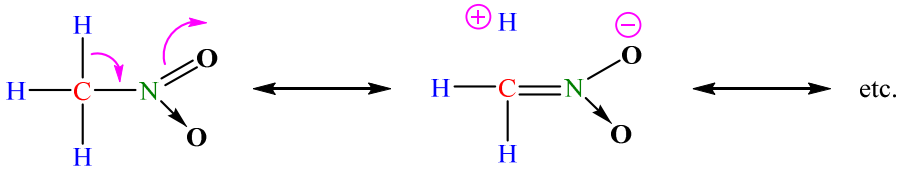
There are many molecules and reaction intermediates which can show hyperconjugation effect. Some of the common examples are as following.

1. **Carbonium ion:** In carbocation or carbonium ion such as ethyl carbocation, the σ electrons of C_{sp3}-hydrogen bond are delocalized with an empty *p*-orbital of positively-charged carbon

atom and can show four contributing structures, similar to that of propene as discussed above.



2. **Free radicals:** Like carbonium ion, free radicals get stabilized through hyperconjugation. The σ electrons of C-H bonds of methyl group next to the carbon atom contain an odd electron and interact with *p*-orbital having an odd electron. As the number of α-carbon-hydrogen bond increases, the number of contributing structures also increases resulting in greater stability.
3. **Alkene:** In 2-butene, the interaction of π-bond with α-carbon-hydrogen bond can form six resonating structures of 2-butene (not shown here).
4. **Nitromethane:** The nitrogen-oxygen π-bond can interact with α-carbon-hydrogen bond as shown below.



5. **Toluene:** The carbon-hydrogen σ bond interacts with π-bond of aromatic ring to form four contributing structures of toluene (Figure 8).

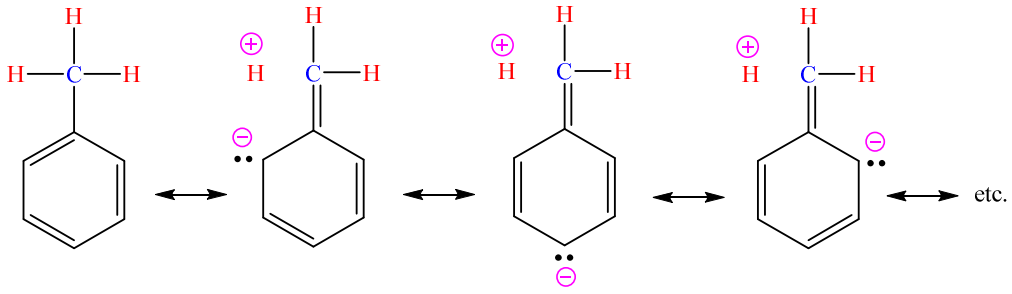


Figure 8 The orientation influence of methyl group in toluene due to hyperconjugation effect

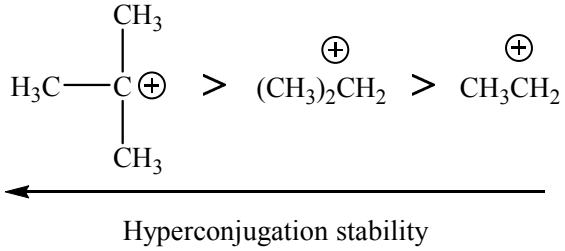
Applications of hyperconjugation effect

1. Stability of alkenes and other unsaturated hydrocarbons:

The stability of unsaturated hydrocarbons like nitriles and alkenes depends upon hyper conjugation. The more possible contributing structures in hyperconjugation usually increase the stability of the molecule. Since hyperconjugation mainly involves α-carbon-hydrogen σ bond and π-electrons, therefore, as the number ofα-, σ bonds increases, hyperconjugation also increases. For instance, 2-butene consists of six α-carbon-hydrogen σ bonds while there are only two carbon-hydrogen bonds next to the double-bonded carbon atom in 1-butene. Hence 2-butene can shows six contributing structures while 1-butene shows only two structures, making 2-butene more stable over 1-butene (**Exercise: can you draw these structures? give a try by yourself**). In other words, most- substituted alkenes are more stable than those of less-substituted alkenes.

2. Stability of reaction intermediates

Hyperconjugation is also observed in reaction intermediates like carbocations and free radicals which stabilize the intermediates as it helps in the dispersal of positive charge. Thus, we can say that greater the number of alkyl groups attached to a positively-charged carbon atom, the greater is the hyperconjugation interaction, and thus the stabilization of the carbonation. For example; in primary carbocation like ethyl carbocation, there are three α-carbon-hydrogen bonds which can delocalize into an empty *p*-orbital. However, in secondary (isopropyl) and tertiary (tert-butyl) carbocations, there are six and nine α-carbon-hydrogen bonds, respectively. Consequently, the increasing order of stability of carbocations can be written as:



Similarly, the increasing order of stability of free radicals would be **primary < secondary < tertiary free radical.**

3. Dipole moment & bond length

Hyperconjugation induces polarity in the molecule which influences both the dipole moment and bond length of the molecule. As the polarity increases, dipole moment also increases while bond length decreases.

4. Anomeric effect

Anomeric Effect may explain as the tendency of anomeric substituents to favor an axial configuration over an equatorial position. The high stability of αα-methyl glucoside than that of ββ-anomer can be explained based on the hyperconjugation effect. Whereas an αα-anomer can show hyperconjugation of lone pair of oxygen atom with axial methyl group, hyperconjugation is not possible in ββ-anomer due to equatorial position.

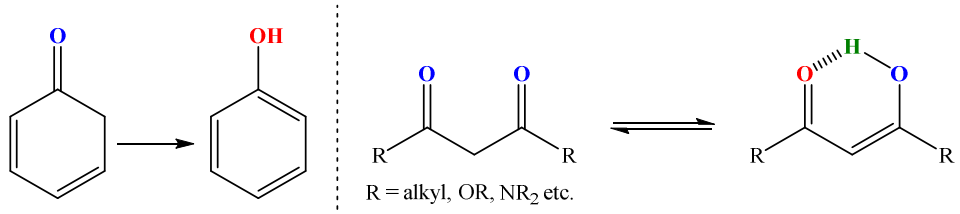
1.7 TAUTOMERISM

Tautomerism is defined as the phenomenon in which a single compound exists in two readily interconvertible structures that differ noticeably in the relative position of at least one atomic nucleus, generally hydrogen. The term 'tautomer' is made by two words; one is tauto (same) and meros (parts). The term tautomerism is also known as desmotropism (Greek desmos-bond; tropos-turn) based on the interconversion of the two forms involving a change of bonds or dynamic isomerism (as the two forms are in dynamic equilibrium with each other). The most common tautomers exist in pairs, which mean that the proton is located at one of the two positions. In other words or more specifically, the most common form involves a hydrogen changing place with a double bond.

The tautomerism is frequently observed in carbonyl or keto compounds and unsaturated hydroxyl compounds or enols. For this reason, the tautomerism is also known as keto-enol tautomerism. In this context, the structural change is the shift of a hydrogen atom between atoms of carbon and oxygen with the rearrangement of bonds. Needless to say that the enol form differs from the keto form in its polarity, acidity, and nucleophilicity. However, the keto form is typically much more stable than the enol form with K's of ca. 10^{-5}. Indeed, this is essential because the C=O bond is much more stable than the C=C double bond. The keto form is also more thermodynamically stable than enol form by 12 kcal/mol (48 kJ/mol). Although

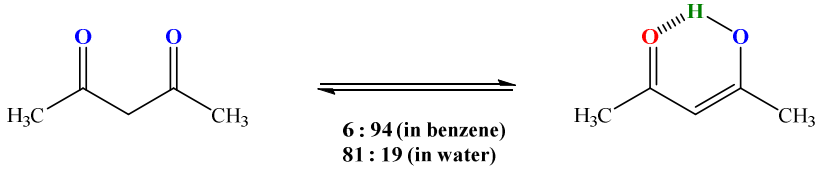
the keto form is mainly stable for aldehydes and ketones in most situations yet some factors can shift the equilibrium towards the enol form as mentioned below.

1. **Aromaticity:** In case of phenol, theoretically keto form should be more stable, but the enol form is greatly favored due to an aromatic stabilization (see left below).
2. **Hydrogen Bonding:** In the presence of a Lewis basic group, the intermolecular hydrogen bonding stabilizes an enol form (see right below). However, the ratio of the two forms will also depend upon the solvent(s) used.

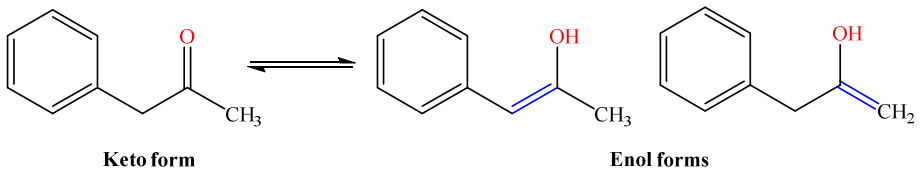


Besides these two factors, three more subtle effects are also observed in keto-enol tautomerism.

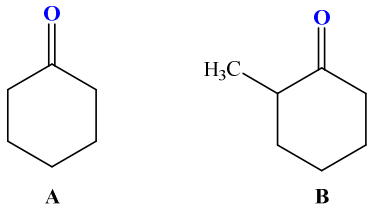
Solvent: Solvent play an important role in the relative stability of the enol form. For example, the enol form of 2,4-pentanedione predominates over the keto form in benzene. However, the stability reverses completely in the water i.e. the keto form becomes more stable in water as shown below. In a protic solvent, the lone pairs will be occupied in hydrogen bonding with the solvent, making them less accessible to hydrogen bond with the enol form.



Conjugation and substitution: The presence of conjugation and substituents in a molecule always shift the equilibrium towards enol form. (**Exercise 1**: Which enol form will be favored for a given below ketone?)



Exercise 2: Which one of these given below ketones will more favor the enol form? Hint: what is the stability pattern of alkenes?



Types of Tautomerism:

The tautomerism can occur in both diad and triad systems. In diad system, hydrogen or any other group migrates from atom no. 1 to an electronegative atom no. 2 as shown below. The same can be applied for a triad system. Some selected examples of triad systems are given in Figure 9.

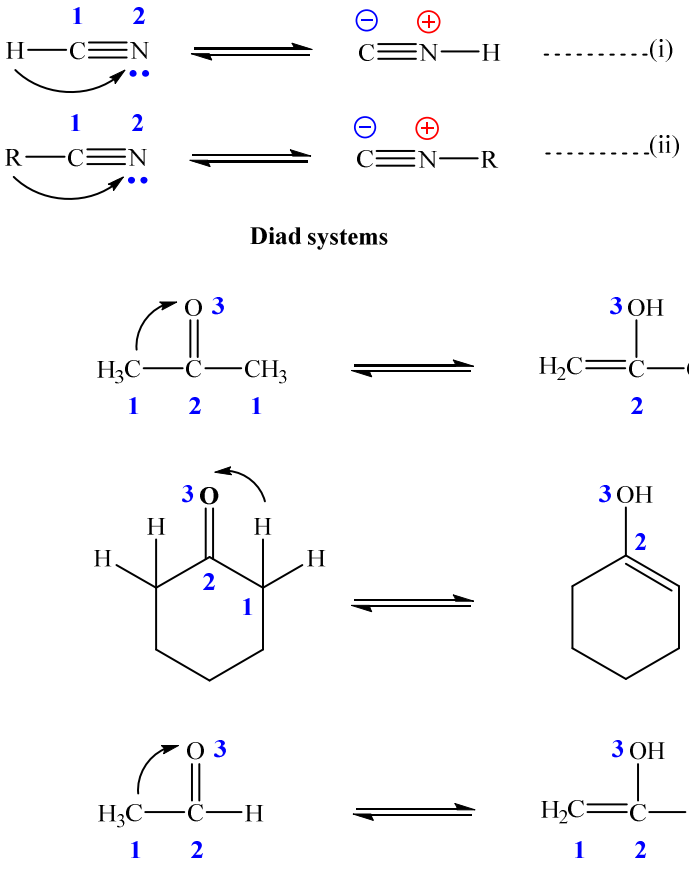
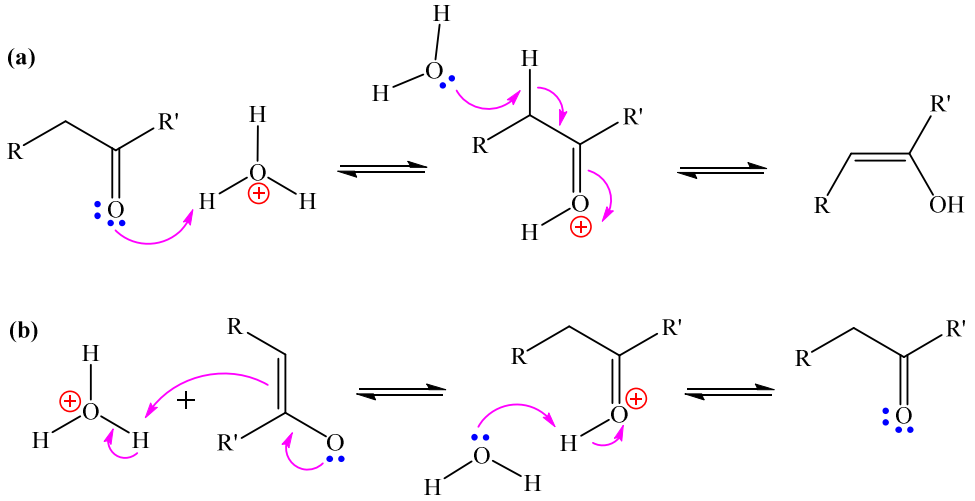


Figure 9 Keto-enol tautomerism in triad systems. In systems (a-c), all keto forms exist as major (>99.97%)

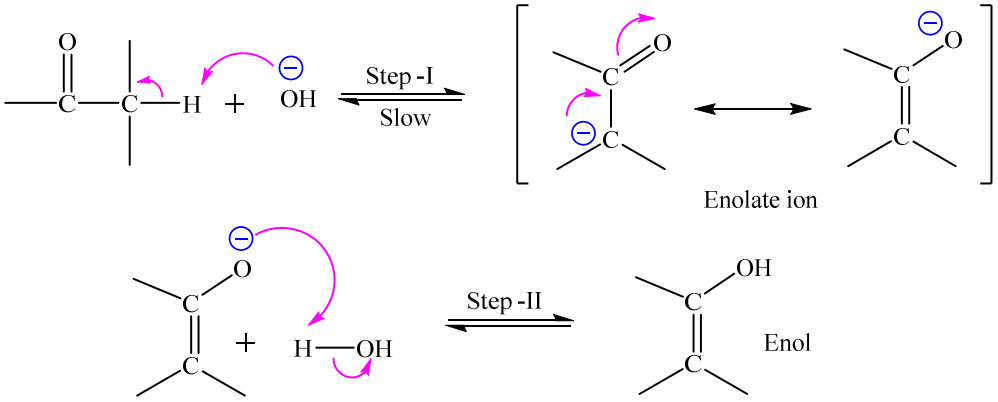
Mechanisms of Tautomerism:

1. **Acid-catalysed mechanism:** In acid-catalysed enolization, a proton (from an acid) reacts with water molecule and forms hydronium ion (H_3O^+). A lone pair of electrons is removed from the carbonyl oxygen by the H_3O^+. Finally, water abstracts a proton from α-carbon atom, resulting in the formation of the enol form (Scheme 1a). However, if the starting compound is an enol, Markovnikov's addition of hydrogen ion occurs (Scheme 1b).



Scheme 1 An acid-catalyzed mechanism for keto-enol tautomerism

2. **Base-catalyzed mechanism:** The formation of an enol under base catalysis involves the formation of an intermediate enolate, the conjugate base of the carbonyl compound. In the first step, hydroxyl group abstract an α-proton and an enolate ion is formed. The enolate ion is stabilized by resonance and accepts a proton from water to form enol compound in the final step (Scheme 2).



Scheme 2 A base-catalyzed mechanism for keto-enol tautomerism

Differences between tautomerism and resonance:

The tautomeric forms are chemically distinct entities and can be separated and characterized. On the other hand, resonating forms differ only in the distribution of electrons and can never be separated from one form to another since neither of them have any real existence. The important differences between resonance and tautomerism are given below.

1. Tautomerism engages a change in the position of atom (generally hydrogen), while resonance involves a change in the position of the bonds and electrons.

2. Tautomers may be separated and isolated. Resonating structures are only imaginary and cannot be isolated.

3. The two tautomeric forms have different functional groups but the various resonating structures have the same functional group.

4. In case of tautomerism, bond length does not change while resonance significantly affects the bond length (single bond is shortened while the double bond becomes longer).

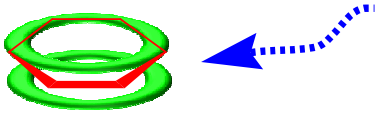
5. Resonance decreases the energy and hence increases the stability of compounds, while tautomerism does not lower the energy of the molecule, and hence does not play any role in stabilizing the molecule.

6. Tautomerism is represented by ($\rightleftharpoons$) but the resonance is represented by ($\longleftrightarrow$) symbol.

7. Tautomerism can occur in planar as well as non-planar molecules while only planar molecules can show the phenomenon of resonance.

1.8 HUCKEL'S RULE AND AROMATICITY

Compounds such as benzene having relatively fewer hydrogen atoms than those of carbons are typically found in oils, which, in turn are produced from trees and other plants. Because of their pleasant fragrance (aroma), early chemists called such compounds as aromatic compounds. However, the chemical definition of aromatic now signifies certain kinds of chemical structures. Aromatic compounds are a special class of organic compounds and have attracted considerable attention due to their potential applications in various fields of chemistry. Among them, the formation, reactions and stability of such cyclic (aromatic) compounds are always of particular interest owing to their vast array of potential applications.



Aromaticity:

Benzene is a planar compound with a cyclic cloud of delocalized electrons both above and below the plane of the ring as shown above. Because its π-electrons are delocalized, all the C-C bonds in benzene have the equal length- partway between the length of a typical single and double bonds. We have noticed that the benzene is a particularly stable compound because it has extraordinarily large resonance energy (36 Kcal/mol). The compounds such as benzene with unusually large resonance energies are typically called aromatic compounds, and the cause which explains the extra stability of such cyclic molecules is termed as 'aromaticity'. In aromatic compounds, resonance phenomenon (for details, see resonance section) typically increases the stability of the molecule, and therefore, the energy is called resonance energy. The concept of aromaticity can be best explained based on the Hückel's rule as discussed below:

Hückel's rule: For a compound to be aromatic, the following conditions must be followed

(i) A compound must have an uninterrupted cyclic cloud of π-electrons. For the πcloud to be cyclic, a compound must be cyclic and planar or nearly planar.

(ii) The πcloud must contain an odd number of pairs of π-electron.

(iii) The German chemist Erich Hückel was the first to recognize that an aromatic compound must obeys [4n + 2] π-electron rule. The rule states that a cyclic and planar compound would be aromatic, if its uninterrupted πcloud contains [4n + 2] π-electrons, where n = 0,1,2,3… n is generally called Hückel's number or aromaticity index (For clarity about the concept, also see Table 1).

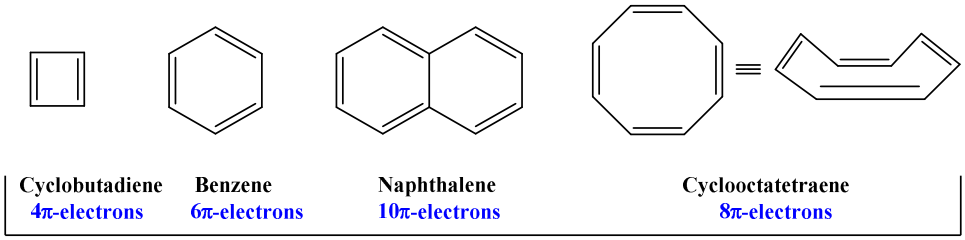
Table 1: Concept of aromaticity

[4n + 2] π-electrons			**4n π-electrons**		
Resonance	Never Anti-Aromatic	Resonance	Resonance	**Never Aromatic**	Resonance
Planar		Non-Planar	Planar		Non-Planar
Aromatic		Non-	Anti-		Non-

		Aromatic	Aromatic		Aromatic

For applying Hückel's rule in any system, one will need to count the number of π-electrons. The number of π-electrons can be calculated as follows:

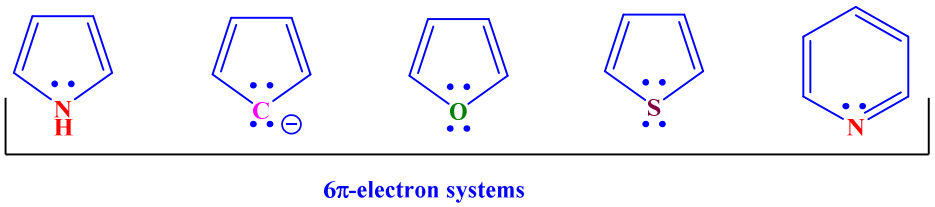
- Double bond or triple bond contributes 2 π-electrons to the system.



Cyclobutadiene, benzene, naphthalene and cyclooctatetraene has two, three, five and four pairs of π-electrons, respectively. Benzene and naphthalene fulfill the conditions for aromaticity but cyclobutadiene and cyclooctatetraene are not aromatic because they have an even number of pairs of π-electrons. There is an additional reason why cyclooctatetraene is not aromatic – it is not planar but, instead tub-shaped.

- Negative charge or lone pair of electron also contributes 2p electrons, if they are in conjugation with π-electrons. However, if they are not involved in resonance, then not counted.

Aromaticity in heterocyclic compounds: So far, we have only considered compounds having a carbon skeleton. However, many compounds found in nature are cyclic compounds with an element other than carbon in the ring. These are called Heterocyclic compounds. Further, some of them may be aromatic compounds and are termed as heteroaromatic compounds as given below.



1.9 ANTI-AROMATICITY

Cyclic conjugated flat or planar molecules having 4n π-electrons are termed as anti-aromatic compounds. Unlike highly stable aromatic compounds, which typically follow Hückel's rule ([4*n* + 2] π electrons), anti-aromatic compounds are highly unstable as well as quite reactive.

The unexpected instability of 4n π-electron cyclic conjugated system has been termed as "anti-aromaticity". For instance, the cyclopentadienyl cation is extremely unstable and difficult to make. Similarly, the oxirene itself has never been observed despite having an exciting traces of its fleeting existence, and by the way, neither has the 1H-azirene and/or thiirene, the nitrogen analogues (Figure 10).

Cyclopentadienyl cation Oxirene 1H-Azirene Thiirene

Figure 10 Structures of cyclopentadienyl cation and some elusive three-membered anti-aromatic ring compounds

The simple pentalene hydrocarbon is quite unstable above -100°C and does not exist while its hexaphenyl derivative is air sensitive. Similarly, though the 12π-electron-containing planar heptalene has been prepared yet is found to be extremely reactive (even more than that of cyclooctatetraene). Apart from that, all attempts to isolate 1,3-cyclobutadiene (4π-electron system) have always resulted a dimer. The structures of as-mentioned anti-aromatic compounds are shown in Figure 11 (Upper column).

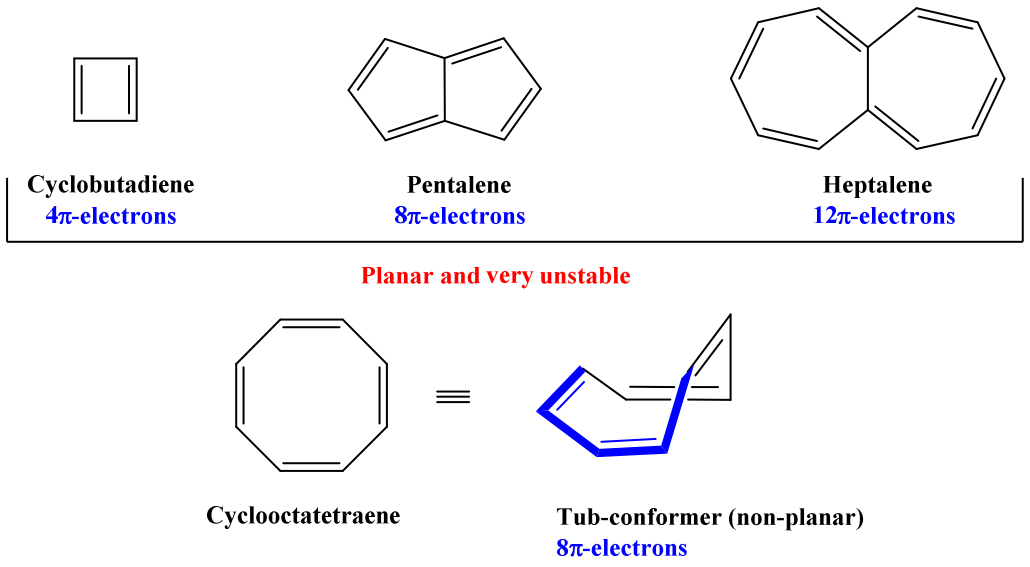
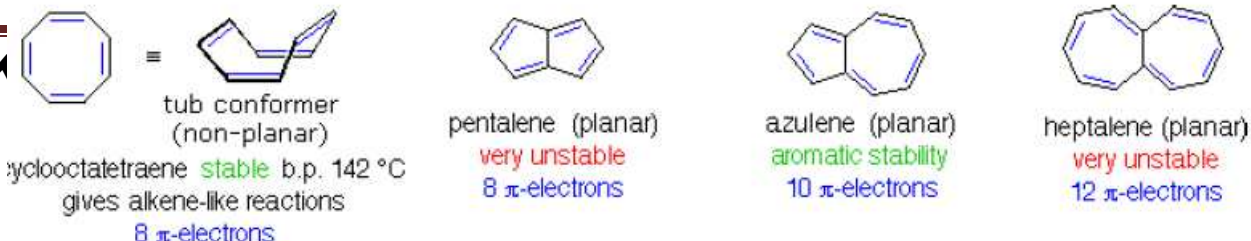


Figure 11 Upper column: Structures of some typical anti-aromatic compounds; Lower column: structure of cyclooctatetraene and its tub conformer

It would be worthwhile to mention here that some molecules may change shape and become non-planar in order to avoid the instability due to anti-aromaticity. As such, the molecules can break some of the typical π interactions. For instance, 1,3,5,7-cyclooctatetraene is a non-planar compound and adopts a tub-shaped conformation to avoid the destabilization that results from anti-aromaticity (Figure 11, lower column). If it were planar, it would have a single 8π-electron system around the ring, but it instead adopts a boat-like shape having four individual π bonds. The compound can be readily prepared and undergoes addition reactions, typical of alkenes. The catalytic hydrogenation of this cyclooctatetraene produces cyclooctane.

1.10 HOMOAROMATICITY

In the previous section, we discussed about aromaticity. In 1959, Saul Winstein introduced a new class of aromatic compounds based on the structural properties of "tris-homocyclopropenyl" cation. In this cation, aromaticity was found to be discontinued due to the presence of single sp^3-hybridized atom. These types of molecules were termed as homoaromatic molecules. Thus, we can say that **homoaromaticity** refers to a special case of aromaticity in which conjugation is interrupted by a single sp^3-hybridized carbon atom. Due to the poor overlapping of p-orbitals, these compounds are definitely less stable than the aromatic compounds (having complete delocalization of electron). To date, homoaromatic compounds are known to exist as both cationic and anionic species while some studies also support the existence of neutral homoaromatic molecules, though these are less common. Among these, the cationic homoaromatic compounds are the most studied species for homoaromaticity. For example, the homotropylium cation (Figure 12). Similar to those of cationic counterparts, the anionic homoaromatics have also been accepted to exhibit the "true" homoaromaticity. The anionic homoaromatics are generally prepared from their neutral parent compounds through reduction with lithium metal. Notably, in bis, tris, (etc.) homoaromatic species, two, three, (etc.) single sp^3-hybridized centres separately interrupt the pi-electron system.



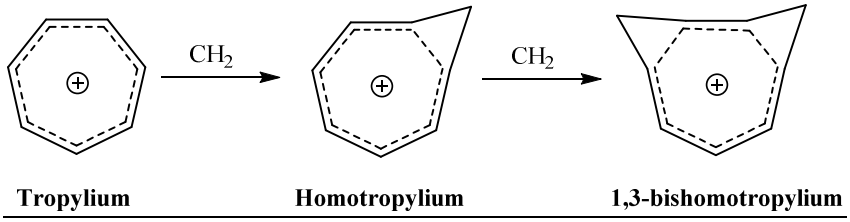


Figure 12 Structures of different tropylium cations

Synthesis of homotropylium cation:

When cyclooctatetraene is dissolved in concentrated sulfuric acid, a proton adds to one of the double bonds to form the homotropylium ion. In this species, an aromatic sextet extends over seven carbon atoms similar to that of tropylium ion (Figure 13). As the eighth carbon atom is sp^3-hybridized, it cannot take part in the aromaticity.

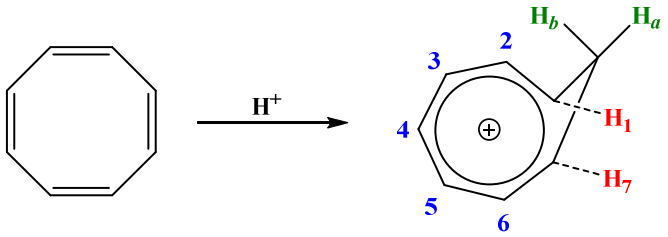


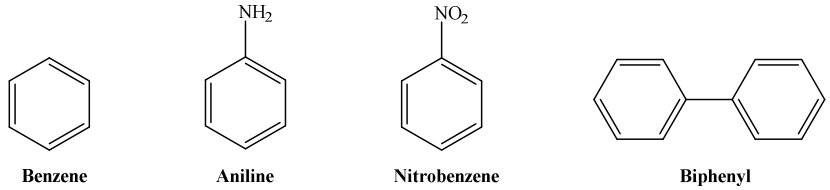
Figure 13 Synthesis of homotropylium cation from cyclooctatetraene

1.11 BENZENOID AND NON-BENZONOID AROMATIC COMPOUNDS

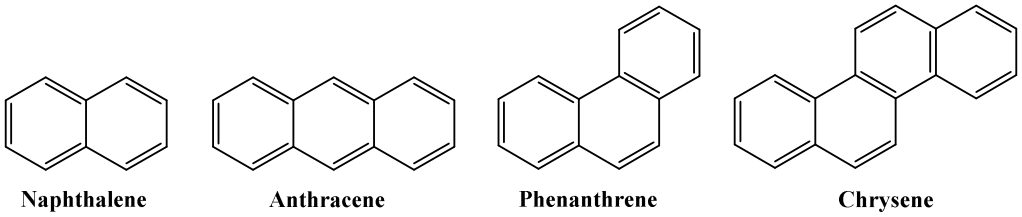
Benzene is simplest aromatic compound. There are three alternative π-bonds in the cyclic ring of benzene. However, it is not essential that all aromatic compounds contain a benzene ring. On these ground, aromatic compounds can be classified as benzenoid and non-benzenoid compounds.

Benzenoid compounds: Those compounds which are derived from benzene are known as benzenoid compounds. These compounds show a complete delocalization in the ring. benzenoid compounds can be further divided into isolated and fused benzenoid compounds.

Isolated benzenoid compounds: These types of compounds usually contain a benzene ring or benzene ring is connected by only one bond. Some selected examples of isolated benzenoid compounds including benzene are given below.



Fused benzenoid compounds: Benzene rings may be fused together to give larger polycyclic aromatic compounds. Such type of molecules containing these kinds of fused rings are generally referred as linear or angular polyacenes. Thus, acenes are a class of organic compounds and/or polycyclic aromatic hydrocarbons made up of linearly-fused benzene rings such as naphthalene, anthracene, phenanthrene, and chrysene. The structures of these compounds are given below.



Non-benzenoid compounds: Non benzenoid aromatic compound are the compounds containing five to seven carbon atom rings with conjugated π-electron system. Thus, these compounds exhibit aromaticity due to an arrangement of alternate π-bonds in the molecule. As these compounds do not contain any benzene ring, they are termed as non-benzenoid compounds. Nevertheless, the chemical reactions of these compounds are like benzenoid compounds only. The chemical structures of some non-benzenoid compounds are given in Figure 14 followed by a brief discussion of some selected compounds from Figure 14.

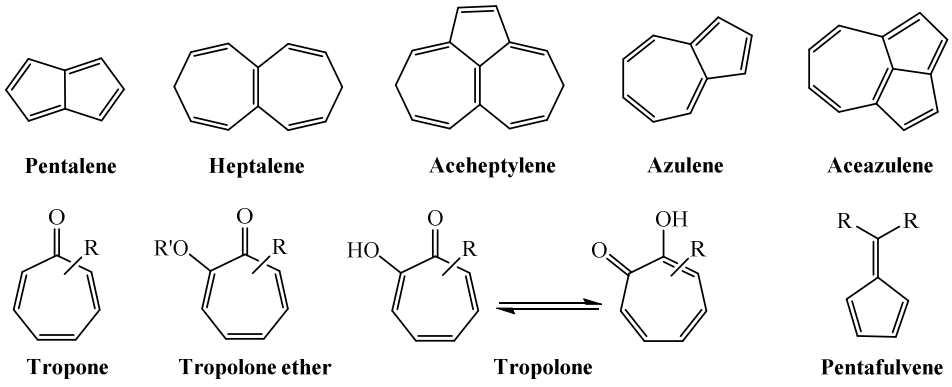


Figure 14: Examples of non-benzenoid compounds

Tropone and Tropolone: Tropone and tropolone are non-benzenoid seven-membered aromatic compounds having three conjugated double bonds. While former contains a keto group, the latter contains an α-hydroxy group w.r.t. a keto group, and can show keto-enol tautomerism. The tropone moiety has been found in several natural products. However, tropolone and tropolone ether (with an α-alkoxyl group) are much more common in nature.

Tropyliumion: The carbonium ion with a molecular formula of $[C_7H_7]^+$ is known as tropylium ion. Salts of tropylium ions are stable due to aromaticity and have greater stability than most other typical carbonium ion (For detail: see homo- and anti-aromaticity section).

Azulene: Azulene is a 10π-electron system made up of the 'fusion' of two aromatic ions; cycloheptatrienyl (tropylium) cation and cyclopentadienyl anion. Azulene is an isomer of naphthalene and has a similar smell, but instead of white, its crystals are dark blue. The word 'Azul' is derived from the Spanish word, which means blue. Azulene can be synthesized from an octahydronaphthalene. Azulene can undergo many reactions such as Friedel-Crafts substitutions. Like cyclopentadienyl anion and tropylium cation, it can also form π-complexes with certain metals.

Pentafulvene: Fulvenes are cyclic cross-conjugated olefins. Pentafulvenes have same formula as that of benzene but the ring contains five carbon atoms only. Pentafulvene contains alternative π-bonds making it an aromatic compound. They have been widely used as valuable building blocks in the synthesis of several natural products such as hirsutene,[1] capnellene,[2] and *β*-vetivone[3].

1.12 ALTERANANT AND NON-ALTERANANT HYDROCARBON

An alternant and non-alternant classification is one of the suitable ways to predict the properties of a conjugated hydrocarbon. As such, the alternant and non-alternant classification is a starring process in which the carbon atoms are divided into two sets; all the carbons in one set are marked with a star in such a way that no two starred or unstarred atoms are bonded to each other. A conjugated hydrocarbon will be alternant if no two stars are adjacent to each other. However, it will be non-alternant if two or more adjacent centers receive the stars (Figure 15).

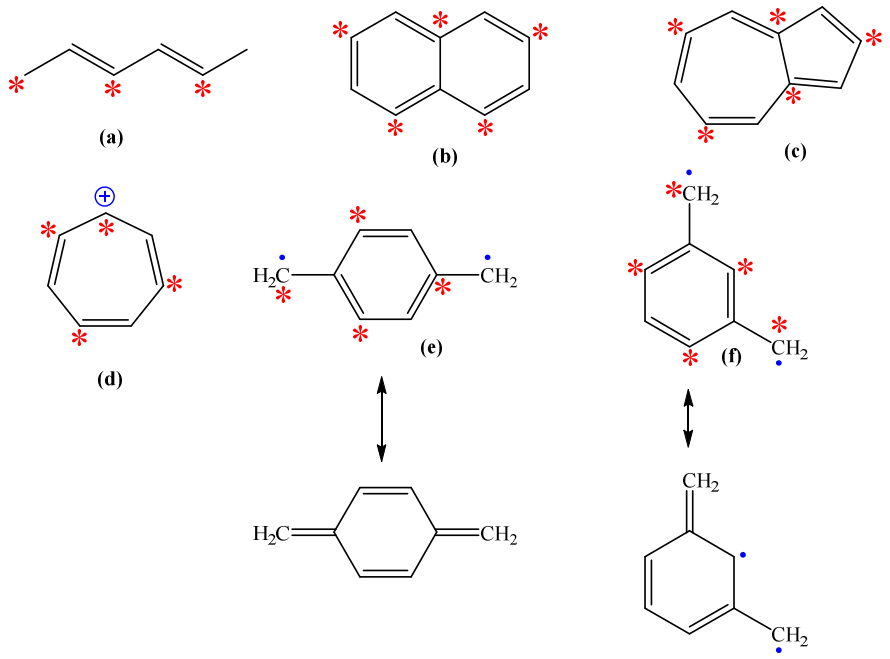


Figure 15 Selected examples of alternant and non-alternant hydrocabons

As can be seen in Figure 15, structures (a), (b) and (e) are alteranant hydrocarbons because no two stars are adjacent to each other in these structures. However, in remaining structures, a random way of placing the stars on alternate carbon atoms eventually leads to two adjacent stars. An alternant hydrocarbon is any conjugated hydrocarbon which does not possess an odd-membered ring. For this reason, the tropylium ion (d) is also considered as a non-alternant hydrocarbon. The alterant hydrocarbons can be divided into two categories as mentioned below.

1. **Even-alternant hydrocarbon:** If system has an equal numbers of starred and unstarred carbons, it is known as even-alternant hydrocarbon. An even-alternant molecule has an equal numbers of bonding and antibonding orbitals, which are symmetrically, distributed with no non-bonding orbital.For these hydrocarbons, all the bonding orbitals are filled and the electrons are uniformly spread over the unsaturated atoms (Figure 16).
2. **Odd-alternant hydrocarbon:** If the numbers in the two sets are not equal, it is called an odd-alternant hydrocarbon. An odd-alternant system will have more starred than unstarred atoms. The odd-alternant structures have an equal numbers of bonding and antibonding orbitals along with a non-bonding orbital.As in allylic systems, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) also have a non-bonding orbital of zero

energy in addition to an equal and opposite bonding and antibonding orbitals. When an odd number of orbital overlaps, an odd number is created.

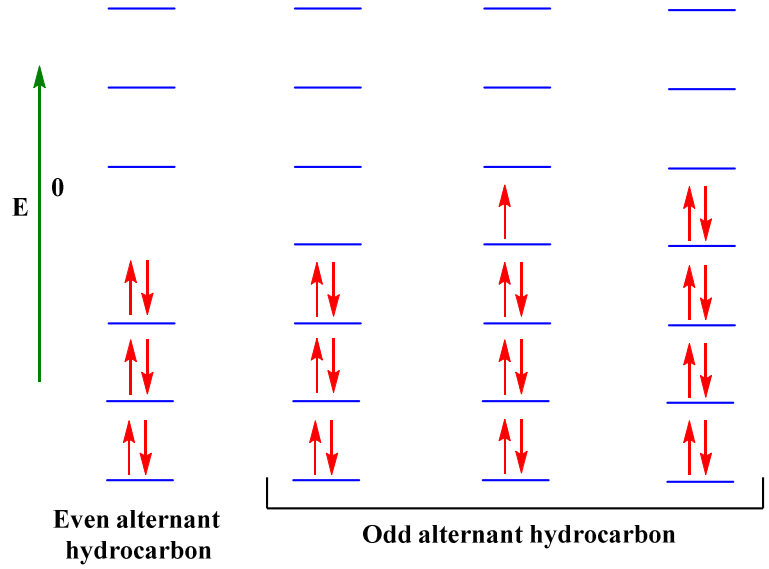


Figure 16 The energy levels in odd- and even-alternant hydrocarbons. The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

1.13 ANNULENES

Monocyclic and completely conjugated polyenes or hydrocarbons having alternate single and double bonds are usually called annulenes. A prefix in brackets denotes the number of carbons in the rings. They are either aromatic or non-aromatic, but can never be anti-aromatic. For instance,

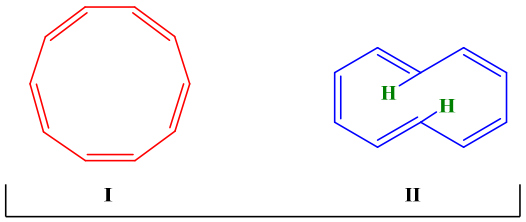
[4]Annulene: ex. Cyclobutadiene– either anti-aromatic on non-aromatic, but never be aromatic

[6]Annulene: ex. Benzene– They are either aromatic or non-aromatic, but never be anti-aromatic.

[8] Annulene: ex. Cyclooctatetraene

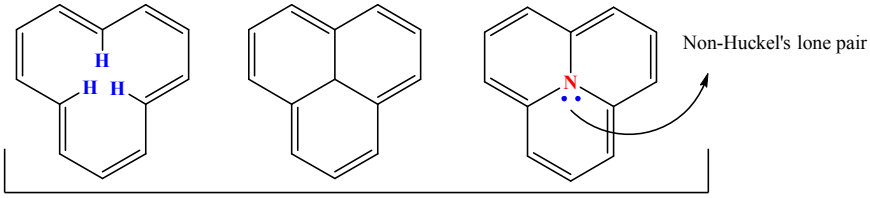
[10] Annulene: Beyond benzene, [10] annulene is the first hydrocarbon to satisfy the Hückel's rule. A structure in which all the double bonds are *cis*, however, would be a regular 10-sided polygon requiring bond angles of 144° (instead of the 120° as required for sp^2-hybridized carbon), and would suffer a significant angle strain (see left below). The destabilization (owing to the angle strain) apparently exceeds the stabilization associated with aromaticity, and makes all-*cis*-cyclodecapentaene a highly reactive substance. Aside from this, an isomer in which two

of the double bonds are *trans* should, in principle, be free of angle strain. It is destabilized, however, by a repulsive force between two hydrogen atoms (that are forced together in the interior of the ring), and for this reason, it is relatively reactive. As can be seen at right below, the planarity of ring is disturbed in II isomer by the repulsion of internal H atom. However, if this H-atom is replaced by rings then aromaticity can be achieved with slight disturbance in planarity.



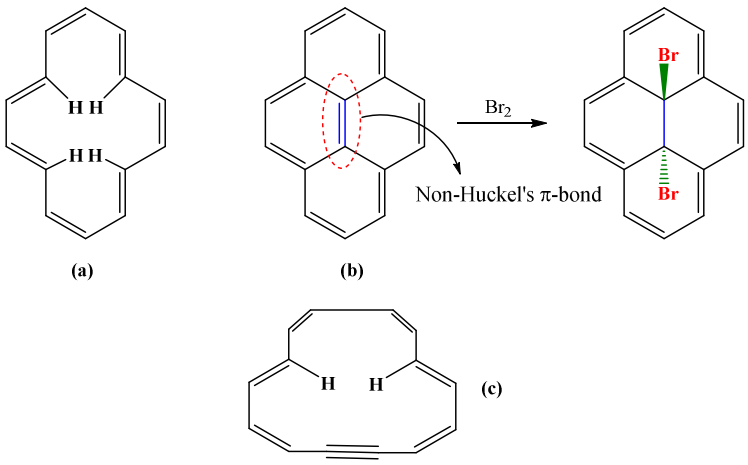
Isomeric [10] annulenes, Non-aromatic

[12]Annulene: Anti-aromatic or non-aromatic, but never be aromatic.

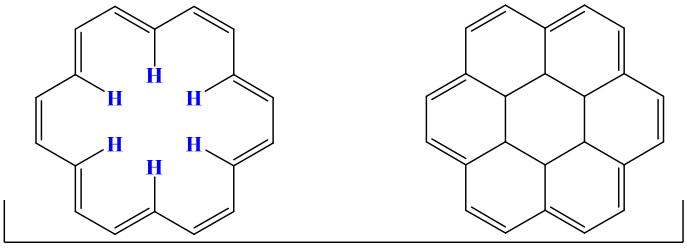


12π-electron systems

[14] Annulene: Some selected examples are given below. Whereas system (a) is not exactly planar (slightly aromatic), the central π-bond does not involve in resonance in system (b), and it simply behaves like an ethylenic bond as exemplified by its bromination reaction. Dehydro [14] annulene (c) is another example of [14] annulene system and is counted as aromatic compound.



[18] Annulene: [18] Annulene is predicted to be aromatic by the Hückel's rule ($4n + 2 = 18$ when $n = 4$). The structures shown below have a shape that make them free of angle strain and large enough so that the repulsive forces between hydrogen atoms in the interior are minimal. The thermochemical measurements indicate that the molecules have a resonance energy of ca.100 kcal/mole while the structural studies have revealed that the molecule are planar with all its bond distances falling in the range of ca. 1.37-1.43 Å. In terms of chemical reactivity, however, the [18]-annulene system resembles more an alkene than that of benzene.



[18] annulenes, Aromatic

1.14 ADDITION COMPOUNDS

When two compounds reacted to form a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. Here we will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. Examples: crown ethers complexes and similar compounds, inclusion compounds, and catenanes.

1.14.1 CROWN ETHER COMPLEXES

Cyclic heterocyclic compounds that consist of a ring with several ether groups are known as crown ethers. The most common crown ethers constitute the cyclic oligomers of ethylene oxide having ethyleneoxy ($–CH_2CH_2O–$) as the repeating unit. The most common and important members of crown ethers are tetramer ($n = 4$), pentamer ($n = 5$), and hexamer ($n = 6$) as shown in Figure 17. Due to the resemblance of their cavity shape with a crown, the term "crown" is generally used in their nomenclature, and they are named as x-crown-y. The first number (x) consigns to the total number of atoms in the cycle while the second number (y) refers to the number of oxygen atoms. However, in place of oxygen, S and N atoms may also be present, and such crown ethers are known as thia and aza crown ethers, respectively.

Crown ethers has high binding affinity for a variety of metal ions, and neutral and ionic organic species. Thus crown ethers play a key role in the area of host-guest chemistry and in the construction of a variety of non-covalent supramolecular assemblies. Specifically, a crown ether has an electron rich (oxygen lone pairs) cavity which facilitates binding with certain cations. This hydrophilic cavity (with ether oxygen atoms) is surrounded by hydrophobic ethylenic groups. The wrapping around of crown ether on the metal ions makes it feasible to solubilize metals into organic solvents. In particular, the oxygens-rich cavity of crown ether possess great affinity towards certain alkali and alkaline earth metal cations leading to the formation of complex compounds. This property of crown ethers makes them an appealing candidates in the field of coordination chemistry while also opens the window for numerous other applications. However, a stable complex is not formed if the size of the cation is very large or it does not fit in the cavity of the crown ether. It has been well documented that the ionic diameters of certain crown ethers such as 12-crown-4, 15-crown-5 and 18-crown-6 are well matched with Li^+, Na^+, and K^+ alkali metal cations, respectively.

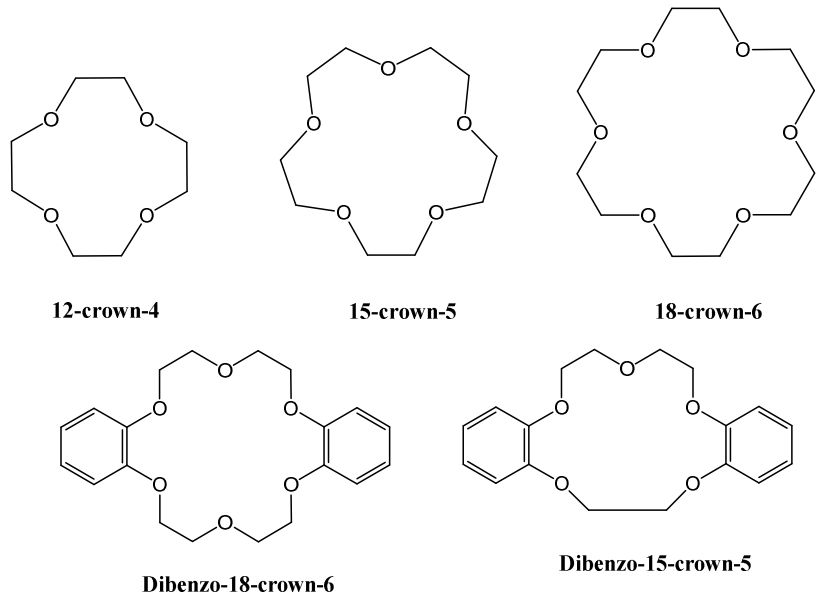
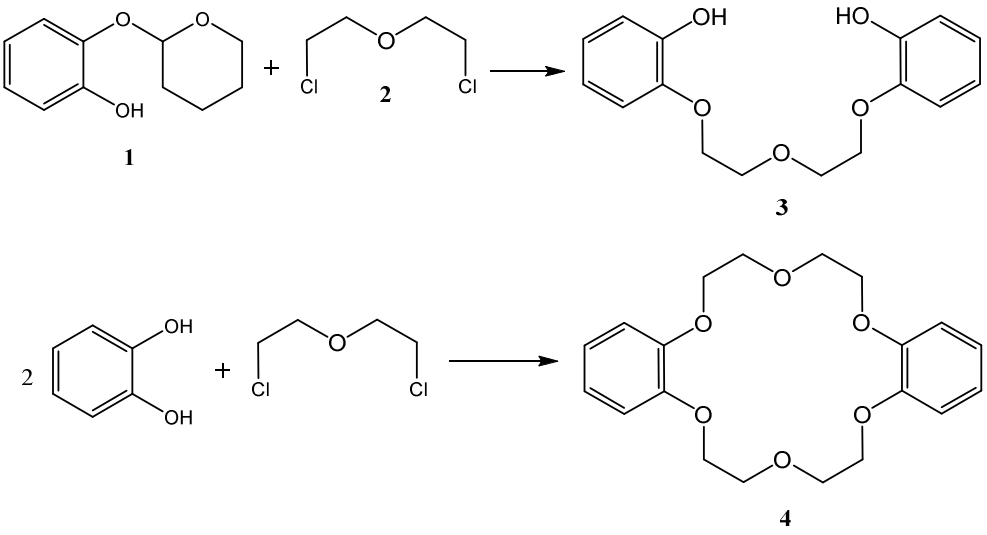


Figure 17 Representative examples of crown ethers

1.14.1.1 Synthesis of Crown Ethers: A historic background

The initial credit for the discovery of crown ethers goes to Charles J. Pedersen (Retired from the DuPont company), one of the three recipients of Nobel Prize for chemistry in 1987 for

the development of crown ethers and other molecules. While working in the lab, Pedersen obtained a very small amount of a white, fibrous, and crystalline 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,ll-diene **4** crown ether as a by-product from the reaction of bis(2-chloroethyl) ether **2**with the sodium salt of 2-(*o*-hydroxyphenoxy)tetrahydropyran**1** forming bis[2-(o-hydroxyphenoxy)ethyl] ether**3** (Scheme 3).



Scheme 3 Pedersen's synthesis of Dibenzo-18-crown-6

Having gone through the analysis, Pedersen found an unusual solubility of the compound **4** in the presence of sodium salts, and later he recognized that the cyclic polyether ring **4** can form a complex with the sodium cation (Figure 18).

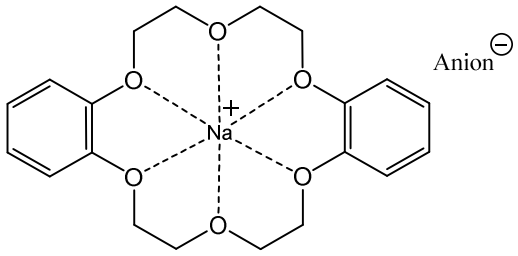


Figure 18 A complex of Dibenzo-18-crown-6 with sodium salt

Template synthesis of crown ethers:

The crown ether macrocycles can be synthsized following atemplate synthesis using certain metal ions as organizing agents. The basic principleof template effect synthesis is that the cyclic

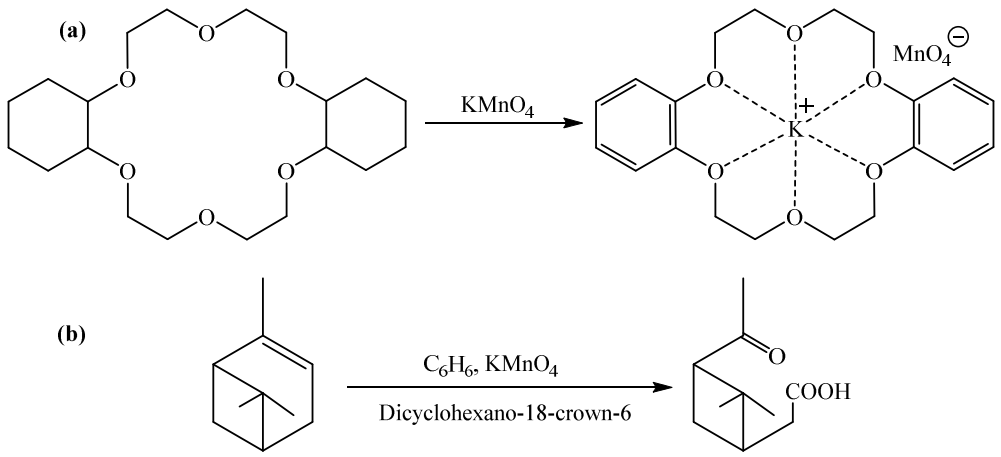
compound may be formed using a particular compound which can work both as the nucleophile and elcetrophile with ease.

1.14.1.2 Applications of Crown ethers

Crown ethers are of enormous interest and importance in different areas of science covering, but not limited to, chemical science, catalysis, materials science, separation, transport and encapsulated processes. In line with this, they are useful in the design and synthesis of various synthetic systems with definite properties, diverse capabilities, and programmable functions. The chemistry of crown ethers involves the complexation of oxygen atoms (host) with a variety of ionic species (guest), and this phenomenon is termed as 'host-guest chemistry' as mentioned above. The 'phase-transfer catalysis' is probably one of the most attractive applications of crown ethers and increasingly used to boost the solubility of inorganic salts in organic solutions for a variety of reactions such as esterifications, oxidations, saponifications, elimination reactions, alkylations, aromatic substitution reactions, displacement reactions, and carbene generation, to name but a few. Some of these reactions are appropriately discussed below.

1. "Purple benzene" or potassium permanganate oxidation

Potassium permanganate ($KMnO_4$) is a well-known oxidizing agent and routinely used for the oxidation of organic compounds in aqueous solutions. However, many organic compounds are either insoluble or poorly soluble in water, and thus restrict the wide use of $KMnO_4$ in some commonly employed organic solvents except acetone, butanol, acetic acid etc. This problem can be addressed effectively using crown ether such as dicyclohexano-18-crown-6 in conjunction with benzene and $KMnO_4$. Specifically, crown ether forms a permanganate complex (Scheme 4a) and permanganate becomes soluble in benzene forming an ion-pair. The as-resulted "purple benzene" works as an excellent oxidizing agent for a variety of substrates in organic solvents. For example, the oxidation of α-pinene furnishes pinonic acid in 90% yield under above-described conditions (Scheme 4b).[4] As such the solubilizing effect of crown ethers on insoluble inorganic salts are spectacular. For instance, the solubility of potassium thiocyanate complex can increase by 100-times using crown ethers. Aside from that of$KMnO_4$, potassium tertiary-butoxide and a mixture of $PdC1_2$+ 2KCl can be dissolved in liquid aromatic hydrocarbons simply by adding dicyclohexano-18-crown-6.



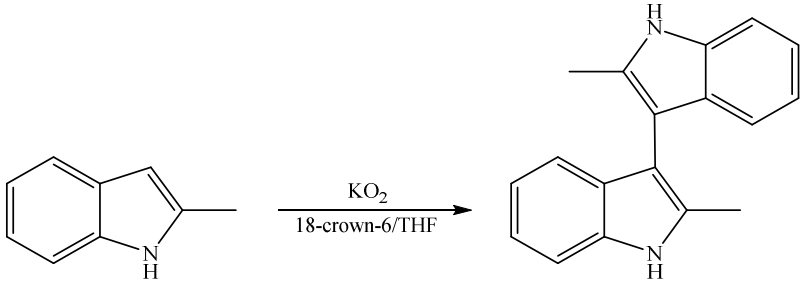
Scheme 4 (a) Complexation of potassium ion with crown ether and (b) Conversion of α-pinene into pinonic acid

2. Superoxide anion reaction

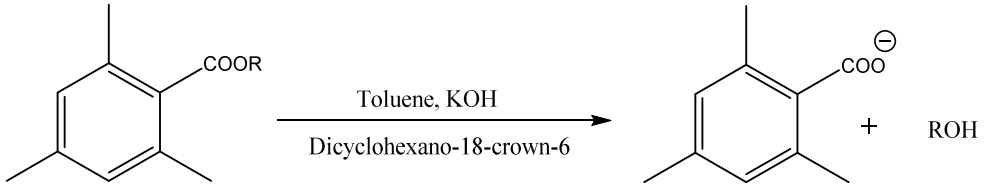
Superoxides such as K_2O or NaO_2 also suffer with their limited solubility in organic solvents, similar to those of inorganic salts. However, the use of crown ethers with a superoxide has been proven as an excellent way for the oxidative dimerization reaction (Scheme 5).[5]

3. Saponification

The hydrolysis of sterically hindered esters can be easily done using a hydrophobic and hydrocarbon soluble crown ether that can form a potassium hydroxide complex in toluene (Scheme 6).[6]



Scheme 5 Crown ether-assisted dimerization of indole derivative



R = Me, t-Bu, neopentyl

Scheme 6 Crown ether-assisted saponification reaction

4. Generation of carbene

Trans-stilbene and cyclohexene can be converted into gem-dihalocyclopropanes in moderate to good yields at 40°C using a mixture of dicyclohexyl-18-crown-6 and sodium hydroxide toluene. Similarly, dibenzo-18-crown-6 has been found suitable as liquid-liquid phase-transfer catalyst in carbene generation.[7] Aside from those of typical applications of crown ethers in Organic Chemistry; the derivatives of the same have recently been touted as powerful anti-tumor agents.

1.14.2 CRYPTANDS

Cryptands are three dimensional (3D) flexible molecules with two nitrogen atoms connected by three bridges composed of ethyleneoxy units. The term cryptand implies that this ligand can bind a substrate in a crypt, interring the visitor as in a burial. The 3D interior cavity of a cryptand provides a binding site for specific "guest" ions. The complex formed of a guest and a cryptand is called a cryptate, and are generally lipophilic. The cryptates (meaning hidden) are so called because they can wrap around and hide the metal ions. This arrangement allows the molecule to completely encapsulate a metal ion. Because of their highly selective (than those of crown ethers) and unique complexing properties, cryptands are of great interest to chemists worldwide. These interesting compounds were first prepared over twenty years ago in the laboratory of Jean-Marie Lehn (the father of supramolecular chemistry), who shared the Nobel Prize in Chemistry (1987) with Donald J. Cram and Charles J. Pedersen for their efforts in discovering and determining the applications of cryptands and crown ethers. As mentioned above, the more rigid 3D structures of cryptands confer higher selectivity and complex the guest ions more strongly than similar-sized crown ethers. Presumably, this is due to a combination of cryptands having a more defined ‘hole’ size than the more flexible crown ethers, which means that cryptands cannot expand to accommodate the ions of the wrong size. In addition, the 3D cryptands are relatively more preorganized into a binding conformation than crown ethers, providing the limited or less rearrangement for the cryptand as it goes from an uncomplexed to a complexed state. Due to the presence of N and O atoms (sometimes S or P atoms), cryptands show relatively a higher density than the crown ethers. 1,10-diaza-4,7,13,16,21,24-

hexaoxabicyclo[8.8.8]hexacosane is one of the most widely used cryptands (Figure 19), and also termed as [2,2,2] cryptand based on the number of ether oxygens in the chains.

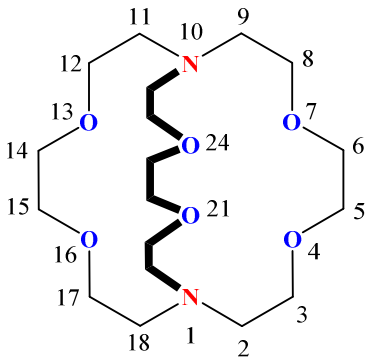
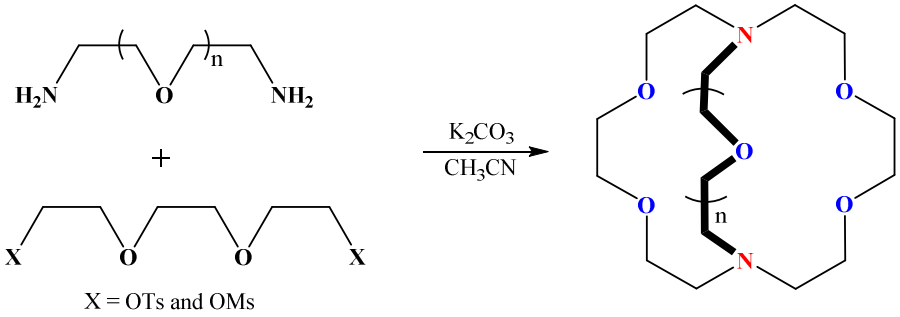


Figure 19 Chemical structure and numbering of a [2,2,2] cryptand

1.14.2.1 SYNTHESIS OF CRYPTANDS

The synthesis of cryptands remained a challenging task for chemists over the years. As the synthesis involves many steps and requires high dilution techniques, the yields of cryptands are generally low. In pioneering work, Lehn (1985) described the major strategies adopted in the synthesis of cryptands starting from acyclic components. Later on, a number of cryptands were synthesized following a one-pot Kulstad-Malmsten synthesis approach. Specifically, the base-catalyzed treatment of ditosylate derivative of triethylene glycol with its diamine analog furnished a [2,2,2]cryptand in ca. 38% yield (Scheme 7).[8] Almost similar results were obtained when dimesylate was used in place of ditosylate derivative. However, the use of ditosylate is preferred due to its easy availability. Aside from that of [2,2,2]cryptand, the use of ditosylate also allows the preparation of [2,2,1], [3,2,2] (50%), [3,3,2] (40%), and other similar cryptands.



Scheme 7 Synthesis of [2,2,2]Cryptand

1.14.2.2 PROPERTIES AND USES

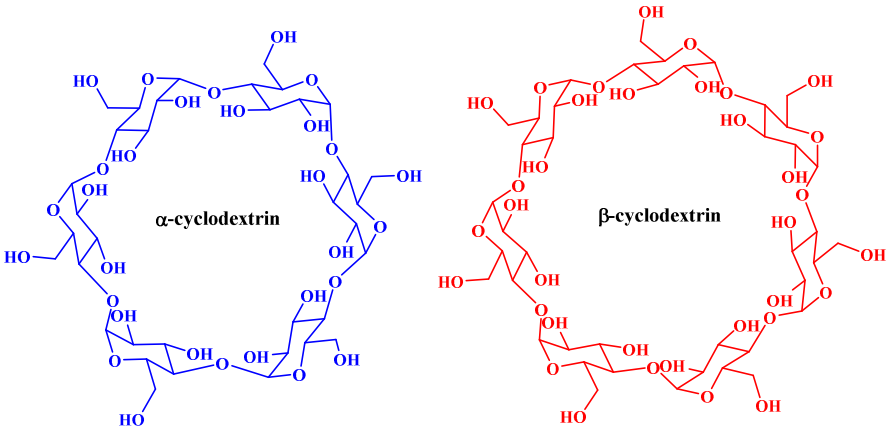
Cryptands find applications in many attractive areas of chemistry, material sciences and biochemistry due to their architectural and functional plasticity. Though cryptands are more expensive and difficult to prepare, they offer much better selectivity and strength of binding (binding constants) than other complexants for alkali metals such as crown ethers. For instance, the binding constant of [2,2,2] cryptand for K^+ is ca. 10^4 times higher than for 18-crown-6. Aside from those of alkali metals, cryptands can also form complexes with hard acids such as ammonium ion, alkali earth metals, and few transition and lanthanide ions. Their 3D encapsulation mode offer ssome size-selectivity, enabling discrimination among alkali metal cations (e.g. Li^+, Na^+ and K^+). For example, [2,1,1] cryptand exhibits a binding constant for Li^+ over 100-times higher than that for Na^+ in water. Similarly, [2,2,1] cryptand has been found to have a high preference for Na^+ over K^+. The cryptands are able to extract otherwise insoluble salts into organic solvents. Cryptands increase the reactivity of anions in salts since they can successfully break up ion-pairs. Besides their importance in supramolecular chemistry, cryptands can also be used as potential carriers in ion-transportation, as stationary phases in column chromatographic separations, as redox active materials, and in photophysical studies and non-linear optics.

1.14.3 INCLUSION COMPOUNDS

Inclusion compounds are unique type of chemical compounds or complexes which are formed as a result of the inclusion of one type of molecule (guest) in the cavities of molecules of another type (host). The incoming molecules are also referred as foreign substances. This type of spatial complex formation does not occur by means of any ionic, covalent, or coordinate covalent bonds but rather depends upon dispersion forces like electrostatic, van der waals, hydrogen bonding and hydrophobic interactions, and possibly upon highly oriented dipoles for stability, contrasting markedly with the usual concept of chemical complexation. The capacity of a substance to form inclusion compounds depends on the presence of molecular-sized cavities. Inclusion compounds are generally formed by mixing two components and, less often, triturating the components. They are usually unstable, and often decompose to the original substances in solutions. Despite having a wide variety of inclusion compounds, we will briefly focus on two most important types for the same.

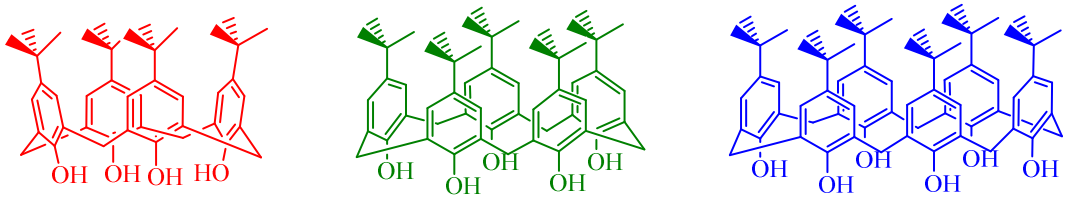
1.14.3.1 CYCLODEXTRINS

Cyclodextrins (CDs) or cycloamyloses belong to a family of compounds composed of sugar molecules bound together in a ring. In particular, the naturally occurring CDs (α, β, and γ) are cyclic oligosaccharides consisting of 6, 7 and 8 glucopyranose units, respectively. These compounds have relatively stiff doughnut-shaped structures, and have proven to be very practical monomolecular hosts in supramolecular chemistry. The CDs and their inclusion compounds can be crystallized from water and have studied by X-ray crystallography as either empty molecules or host-guest complexes. The chemical structures of α- and β-CDs are given below.



1.14.3.2 CALIXARENES

Calixarenes are conformationally flexible macrocycles or cyclic oligomers that are produced by the hydroxyl alkylation of phenols and aldehydes. The word calixarene is derived from calix or chalice (as they resemble a pot) while the word arene refers to an aromatic component. The nomenclature of calixarenes relies on counting the number of repeating units in the ring. For instance, a calix[n]arene; where n = 4, 5, 6 and 8 refers to calix[4]arene, calix[5]arene calix[6]arene and calix[8]arene, respectively (Figure 20). Calixarenes have hydrophobic cavities that can hold smaller molecules or ions and thus have significant importance in supramolecular host-guest chemistry. Over the last decade, calixarenes have been used as optical sensors, ion sensitive electrodes, chiral recognition devices for solid phase extraction, as a stationary phase and modifiers, to name but a few.



Calix[4]arene Calix[5]arene Calix[6]arene

Figure 20 The chemical structures of a variety of calixarenes

1.14.3.3 USES OF INCLUSION COMPOUNDS

Separation: The inclusion compounds can be used for the separation of different compounds in a mixture. Urea and thiourea, for example, respectively allow the separation of unbranched and branched hydrocarbons, which they bind in inclusion compounds. Zeolites prepared with various cavity dimensions are used industrially for the drying of gases as well as in the separation of substances through ion-exchange processes.

Drug delivery: Drug delivery is a dynamic process whereby a drug molecule continuously associates with or dissociates from a host molecules such as CD. Specifically, the complexation of a drug molecule (D) to CD occurs through a non-covalent interaction between D and the cavity of CD. Different mechanisms can play important roles in drug release from a D-CD complex. However, assuming a 1:1 complexation, the interaction will be as follows:

$$D + CD \xrightleftharpoons{K} Complex$$

The complexation constant (K) and the lifetime of the complex, are two very important parameters for the drug release mechanism. Besides, dilution also plays an important role in drug delivery as evidenced recently for miconazole, which can bound more strongly than that of prednisolone drug, and thus supports the probable role of dilution. Notably, the dilution is minimal when a D-CD complex is directed ophthalmically.

1.14.4 CATENANES AND ROTAXANES

A mechanically interlocked molecular structure consisting of two or more interlocked macrocycles i.e. molecules containing two or more intertwined rings are known as catenanes. Catenane is derived from the Latin word '*catena'* meaning 'chain'. On the other hand, Rotaxanes are mechanically interlocked molecules consisting of "dumbbell-shaped molecules" which are threaded through a macrocycle. The name rotaxane is derived from the Latin word rota

and axle which means wheel and axis, respectively. The nomenclature of catenanes is determined by the number of rings, i.e. how many rings are interlocked to each other. For instance, a [2]catenane consists of two interlocked rings. A catenand is the free ligand that can form a catenate complex in the presence of a metal centre. Rotaxanes can be named in an analogous manner too. The two rings cannot be separated without breaking the covalent bonds of the macrocycles. Rotaxanes can be separated *via* deformations of one of the components. In other words, rotaxanes are threaded species stabilized by steric interactions.

1.14.4.1 SYNTHESIS OF CATENANES AND ROTAXANES

The Catenanes are synthesized in two different ways; statistical and template-directed synthesis. Over the last few years, the template-directed clipping reaction based on imine chemistry has become one of the most efficient methods for the construction of functionalized rotaxanes and catenanes. The synthesis of both can only be efficiently accomplished, if a suitable template is used, providing a means either to thread a string-like molecule through a macrocycle or to wrap an open macrocycle around a string.

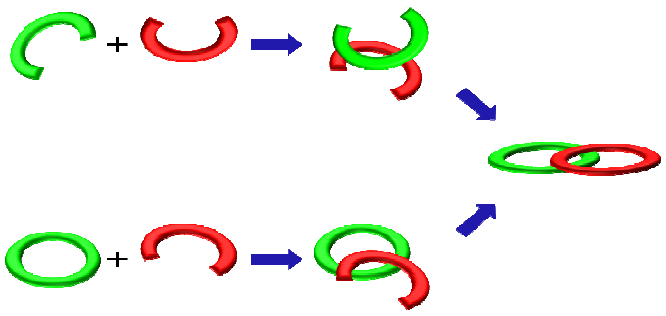


Figure 21 Cartoon representations for the synthesis of catenane (clipping reaction)

As shown in Figure 21, one- or two cyclization reactions can be involved in the clipping synthesis of catenanes. Specifically, in a double-clipping reaction, two macrocycles which are not fully closed are interlocked, and two subsequent ring-closing reactions are performed in order to form the catenanes. Aside from that of catenane, there can be five primary routes enabling the formation of a rotaxane (Figure 22). The first method is capping in which a pseudorotaxane is formed by threading the thread through the macrocycle. The ends of the thread are often closed-off with large stopper groups to make sure that the thread stays inside the macrocycle. Snapping involves two different parts of the thread, both containing a bulky group.

Whereas the one part of the thread is threaded through the macrocycle to form a semi-rotaxane, the end is usually closed-off by another part of the thread, forming a rotaxane. The third route, i.e. the clipping involves the formation of a rotaxane by a ring-closing reaction of the macrocycle. The thread already contains the two bulky groups at the ends of the thread, but the macrocycle is not yet fully closed. The macrocycle clips over the thread and a rotaxane is formed after ring-closing reaction. Slipping, the fourth method, is achievable only when the bulky end groups are of appropriate size to fit through the macrocycle at quite higher temperatures. The last primary route relies on the use of active metal template for the synthesis of rotaxane.

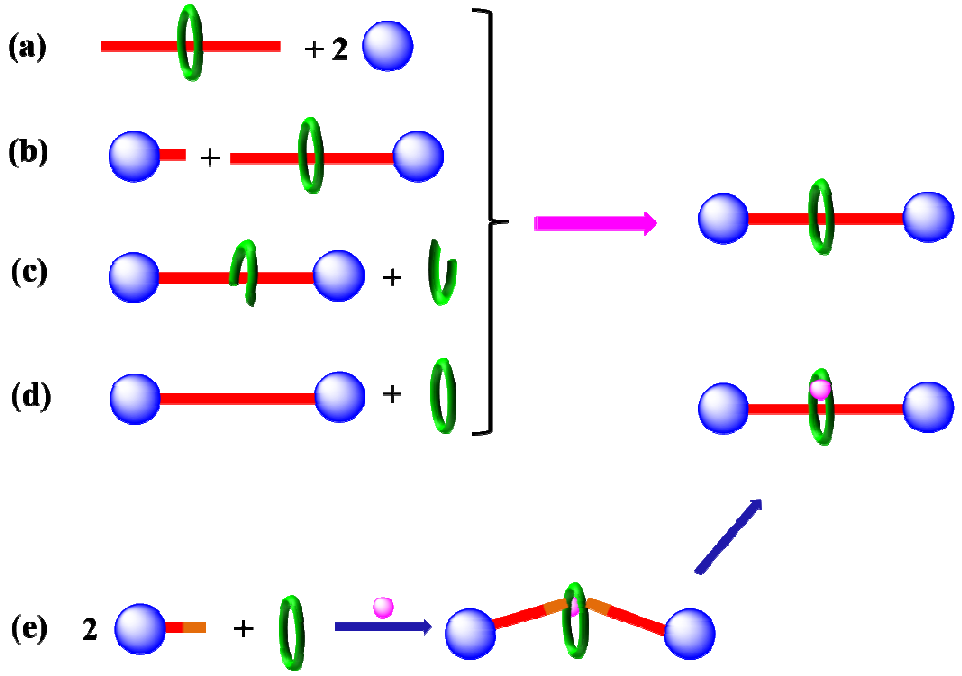


Figure 22 Cartoon representation for the synthesis of rotaxane: (a) capping, (b) snapping, (c) clipping, (d) slipping, and (e) active metal template methods

1.14.4.2. Applications of Catenanes and Rotaxanes

a. Catalysis

The [1]rotaxane contains a weakly basic tertiary amine, which has been used as a catalyst in the Knoevenagel reaction of malononitrile with acetone in $CHCl_3$. It has been proposed that malononitrile reacts with the rotaxane *via* its active hydrogens forming a zwitterionic species.

b. Polymer

The group of Takata *et al.* synthesized a polymer consisting of rotaxane cross-links. Rotaxane with a thread consisting of a polytetrahydrofuran-based bulky group and a vinyl end group was threaded through a γ-cyclodextrin. The as-formed rotaxane cross-linked polymer showed the superior properties in terms of higher elongation, more stress at breakage and fracture energy than covalently cross-linked polymers. Aside from these, both catenanes and rotaxanes have been significantly used in the supramolecular chemistry for binding and recognition of different ions, and as molecular shuttles.

1.14.5 IONIC LIQUIDS

The demand for eco-friendly chemical processes, products and energy requires the development of new fresh and cost-effective approaches to prevent or minimize environmental pollution. In this context, 'green chemistry', mainly introduced by Paul T. Anastas, is one of the most attractive theories in chemical sciences. Scientifically, green chemistry can be defined as the operation of a set of principles that not only reduces or eliminates the use or generation of harmful substances in the design, manufacture and applications of chemical products but also provides an appropriate measurement criteria to measure the environmental acceptability of the processes being used.

Ionic liquids (ILs), one of the most important tenets of green chemistry, are generally defined as liquid electrolytes composed entirely of organic ions that may undergo almost unlimited structural variations. Nevertheless, a melting point criteria is normally used to distinguish between molten salts and ILs (< 100 °C). In general, the term IL implies a material that is fluid at room temperature (or close to), colorless, has a low viscosity and can be simply handled. Since the respective discoveries of ethylammonium nitrate $[EtNH_3][NO_3]$ (1914) and 1-alkyl-3-methylimidazolium salts (1982) by Walden and Wilkes, ILs have received worldwide attention and become a major scientific area. Whereas the former serves as a first IL, the latter are defined as room temperature ILs (RTILs). In general, RTILs are sterically hindered organic salts of a variety of cations, including, but not limited to tetraalkylammonium, tetraalkylphosphonium, N-alkylpyridinium, 1,3-dialkylimidazolium and trialkylsulfonium cations (Figure 23).

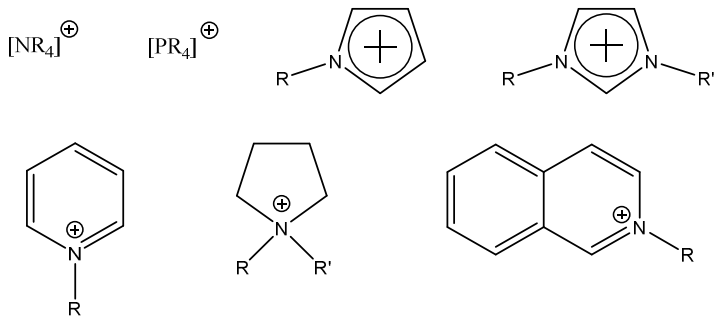


Figure 23 Structures of some common organic cations

Owing to their low or negligible vapor pressure, heat-resistance or tolerance for large temperature variations, non-volatility, absence of flammability and reusability, RTILs have particularly emerged as an alternative revolutionary candidates in the replacement of conventional organic solvents over the last few decades, and increasingly used for large technological applications.

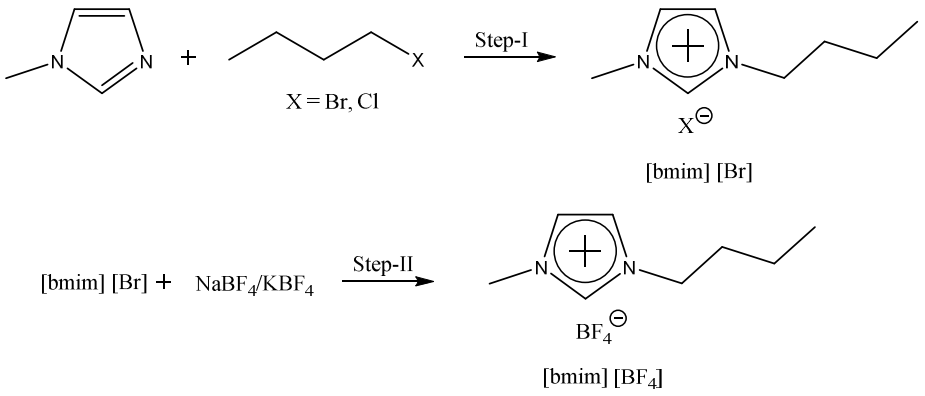
1.14.5.1 Synthesis of Ionic liquids

In a broader context, ILs can be classified into two major categories; first one is simple salts (made up of a single anion and cation) and second one is binary ILs (salts where an equilibrium is involved). For example, $[Et_4N][NO_3]$ is a simple salt whereas a mixture of aluminum(III) chloride and 1,3-dialkylimidazolium chloride constitutes a binary IL system having a number of different ionic species. It is noteworthy that the melting point and properties of a binary IL depend upon the mole fractions of components present, giving them an acidic, basic and neutral characteristics. The synthesis of an IL is usually carried out in two easy steps.

(1) Synthesis of a Desired Cation: A desired cation can be easily synthesized either by a protonation reaction by an acid or through quaternization reactions with a haloalkane.

(2) Anion Exchange Reaction: An anion exchange reaction is usually performed treatment of halide salt with a Lewis acid following an anion metathesis.

As a representative case, the overall synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] is depicted in Scheme 8.



Scheme 8 Synthesis of 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4]

1.14.5.2 Properties of Ionic liquids:

The innovative fluids, ILs, exhibit a significant number of intriguing properties as briefly mentioned below.

- **Stability/Thermal decomposition: Most** ILs are quite stable at high temperature. For instance, the imidazolium cation is stable even above 300°C.
- **Density:**The density of ILs are least effected by temperature variation or impurity. The density of all imidazolium-based ionic liquids are greater than 1.
- **Viscosity:** Though least viscous RTILs are quite viscous when compared to conventional solvents yet the viscosity of ILs can be fairly manipulated with ease. For example, ILs with short alkyl chain and/or functionalized alkyl chain has lower viscosity than those having longer alkyl chain. This can be attributed to the increased van der Waals. Similarly, the use of BF_4 anion contributes toward lower viscosity of ILs than that of PF_6 anion.
- Non-flammable
- Negligible vapor pressure
- High thermal/chemical/electrochemical stability
- Solvating ability
- Large liquids range (span of temperatures between melting and boiling point of a liquid)
- Facile recovery and recyclability
- Non-coordinating with metals and enzymes
- Tunable polarity and miscibility with water/organic solvents

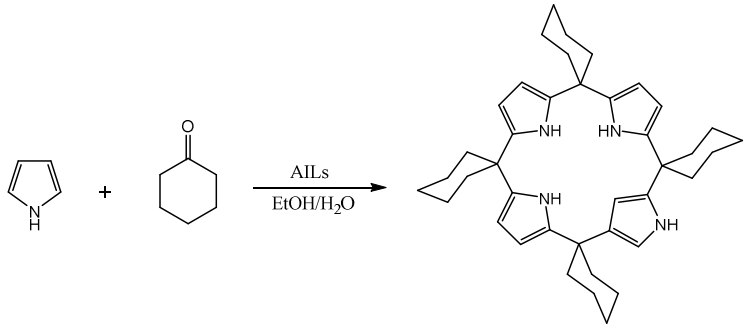
- Highly stable; can be stored for longer duration without decomposition
- Chiral ionic liquids may control stereoselectivity

1.14.5.3 Applications of Ionic liquids

Indubitably, over the last decade, the above-stated properties of ILs have triggered an enormous interest among scientific community to be used them with a diversified range of applications such as sensors, plasticizers, fuel cells, batteries, capacitors, thermal fluids, extractants, ionogels, lubricants, and most importantly as catalysts and solvents in the synthesis, analysis and separation, to name but a few. In line with this, the newer applications of ILs in pharmaceutical industry or as energetic compounds are still emerging. Some of these applications of ILs are briefly outlined below.

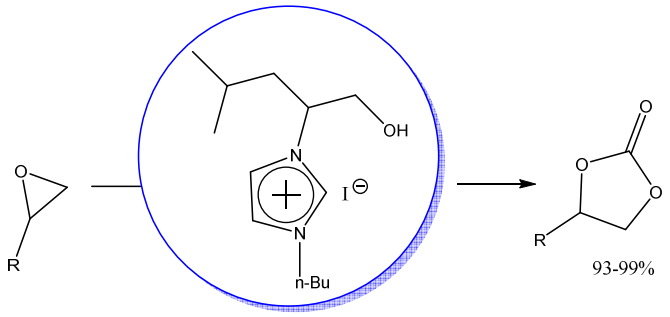
1. **As an extractant:** The water insoluble ILs such as [bmim][PF_6] are used in the extraction of water soluble by-products following simple extraction techniques. Some transition metal catalysts that are soluble in ILs may be recycled together with the ILs, after extraction with water and the non-polar organic solvents used in the product separation.
2. **As a separation and storage media for toxic gases:** It has been found that many gases, including CO_2, are highly soluble in ILs, and thus ILs can also be used as a gas separator. Further, if an IL preferentially dissolves a definite gaseous species, it can be conveniently used for conventional gas absorption applications. Specifically, the non-volatile nature of ILs plays two important roles. Firstly, the regeneration of the solvent becomes easy. However, an easy flash or mild distillation step is required to remove the gas from the solvent. Secondly, during operation, there will be no cross-contamination of the gas stream by the solvent, meaning no solvent loss and air pollution.
3. **As a lubricant:** Due to their tribological performance, ILs was first introduced as lubricants in 2001. The primary advantages of ILs over conventional lubricants lie in their better capability to form tribo films in conjunction with eco-friendliness, high thermal stability, and adaptability to a variety of such applications. A notable reduction in friction and wear has been observed after the addition of ILs in oil- or water-based media and even in grease, suggesting that ILs are quite capable materials to be used either as neat lubricants or lubricant additives.

4. **As a catalyst for organic transformations:**Although ILs were originally introduced as alternative green reaction media because of their unique physicochemical properties yet a wide range of ILs have been designed and synthesized over a period of time for catalytic applications. In this regime, an easy recovery and recyclability of IL catalysts certainly leading to the reduction in the costs of different chemical processes. Despite having a huge library of catalytically active ILs at present, herein, we will limit our discussion to only acidic and basic types of IL catalysts. Generally speaking, the incorporation of acidic or basic functional groups into either cations or anions of the ILs results in the formation of a variety of acidic and basic ILs. Such functionalized ILs are particularly important and referred as task-specific ILs (TSILs).
5. **Brønsted acidic ionic liquids as catalysts:** ILs made up of polynuclear metallic anions such as chloroaluminate (III) have been known for a long time as powerful Lewis acids and can promote certain reactions based on the use of $AlCl_3$. For instance, a typical Friedel-Crafts reaction can work well with such ILs. However, supporting a Brönsted acid (HF or HCl) in the ILs through the formation of $X(HX)_n$ type anion (X = F or Cl) is one of the most intriguing ways to reduce the volatility of an acid catalyst, and thus imparting the Brönsted acidity to the resulting IL. Aside from that, carboxylate or a variety of alkane sulfonic groups can be covalently tethered to imidazolium, pyridinium, ammonium, and other different cations. The as-formed Brönsted acidic ILs (AILs) have emerged as revolutionary candidates in the replacement of conventional homogeneous and heterogeneous acid catalysts, and have been exploited for many organic reactions or transformations, including, but not limited to, Aldol condensation, Beckmann rearrangement, Pechmann reaction, Koch carbonylation, Mannich reaction, Aza-Michael reaction, Hantzsch reaction, synthesis of chalcones, furfural, and biodiesel.
6. Interestingly, the use of AILs (containing sulfobutylimidizolium and pyridinium, N-methyl-2-pyrrolidonium, and prolinium cations) as catalysts has been proved as a highly productive methodology in the one-flask condensation reaction of pyrrole with cyclohexanone in aqueous solution. In particular, under experimental conditions, the reaction can produce primarily N-confused calix[4]pyrrole, a valuable tetrapyrrolic macrocycle in supramolecular chemistry, in significantly higher yields (Scheme 9).



Scheme 9 Brønsted AILs-catalyzed synthesis of N-confused calix[4]pyrrole

7. **Basic ionic liquids as catalysts:** Since the pioneering discovery of functional basic ILs for CO_2 capture application, basic ILs have aroused significant interest in green catalysis. In these types of ILs, an amine organic base is generally tethered to IL cations. Despite their lesser development than AILs, basic ILs have been successfully used to catalyze a number of reactions including Michael addition, aza-Michael addition, condensation of aldehydes and ketones with hydroxylamine, and in the synthesis of quinolines. Scheme 10 highlights a β-hydroxyl-functionalized imidazolium cation-based basic IL that exhibit superior catalytic activity in the synthesis of cyclic carbonates from CO_2 and epoxides. The catalyst could be re-used up to five consecutive times without much loss in the catalytic activity.



Scheme 10 A schematic for the synthesis of cyclic carbonates using a basic IL catalyst

1.15 SUMMARY

This chapter provides concise details about the fundamentals of the concepts in organic chemistry. Chapter covers several important topics including delocalized chemical bond, resonance, conjugation, hyperconjugation, and aromaticity etc.. Other topics such as benzenoid and non-benzenoid compounds along with annulenes are given with logical diagrams. A variety

of addition compounds such as inclusion compounds, catenanes, and rotaxenes are reasonably discussed in conjunction with their synthesis and applications. Furthermore, we envisage that the topic on ionic liquids, one of the tenets of green chemistry, may stimulate the interest of readers to the advanced studies in organic chemistry.

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1.17 Suggested Reading

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3. Gottfried Schill, Catenanes, Rotaxanes, and Knots, 1st edition, Academic Press.
4. Lei, Zhigang, Introduction: Ionic Liquids, *Chem. Rev.*, 2017, *117* (10), pp 6633–6635
5. Sylvan G. Frank, Inclusion Compounds, *Journal of Pharmaceutical Sciences*, 1975, 64, 1585-1604.

1.18 Terminal Questions

Q.1 What is the Huckel's rule of aromaticity of organic compounds?

Q.2 Giving suitable examples, discuss the following

a. Cross-conjugation

b. Delocalization involving π, p-conjugation

c. Anti-aromaticity

Q.3 Write short notes on the following topics :

a. Inclusion compounds

b. Annulenes

c. Homo aromaticity

Q.4 What are cryptands?

Q.5 How to synthesize a supramolecular catenane and rotaxane?

Q.6 How will you differentiate resonance and tautomerism with suitable examples?

Q.7 What are alteranant and non-alteranant Hydrocarbons?

Q.8 What is an ionic liquid? Give synthesis and applications of Ionic Liquids?

Q.9 With suitable examples, disuss benzenoid and non-benzenoid compounds?

Q.10 Discuss Inclusion compounds with suitable examples?

UNIT 2: STRUCTURE AND REACTIVITY

CONTENTS:

2.1 OBJECTIVES

The objective of this unit is to educate the students about the relation of structures with their reactive nature. How the molecular structure influence the kinetis and therodynamics of the reactions.To know how the reaction co-ordinates represent the reaction and their thermodynamic and kinetic progress? Generally this unit describes about the terminologies necessary for describibg the mechanisms of organic reactions like Hammon'd postulates, Curtin –Hammond principle, Potential energy diagram, Transition states and intermediates along with the methods of determining mechanisms and Isotope effect.

2.2 INTRODUCTION

Reactivity is an impetus in chemistry for which a chemikcal species undergo reaction, either by itself or with other materials, with an overall release of output of energy. Reactivity refers to the chemical reactions of a single substance, the chemical reactions of two or more substances that interact with each other, the systematic study of sets of reactions of these two kinds, methodology that applies to the study of reactivity of chemicals of all kinds, experimental methods that are used to observe these processes theories to predict and to account for these processes. The chemical reactivity of a single substance (reactant) covers its behavior in which it decomposes, forms new substances by addition of atoms from another reactant or reactants and interacts with two or more other reactants to form two or more products.The chemical reactivity of a substance can refer to the variety of circumstances (conditions that include temperature, pressure, presence of catalysts) in which it reacts, in combination with the Variety of substances with which it reacts, equilibrium point of the reaction (i.e., the extent to which all of it reacts), rate of the reaction.

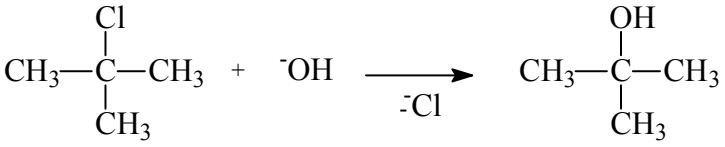
2.3 TYPES OF REACTIONS

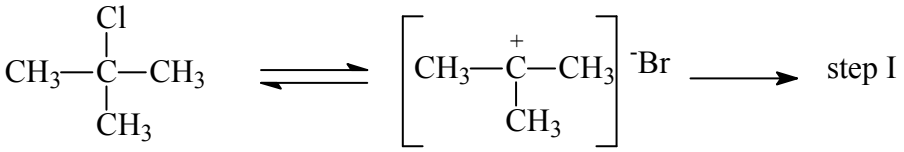
On the basis of their reactivity there are elementary and complex reactions. Simple or elementary reactions are those reactions in which reactants give products in a single step, like conversion of ethyl iodide to ethyle chloride

$$CH_3CH_3I + Cl^- \longrightarrow CH_3CH_2Cl + I^-$$

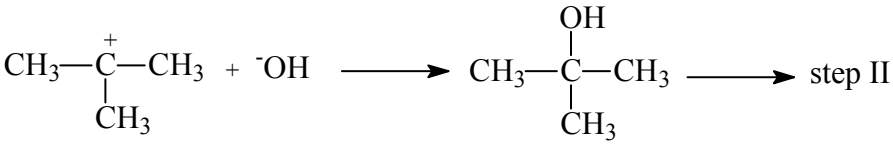
Simple/ elementary reaction

Likewise the complex reactions occur in multiple steps and each individual step of a complex reaction that is proper chemical reaction in its own right is an elementary reaction viz, conversion of *tert*. butyl chloride into *terty*. butyl alcohol with H_2O is a two step reac\tion and each step is elementary in nature



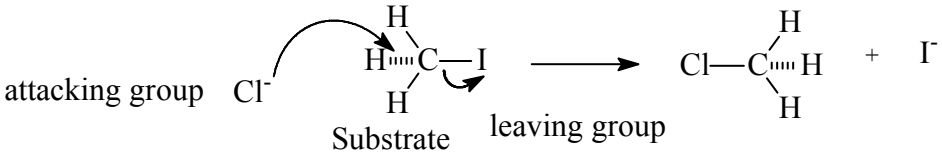


elementary reaction



elementary reaction

Similarly the concerted reactions are those reactions in which bond formation between attacking group and bond breaking between leaving group takes place simultaneously. The concerted reactions are facilitated by transition states.



2.4 KINETICS OF REACTIONS

Kinetic study of the reactions deal with the rate of reactions and their dependence on the concentration of the various reacting species. In contrast to thermodynamics time is very important variable parameter in kinetics. Chemical kinetis is an important technique to investigate the mechanism of chemical reactions. Thermodynamically it is mentioned that change in free energy ΔG tells only relative difference between the stability of the reactants and the stability of the products. It does not tell anything about the energy barrier of the reaction. The energy barrier is the energy barrier that must be crossed for the reactants to be converted into the products. The higher the energy barrier, the slower is the reaction. The energy barrier is indicated by $\Delta G^{\ddagger}$ or Ea and is called enery of activation. It is represented as follow

Ea or $\Delta G^{\ddagger}$ = (free energy of the T.S.) – (free energy of the reactants)

The greater the Ea, the slower is the reaction. ΔG and $\Delta G^{\ddagger}$ both are enthalpy components and entropy components. Notice that any component that relates to thev T.S. is represented by the symble ($\ddagger$ = double dagger)

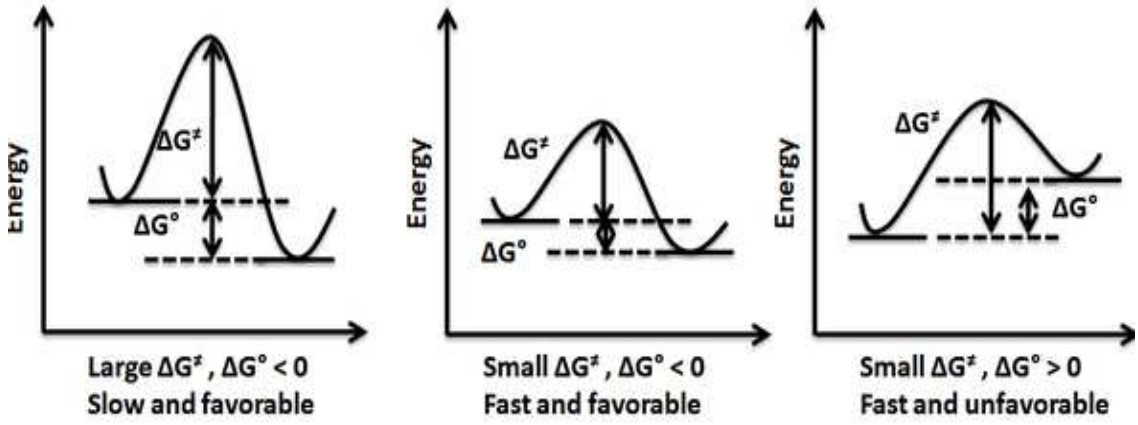
$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$\Delta H^{\ddagger}$ = (enthalpy of the T.S) – (enthalpy of the reactants)

$\Delta S^{\ddagger}$ = (entropy of the T.S) – (entropy of the reactants)

The relative stability of reactant and product does not define the feasibility of any reaction all by itself. For any reaction to proceed the starting material must have enough energy to cross over an energy barrier ($\Delta G^{\neq}$) and the rate of reaction is dependent on the height of this barrier. A low energy barrier corresponds to a fast reaction and high energy barrier corresponds to a slow reaction. A reaction is in equilibrium when the rate of forward reaction is equal to the rate of reverse reaction. Such a reaction is said to be reversible. In principle, all the reactions are reversible but in some cases the equilibrium lies so much towards the product side that it is impossible to see the starting material Fig. 1 describes the relation between ΔG^0 the free energy change and $\Delta G^{\ddagger}$ (energy barrier) –ve value of ΔG^0 indicates exergonic reaction while the +ve ΔG^0 show endergonic reaction

Fig 1



Reaction Coordinate Diagrams showing favorable or unfavorable and slow or fast reactions

Exergonic reaction: The reactions which releases more energy into the system than it consumed

from the system is called exergonic reaction. Is such reactions ΔG of the product is less than the ΔG of the product, for exergonic reaction ΔG^0 = -ve

Endergonic reactions: If products have a higher energy than the reactants, ΔG^0 will be positive and the reaction will consume more energy from system than is released into the system. For exergonic reaction ΔG^0 = +ve

It must be noticed that ΔG relates the equilibrium constant of the reaction , where $\Delta G^{\ddagger}$ relates the rate of the reaction.The thermodynamic stability of a compound is indicated by ΔG^0 Viz; if ΔG is negative, the product is thermodynamically stable compared to reactant and if ΔG is positive than the product will be thermodynamically unstable compared to reactant. The kinetic stability of a compound is indicated by $\Delta G^{\ddagger}$. If it is large, the compound is kinetically stable. In other words, it is not very reactive, while if $\Delta G^{\ddagger}$ is small, the compound is kinetically unstable (it is reactive)

The rate of reaction depends on the following factors;

1. The number of collisions that takes place between the reacting molecules in a given period of time.The greater is the number of collisions, the faster of the rate of reaction

2. The fraction of collisions that occur with sufficient energy to get the reacting molecule over the energy barrier. Smaller the energy of activation/energy barrier (Ea or $\Delta G^{\ddagger}$) more of the collisions will lead to reaction and large the energy of activation/energy barrier(Ea or $\Delta G^{\ddagger}$) less collisions will lead to the reaction.

3. The fraction of the collision that occur with proper orientation, viz; tn the reaction of $CH_3CH=CHCH_3$ with HBr, reaction will occur only if the molecule collide with H of HBr approaching the π –bond of $CH_3CH=CHCH_3$. If collision occurs with H approaching the methyl group of $CH_3CH=CHCH_3$, no reaction will take place regardless of the energy of collision

Rate of reaction = Number of collision/unit of time × Fraction with sufficient energy × Fraction with proper orientation

Increasing the temperature enhance the motion of the molecule. This increase the rate of reaction because it increase the number of collisions that occur in a given period of time and it increases the number of collisions that have sufficient energy to get the reacting molecules over energy barrier.

Ist order reaction: Reactions in which single reactant (R) molecule is converted into a product

(P), in such reaction rate of reaction is proportional to the concentration of reactant. if the con. of R is increased the rate of reaction will be double and if it is increased to triple, the rate of reaction will also be triple

$$R \longrightarrow P$$

$$R = f(P)$$

$$Rat = f(R)$$

$$Rate = k[R]$$

k = proportionality constant known as rate constant.

IInd order reaction: Reaction whose rate of reaction dependends upon the concentrations of two reactants say R and S. If the concentration of R or S is doubled, the rate of the reaction will double. If the concentration of both R and S are doubled, the rate of the reaction will increase by afactor of 4. The rate constant is second order rate constant.

$$R + S \longrightarrow P + Q$$

$$Rate = k[R][S]$$

It is essential to understand the difference between rate of reaction and rate constant.

A. The reaction rate is ameasure of the amount of product that is formed/unit time. That is what we actually measure in the laboratory.

B. The rate constant (k) tells us how easy it reach to the T.S. (how easy it crocss the energy barrier).

The smaller the free energy of activation $\Delta G^{\ddagger}$, the greaterthe rate constant i.e. low energy barriers are associated with large rate constant, whereas high energybarriers have smaller rate constant. From the following reaction co-ordinate (fig.2) the concept of rate of reaction and rate constant can easily be predicted.

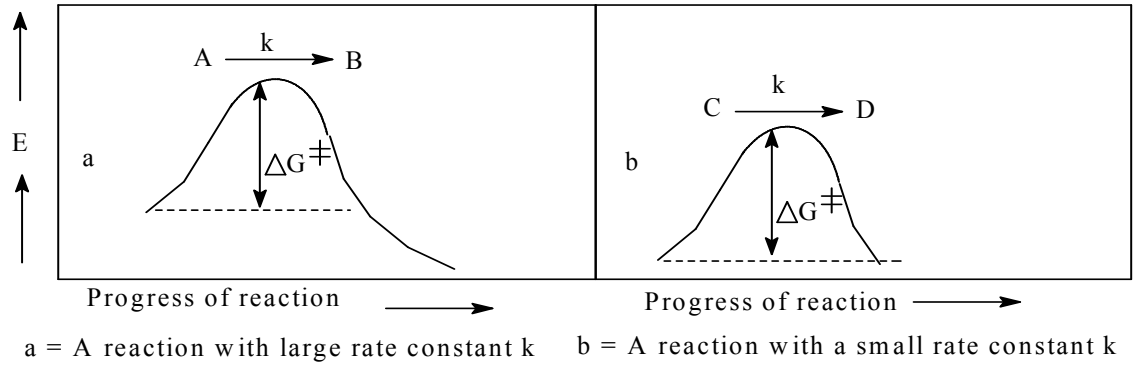


Fig.2 Reaction coordinates for rate constant

The second defference is that the reaction rates are dependent on concentration while rate constant are concentration independent of concentration. The rate constant is temperature dependent. i.e. increasing the temperature increase the rate constant. The Arrhenius equation relates the rate constant of areaction of a reaction to the energy of activation and to the temperature at which the reaction is carried out.

The Arrehenius equation is:

$$k = Ae^{-Ea/RT}$$

or $\log_{10} k = \log_{10} A - Ea/2.303RT$

Where k = rate constant, Ea = experimental energy of activation, R = gas constant, T = absolute temperature, a = frequency factor

2.5 THERMODYNAMICS OF THE REACTIONS

All chemical reactions are reversible and reactant and products interconvert to different degree. A state is said to be in equilibrium if the concentration of both reactant and product do not change. In most of the cases the equilibrium lies on the side of the products.If this happens, the reaction is said to have gone to completion.In such case the arrow indicating reversible reaction is generally omitted chemical reaction proceeds when products are more stable than reactants.The equliberium constant depends upon the enthalpy change (ΔH) and on entropy (ΔS). When entropy change is taken with absolute temperature (T) it gives the free energy change (ΔG) as follow;

$$\Delta G = \Delta H - T\Delta S$$

It should be noted that a reaction proceeds in the forward direction only when ΔG of the reaction is negative. A positive ΔG, on the other hand indicates that the reaction has a tendency to go backward.

The relationship between the equilibrium constant (k) and ΔG^0 is given as follow:

$$\Delta G^0 = - RT \ln K$$

Where k = equilibrium vonstant, R = gas constant, T = Absolute temperature

Consicely it can be predicted as:

Equilibria In Organic Reactions (Thermodynamics)

The equilibrium of a reaction describes how much of a particular reactant

Will be converted to product during the course of the reaction.

A. Equilibrium constant and the Gibbs Free-energy equation

1. The equilibrium constant (Keq) is the molar ratio of products over reactants.

2. The Gibbs free energy equation relates the equilibrium constant to the energy required for the reaction to occur.

$\Delta G° = \Delta H° - T\Delta S°$ or $\Delta G° = -RT \ln Keq$

a. ($\Delta H°$): The bond dissociation energy is the total energy required to homolytically break a bond into two radicals at 25°C in the gas phase.

b. ($\Delta S°$): The entropy factor is the total disorder caused by a given reaction.

B. Equilibria and reaction energy diagrams:

1. A reaction energy diagram describes the relative energies of all species involved in a reaction and how that reaction proceeds.

2. The free-energy ($\Delta G°$) is the energy difference between reactants and products.

a. A negative $\Delta G°$ indicates the products are more stable than the reactants (**exothermic reaction**).

b. A positive $\Delta G°$ indicates the reactants are more stable than the products (**endothermic reactio**n).

Thermodynamics vs Kinetics

Thermodynamicsis all about "if"

• If a process or a reaction can occur or not

• If a systems is in stable or metastable equilibrium

• If sufficient driving force is present to enforce a favourable transformation

Kinetics is all about "how"

• How fast or slow a process can occur, i.e., determining the rate

• How transition from nonequilibrium to equilibrium systems or between two equilibrium states occurs

• How to overcome the energy barrier to finish the transformation from the starting (reactant) state to the final (product) state.

For a reactionirreversible under mild conditions and reversible under vigorous conditions at a certain temperature one product changes to another. At this particular temperature there is

change between a kinetic and a thermodynamic product (fig 3)

Thermodynamics	Kinetics
Talks about how stable a material (or system) is in one state	Considers how quickly or slowly a change can occur
Tells that a reaction should go if the products are more stable (have a lower free energy) than the reactants i.e,the reaction has a negative free energy change.	Tells how fast the reaction will go, it doesn't tell anything about the final state.
The most stable state of a thermodynamic reaction is that of being in the state of products, because the reaction will happen Spontaneously, without the need for energy to be added to make the reaction go forward.	The most stable states of a kinetic reaction are those of the reactants, in which an input of energy will be required to move the reaction from a state of stability, to that of reacting and converting itself to products.
Thermodynamics is related to stability.	Kinetics is related to reactivity.
At high temperature, the reaction is under Thermodynamic control (equilibrium, reversible conditions) and the major product is the more stable system.	At low temperature, the reaction is under kinetic control (rate, irreversible conditions) and the major product is that from fastest reaction.
The thermodynamic product is the most stable product.	The kinetic product is the product that is formed most rapidly
The thermodynamic product predominates when the reaction is reversible thermodynamic control)	The kinetic product predominates when the reaction is irreversible (kinetic control)

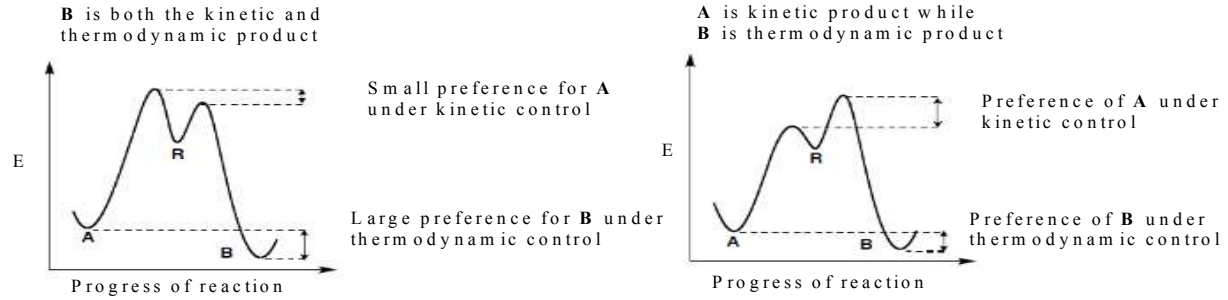


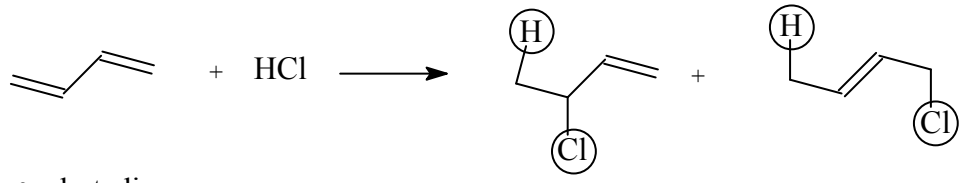
Fig .3.Energy profile for a thermodynamic and kinetic product

Selected Examples of thermodymanicallyand kinetically controlled reactions

Addition of HCl to conjugated dienes

The addition of HCl to 1,3- butadiene can give two products one is 1,2-and another is 1,4-addition product. The amount of each will depend upon the reaction conditions.

The 1,2- product is called kinetic product and 1,4-is thermodynamic product.

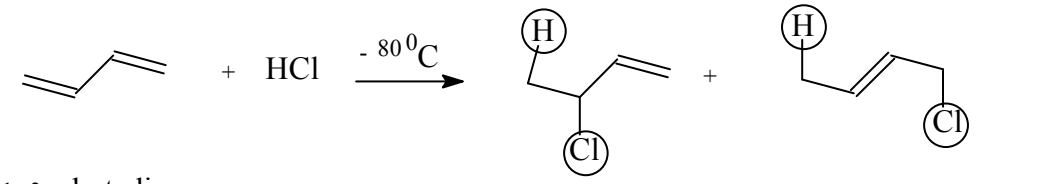


1, 3 – butadiene

1, 2 - addition product
kinetic product

1, 4 - addition product
thermodynamic product

At low temperature -80 or 0 ^{o}C the kinetic product is obtained as major due to low Ea. While at high temperature 40-45^{o}C the thermodynamic product is major, due to greater stability.The 1,4-addition product is more stable as greater the number of alkyl groups attached to a sp^2 carbon more stable it is (more substitute alkene). But, 1,2-addition product is formed faster, as the transition state for formation of 1,2-product is more stable(fig. 4). The transition state for 1,4-addition has positive charge is on lesssubstituted carbon,therefore its activation energy is large and formed slowly. Whereas, thetransition state for 1,2-addition has positive charge on more substituted carbon, and has lesser activation energy thus formed faster.



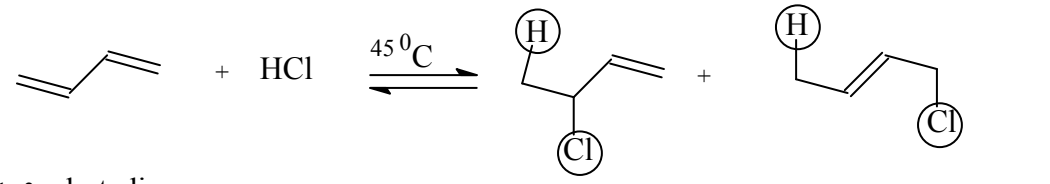
1, 3 – butadiene

1, 2 - addition product

80 %

1, 4 - addition product

20%



1, 3 – butadiene

1, 2 - addition product

15%

1, 4 - addition product

85%

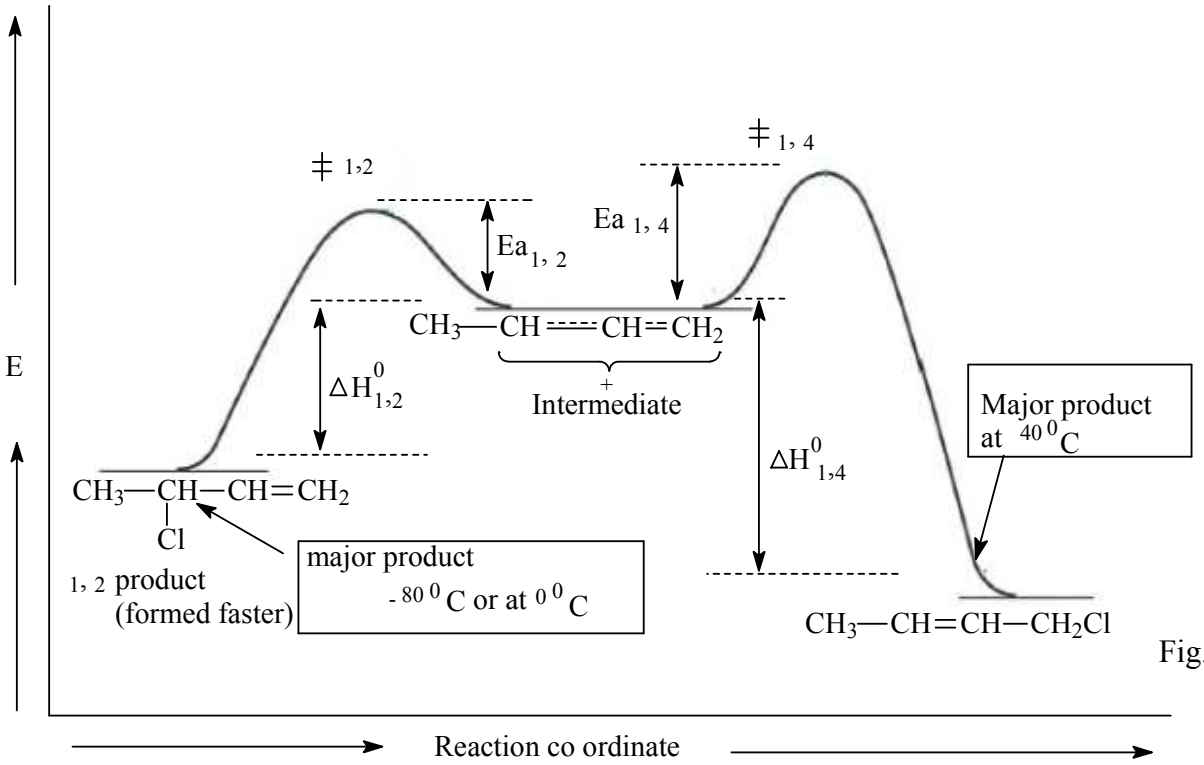


Fig.4: Reaction coordinate diagram for addition of HCl to 1,3-butadiene{‡(1,2) represents Transition state for 1,2-addition; ‡(1,4) represents transition state for 1,4-addition}

2.6 HAMMON'D POSTULATES

"If two states, for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures"

The structure of the transition state for an exothermic reaction is reached early in the reaction, so it resembles reactants more than products. Conversely, the structure of the transition state for an endothermic reaction step is reached relatively late, so it resembles products more then reactants."

- In reactions where the starting material is higher in energy**(A)**, the transition state more closely resembles the starting material
- In reactions where the product is higher in energy**(B)**, the transition state more closely resembles the product (fig.5)
- Explanation: Effectively, the postulate states that the structure of a transition state resembles that of the species nearest to it in free energy. This can be explained with

reference to potential energy diagrams (fig.6):

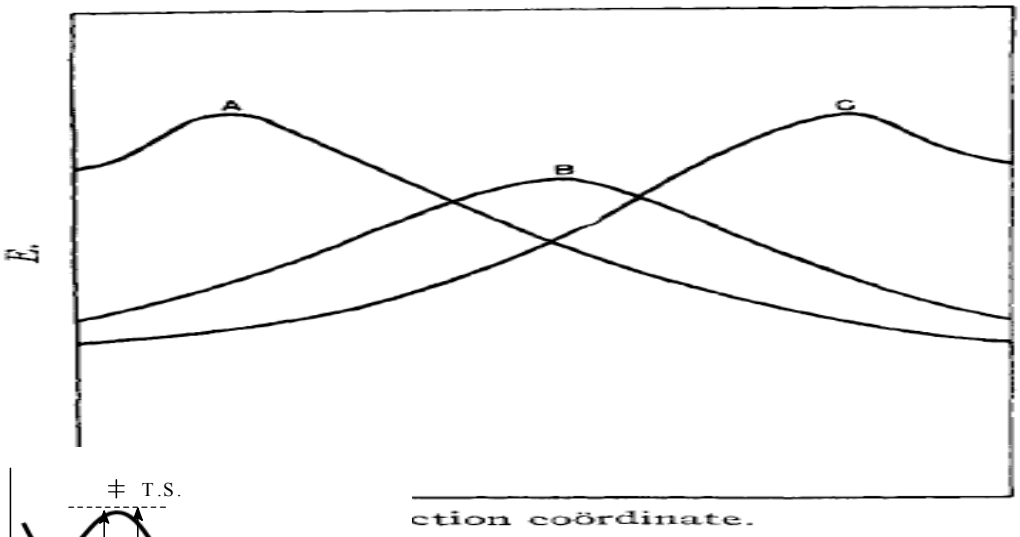
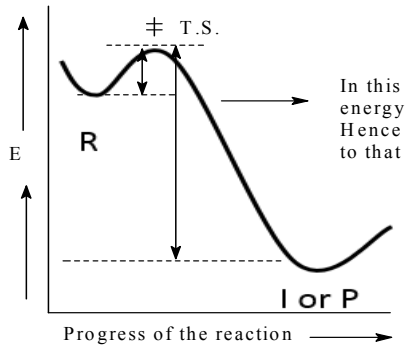


Fig. 5 reaction coordinate for Hammond,s postulate

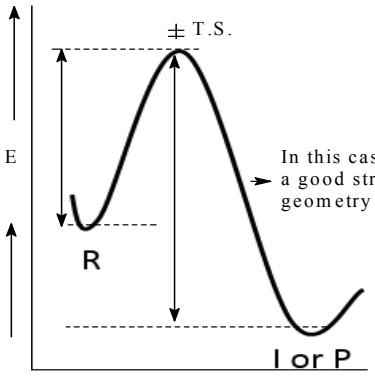


In this case (exothermic reaction) the energy of the T.S. more resemble with the energy of reactant (R) rather than the energy of intermediate (I) or product (P) Hence according to the postulate the geometry of the T.S. more closely resemble to that of the reactant

R = Reactant

I = Intermediate

P = product

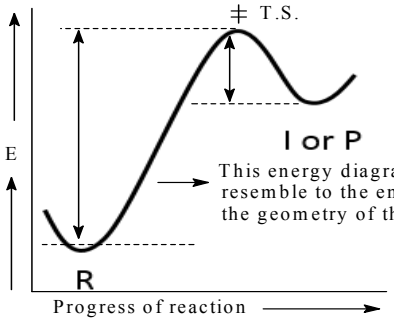


In this case energy of T.S. close to neither the reactant nor the product, making none of them a good structural model for the T.S. Further information is neede in order to predict the the geometry or characteristic of the T.S.

R = Reactant

I = Intermediate

P = product



R= reactant

I = intermediate

P = Product

This energy diagram depict the endothermic reaction and the energy of T.S. more closely resemble to the energy of intermediate (I) or product (P). according to the Hammond's postulate the geometry of the T.S. would more closely resemble with the geometry of intermediate/product

Fig.6. Interpretation of Hammond's postulates

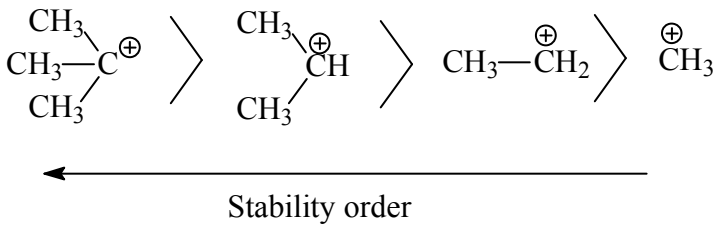
The significance of Hammond's postulate is that it explain the T.S. in terms of the reactants (R), intermediates (I) , or products(P). If the T.S. more closely resembles the reactants, the transition state is called "early" T.S. and if it resembles more with the intermediate or the product, it is called "late" T.S.

Chlorination is the good example of early T.S. as it favors the products because exothermic nature, i.e. products is lower in energy than the reactants. When we look at the adjacent diagram (representation of an "early" transition state), one must focus on the transition state, which is not able to be observed during an experiment. To understand what is meant by an "early" transition state, the Hammond postulate represents a curve that shows the kinetics of this reaction. Since the reactants are higher in energy, the transition state appears to be right after the reaction starts.

Similarly bromination is an example of late T.S. Bromination favors the reactants because it is an endothermic reaction, which means that the reactants are lower in energy than the products.

Structure of transition states:

S_N1 reactions: Hammond's postulate can be used to examine the structure of the transition states of a S_N1 reaction. In particular, the dissociation of the leaving group is the first transition state in a S_N1 reaction. The stabilities of the carbocations formed by this dissociation are known to follow the trend:



Since the tertiary carbocation is relatively stable and therefore close in energy to the R-X reactant, then the tertiary transition state will have a structure that is fairly similar to the R-X reactant. In terms of the graph of reaction coordinate versus energy, this is shown by the fact that the tertiary transition state is further to the left than the other transition states. In contrast, the energy of a methyl carbocation is very high, and therefore the structure of the transition state is more similar to the intermediate carbocation than to the R-X reactant. Accordingly, the methyl transition state is very far to the right fig.7.

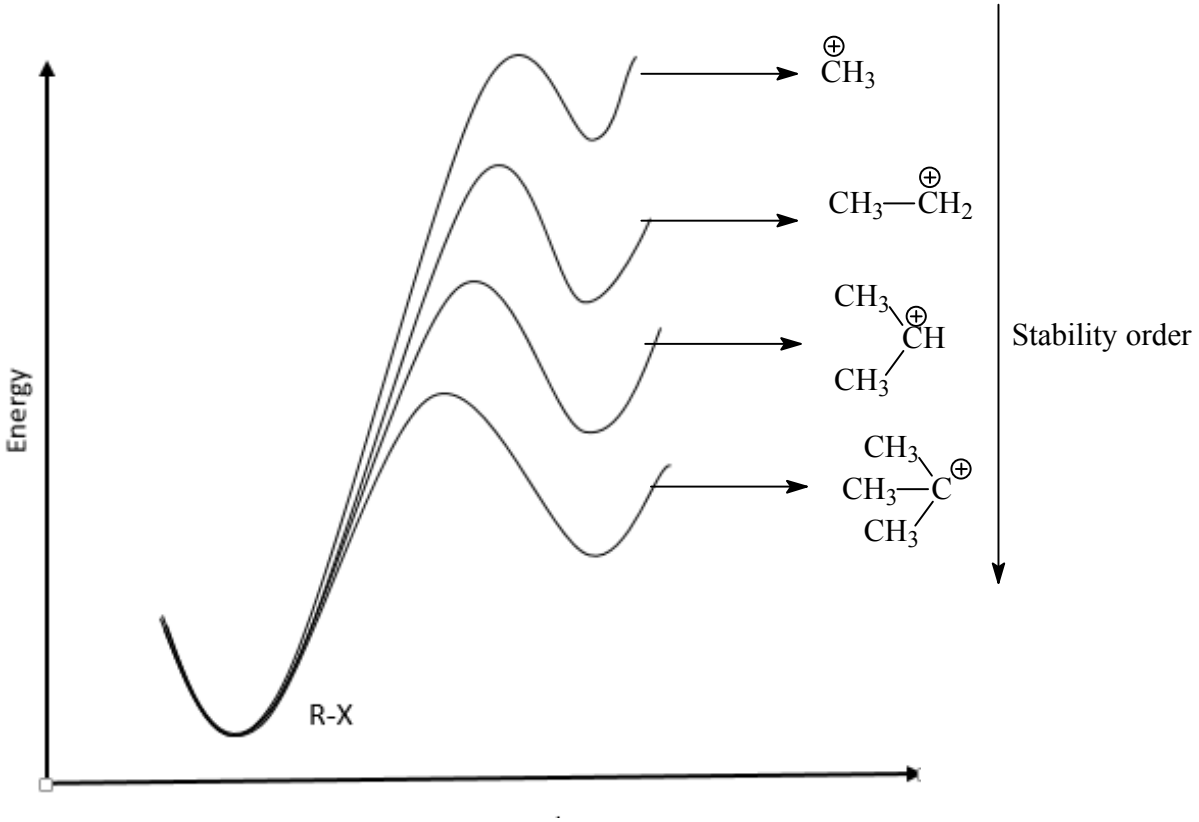


Fig. 7 Reaction coordinates for S_{N1} and S_{N2} reactions

S_{N2} reactions: S_{N2} reactions are concerted reactions, the reaction occurs in one step, where the bonds are broken, while new bonds are formed. Therefore, to interpret this reaction, it is important to look at the transition state, which resembles the concerted rate limiting step. In the "Depiction of S_N2 Reaction" figure, the nucleophile forms a new bond to the carbon, while the halide (L) bond is broken.

E1 reactions: An E1 reaction consists of unimolecular elimination, where the rate determining step of the mechanism depends on the removal of a single molecular species. This is a two-step mechanism. The more stable the carbocation intermediate is, the faster the reaction will proceed, favoring the products. Stabilization of the carbocation intermediate lowers the activation energy.

The reactivity order is (CH3)3C- > (CH3)2CH- > CH3CH2- > CH3

Furthermore, studies describe a typical kinetic resolution process that starts out with two enantiomers that are energetically equivalent and, in the end, form two energy-inequivalent

intermediates, referred to as diastereomers. According to Hammond's postulate, the more stable diastereomer is formed faster (fig.8)

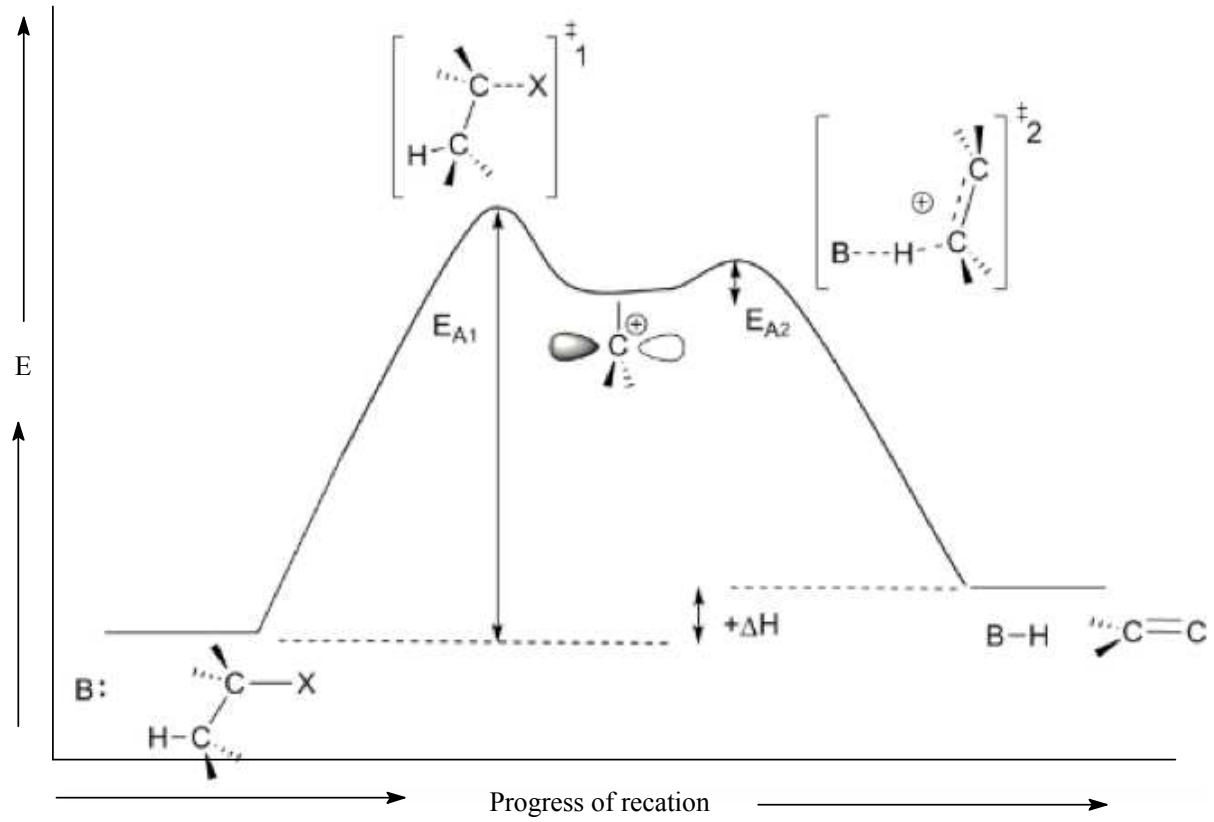


Fig. 8: Unimolecular Elimination Reaction Coordinate

E_2 reactions: E_2 reactions are one step, concerted reaction where both base and substrate participate in the rate limiting step. In an E_2 mechanism, a base takes a proton near the leaving group, forcing the electrons down to make a double bond, and forcing off the leaving group-all in one concerted step. The rate law depends on the first order concentration of two reactants; Factors that affect the rate determining step are stereochemistry, leaving groups, and base strength.

A theory, for an E_2 reaction, by Joseph Bunnett suggests the lowest pass through the energy barrier between reactants and products is gained by an adjustment between the degrees of C_β-H and C_α-X rupture at the transition state. The adjustment involves much breaking of the bond more easily broken, and a small amount of breaking of the bond which requires more energy.

This conclusion by Bunnett is a contradiction from the Hammond postulate. The Hammond postulate is the opposite of what Bunnett theorized. In the transition state of a bond breaking step it involves little breaking when the bond is easily broken and much breaking when it is difficult to break. Despite these differences, the two postulates are not in conflict since they are concerned with different sorts of processes. Hammond focuses on reaction steps where one bond is made or broken, or the breaking of two or more bonds occur simultaneously. The E_2 theory transition state concerns a process when bond formation or breaking is not simultaneous

Applications of Hammonds postulates:

1. It can be inferred from Hammond's postulate is that it is useful for understanding the relationship between the rate of a reaction and the stability of the products. The rate of a reaction depends just on the activation energy ($\Delta G^{\ddagger}$), while the final ratios of products in chemical equilibrium depends only on the ΔG. The ratio of the final products at equilibrium corresponds directly with the stability of those products.

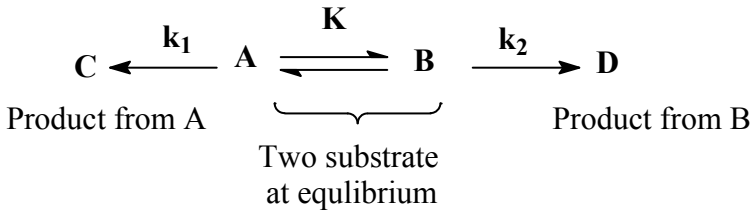
2. Hammond's postulate is helpful for structural comparison between the starting materials, products, and the possible "stable intermediates" that led to the understanding that the most stable product is not always the one that is favored in a reaction process.

3. Hammond's postulate is especially important we look at the rate-determining step of a reaction. However, one must be cautious when examining a multistep reaction or one with the possibility of rearrangements during an intermediate stage. In some cases, the final kinetic productare more stable product than the thermodynamic product. In this case one must examine the rate-limiting step and the intermediates. Often, the rate-limiting step is the initial formation of an unstable species such as a carbocation. Then, once the carbocation is formed, subsequent rearrangements can occur. In these kinds of reactions, especially when run at lower temperatures, the reactants simply react before the rearrangements necessary to form a more stable intermediate have time to occur. At higher temperatures when microscopic reversal is easier, the more stable thermodynamic product is favored because these intermediates have time to rearrange. Whether run at high or low temperatures, the mixture of the kinetic and thermodynamic products eventually reach the same ratio, one in favor of the more stable thermodynamic product, when given time to equilibrate due to microreversal.

2.7 CURTIN –HAMMOND PRINCIPLE

The Curtin–Hammett principle deals with the systems in which different products are formed from two substrates in equilibrium with one another. The rapidly interconverting reactants can have any relationship between themselves like stereoisomers, constitutional isomers, conformational isomers, etc. Product formation must be irreversible, and the different products must be unable to interconvert.

For example, given species **A** and **B** that equilibrate rapidly while **A** turns irreversibly into **C**, and **B** turns irreversibly into **D**:



K = equlibrium constant between A and B

k_1 = Rate constant for the fromation C from D

k_2 = Rate constant for the formation of D from B

If the rate of interconversion between **A** and **B** is much faster than either k_1 or k_2, then the Curtin–Hammett principle tells us that the **C**:**D** product ratio is not equal to the **A**:**B** reactant ratio, but is instead determined by the relative energy of the transition states. If reactants **A** and **B** were at identical energies, the product ratio would depend only on the activation energy of the reactions leading to each respective product. However, in a real scenario, the two reactants are likely at somewhat different energy levels, although the barrier to their interconversion must be low for the Curtin–Hammett scenario to apply. In this case, the product distribution depends both on the relative quantity of **A** and **B** and on the relative activation barriers to the corresponding products **C** and **D**.

The ratio of products only depends on the value labeled $\Delta\Delta G^{\ddagger}$ in the figure: **C** will be the major product, because the energy of **TS1** is lower than the energy of **TS2**. The commonly made assertion that the product distribution does not in any way reflect the relative free energies of substrates **A** and **B** is incorrect; it reflects the relative free energies of the substrates **and** the

relative activation energies. As shown in the derivation below, the product ratio can be expressed either as a function of K, k_1, and k_2, or as a function of $\Delta\Delta G^{\ddagger}$.(fig.9)

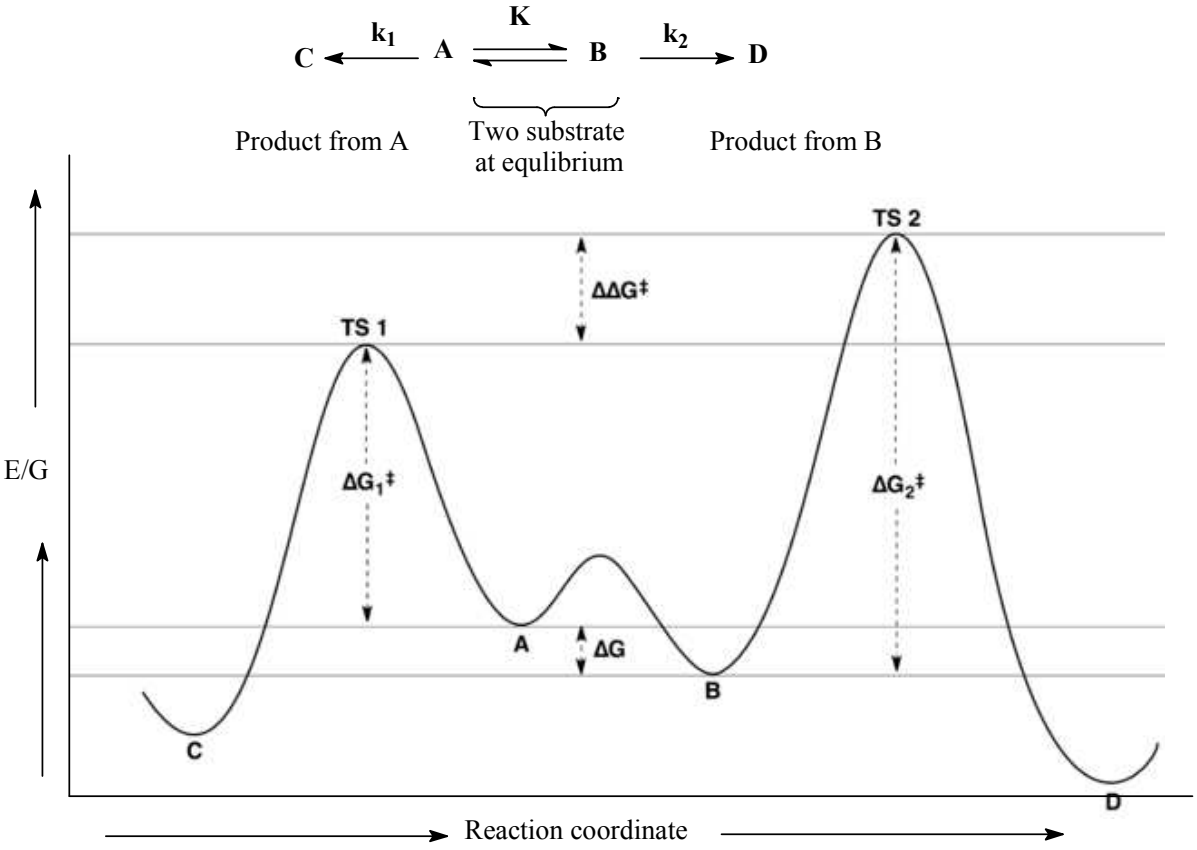
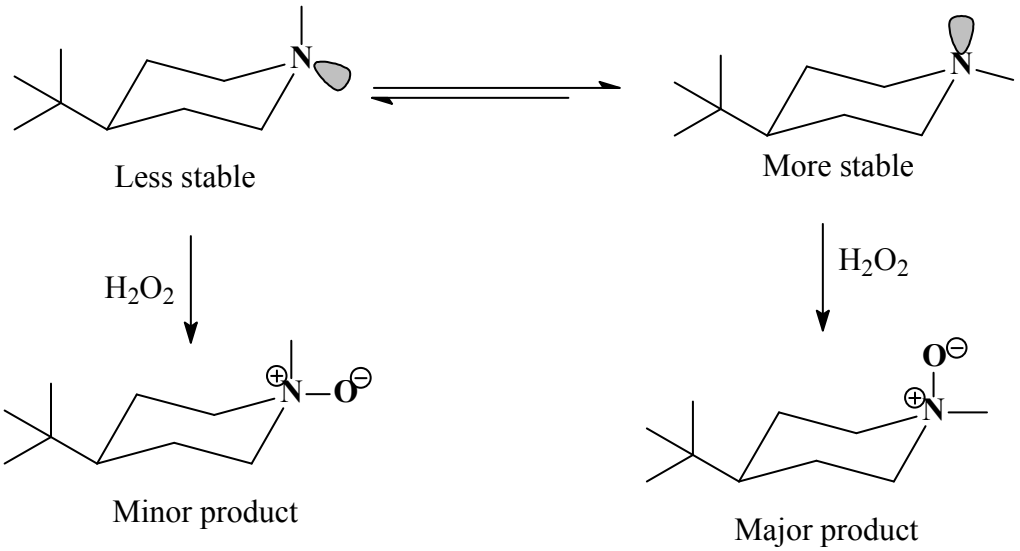


Fig.9. Reaction coordinate for Curtin –Hammond,s princilpal

Classes of reactions under Curtin–Hammett control

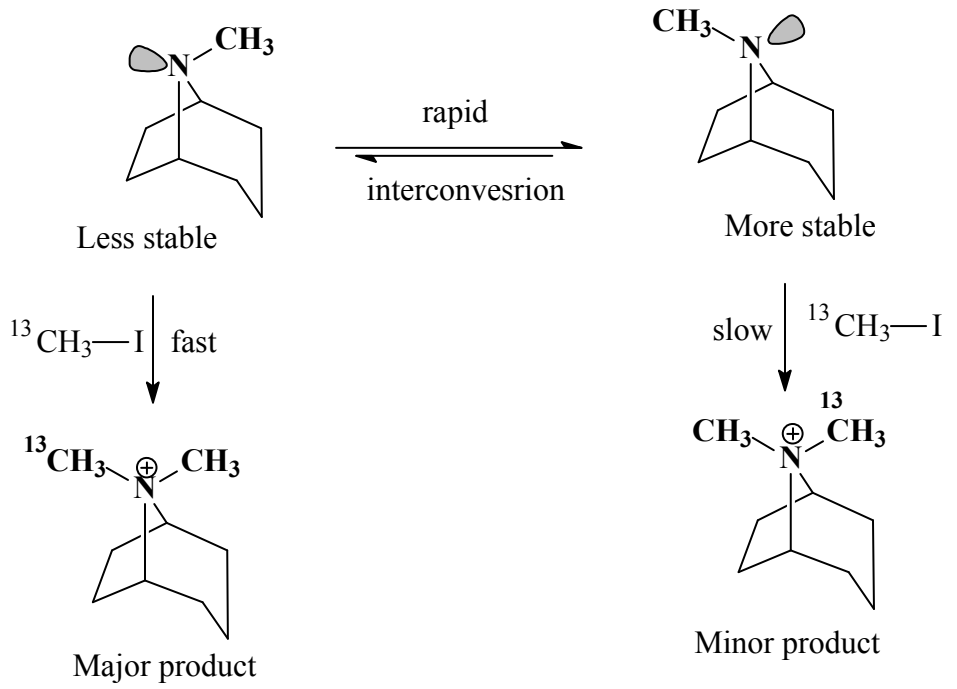
There are three main classes of reactions that can be explained by the Curtin–Hammett principle.

A. One category of reactions under Curtin–Hammett control includes transformations in which the more stable conformer reacts more quickly. This occurs when the transition state from the major intermediate to its respective product is lower in energy than the transition state from the minor intermediate to the other possible product. The major product is then derived from the major conformer, and the product distribution does not mirror the equilibrium conformer distribution. Viz; oxidation of piperidines. In the case of N-methyl piperidine, inversion at nitrogen between diastereomeric conformers is much faster than the rate of amine oxidation. The conformation which places the methyl group in the equatorial position is 3.16 kcal/mol more stable than the axial conformation The product ratio of 95:5 indicates that the more stable conformer leads to the major product



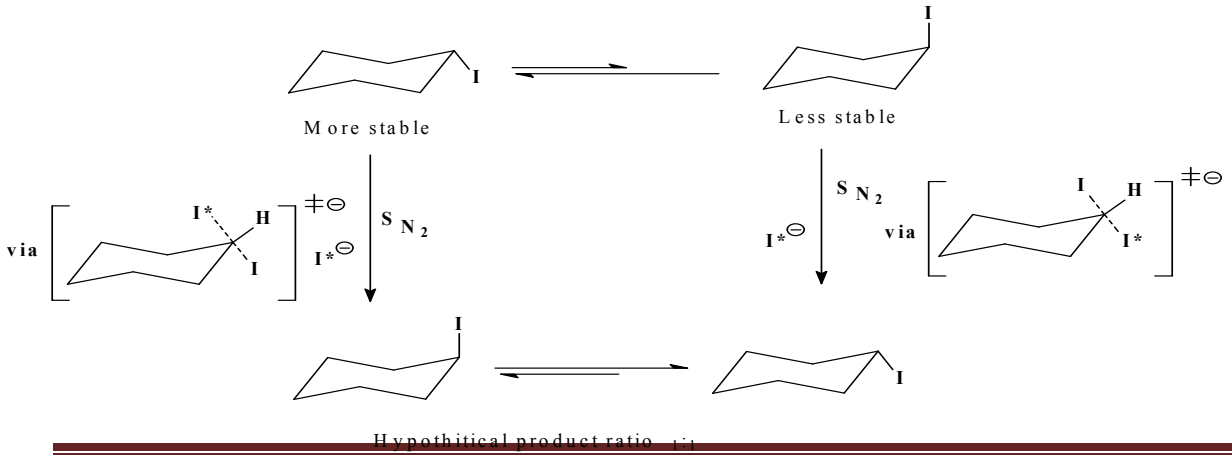
B. A second category of reactions under Curtin–Hammett control includes those in which the less stable conformer reacts more quickly. In this case, despite an energetic preference for the less reactive species, the major product is derived from the higher-energy species. An important implication is that the product of a reaction can be derived from a conformer that is at sufficiently low concentration as to be unobservable in the ground state.

The alkylation of tropanes with methyl iodide is a classic example of a Curtin–Hammett scenario in which a major product can arise from a less stable conformation.[Here, the less stable conformer reacts via a more stable transition state to form the major product. Therefore, the ground state conformational distribution does not reflect the product distribution.



C. It is hypothetically possible that two different conformers in equilibrium could react through transition states that are equal in energy. In this case, product selectivity would depend only on the distribution of ground-state conformers. In this case, both conformers would react at the same rate.

Ernest L. Eliel has proposed that the hypothetical reaction of cyclohexyl iodide with radiolabeled iodide would result in a completely symmetric transition state. Because both the equatorial and axial-substituted conformers would react through the same transition state, $\Delta\Delta G^{\ddagger}$ would equal zero. By the Curtin–Hammett principle, the distribution of products should then be 50% axial substituted and 50% equatorial substituted. However, equilibration of the products precludes observation of this phenomenon.



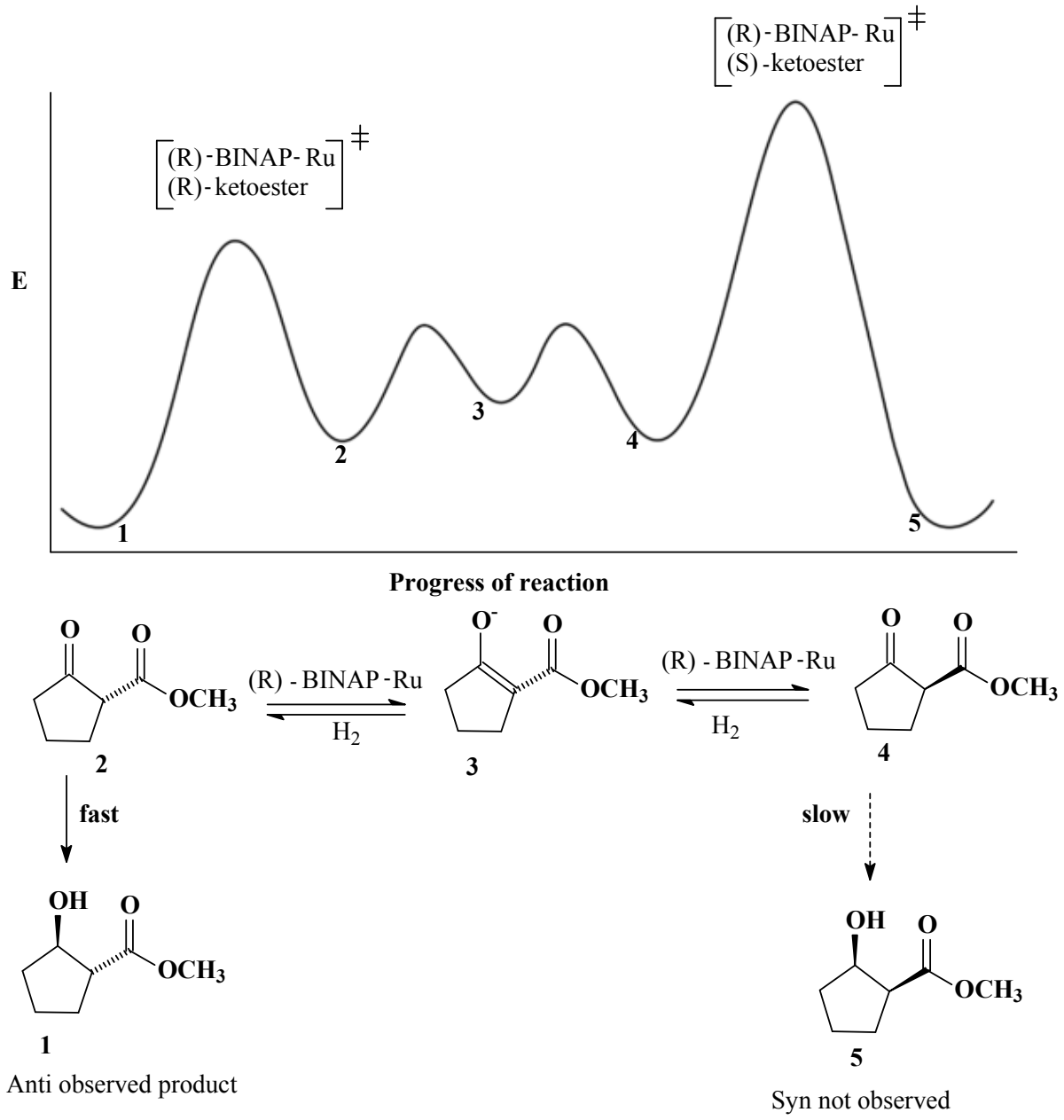
The Curtin–Hammett principle is used to explain the selectivity ratios for some stereoselective reactions.

Application to dynamic kinetic resolution

The Curtin–Hammett principle can explain the observed dynamics in transformations employing dynamic kinetic resolution, such as the Noyori asymmetric hydrogenation and enantioselective lithiation.

Noyori asymmetric hydrogenation

Rapid equilibration between enantiomeric conformers and irreversible hydrogenation place the reaction under Curtin–Hammett control. The use of a chiral catalyst results in a higher-energy and a lower-energy transition state for hydrogenation of the two enantiomers. The transformation occurs via the lower-energy transition state to form the product as a single enantiomer.[14] Consistent with the Curtin–Hammett principle, the ratio of products depends on the absolute energetic barrier of the irreversible step of the reaction, and does not reflect the equilibrium distribution of substrate conformers. The relative free energy profile of one example of the Noyori asymmetric hydrogenation is shown below:



2.8 REACTION CO-ORDINATE

During the course of reactions energy change takes place, as the erwactant are converted to products. This reactant to product conversion can be visualized by using coordinate diagrams known as enery coordinate or energy profile diagram. In energy profile diagrams the energy of the reaction involved is plotted against the progress of the reactions or reaction coordinate

Generally a chemical reaction progresses from left to right starting with the reactant and ending

with the products. In energy profile diagram the energy of the reactant is plotted on left side on the x-axis and that of product is plotted on the right side on the x-axis. Thermodynamically the stability of the species on diagram is indicated by lower energy. A typical reaction coordinate diagram of the following reaction can be depicted in fig.10

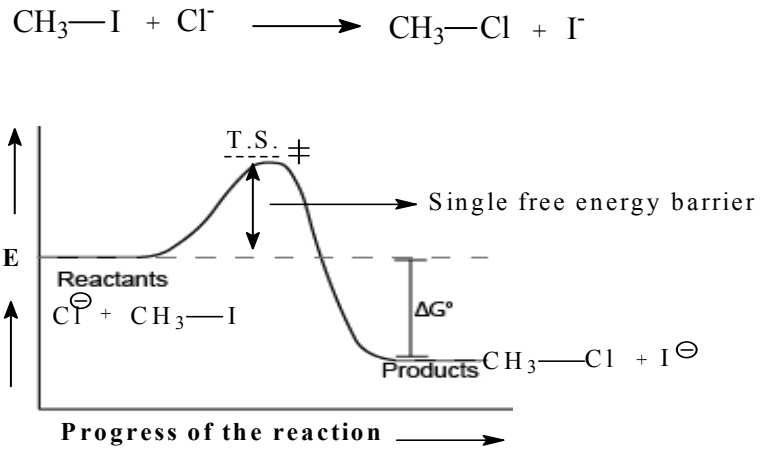


Fig.10 reaction coordinate diagram for the reaction between CH_3-I and Cl^-

There are many reactions in organic chemistry which takes place in steps with the involment of short lived reactive species known as reaction intermediate and follow more than one T.S. to convert the final product. Such reactions can be represented as in fig. 11 (a-b) energy profile diagram. The thermodynamic stability of products and intermediates can be indicated by low energy

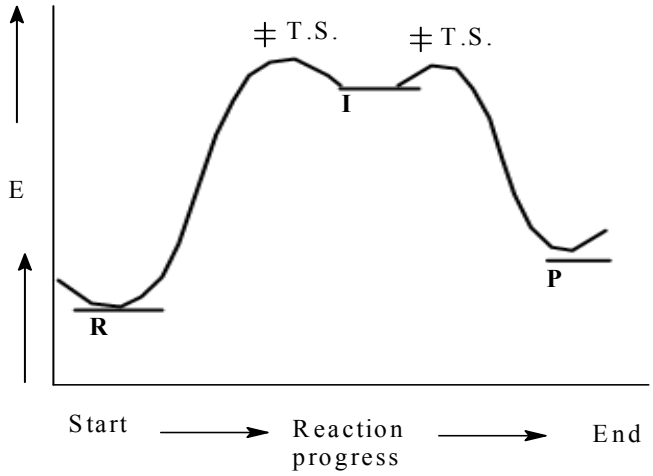
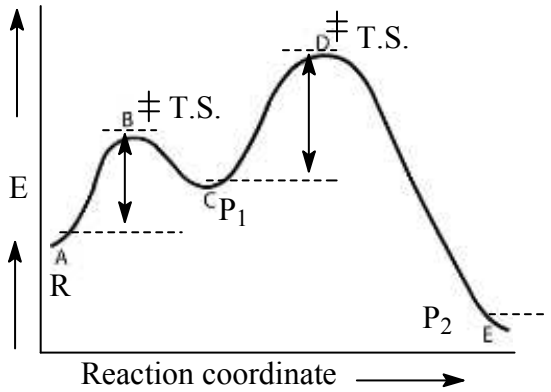


Fig.11a reaction coordinate diagram for multistep reactions



Multistep reaction involving intermediate

A ⟶ C ⟶ E

R = reactant

C = product P_1 obtained from A via T.S. B

E = product P_2 obtained from C (P_1) via T.S. D

Fig.11 b reaction coordinate diagram for multistep reactions

2.9 POTENTIAL ENERGY DIAGRAM

In a chemical reaction, some bonds are broken and some bonds are formed. During the course of the reaction, there exists an intermediate stage, where chemical bonds are partially broken and partially formed. This intermediate exists at a higher energy level than the starting reactants; it is very unstable and is referred to as the transition state. The energy required to reach this transition state is called activation energy. We can define activation energy as the minimum amount of energy required to initiate a reaction,

An potential energy diagram can be defined as a diagram showing the relative potential energies of reactants, transition states, and products as a reaction progresses with time. Viz; in energy potential diagrams for endothermic reaction, the reactants are at a lower energy level compared to the products—as shown in the energy diagram below. In other words, the products are less stable than the reactants. Since we are forcing the reaction in the forward direction towards more unstable entities, overall ΔH for the reaction is positive, i.e., energy is absorbed from the surroundings. In the case of an exothermic reaction, the reactants are at a higher energy level as compared to the products, as shown below in the energy diagram. In other words, the products are more stable than the reactants. Overall ΔH for the reaction is negative, i.e., energy is released in the form of heat (fig.12)

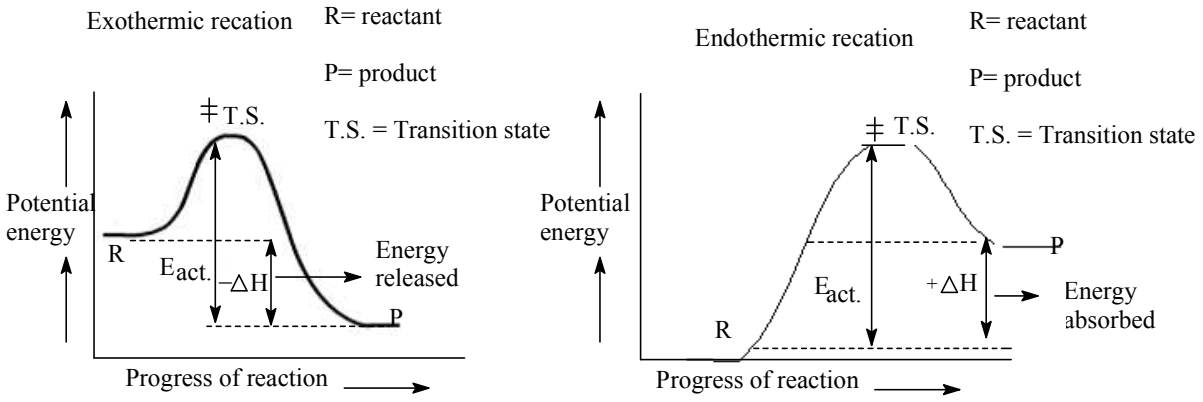


Fig.12 Energy coordinate diagram for eno and Exothermic reactions

2.10 TRANSITION STATES AND INTERMEDIATES:

The concerted reactions takes place in a single step in which bond breaking and bond formation takes place with the involvement of thermodynamically unstable state having a particular configuration along the reaction coordinate known as transition state. The transition state of a chemical corresponding to the highest potential energy along the reaction coordinates. Similarly a reaction intermediate is a molecular entity which is formed from the reactants or preceding reaction intermediates (multisteped reactions) and reacts further to give the directly observed products of a chemical reaction.

The reaction intermediates are generated in either unimolecular reactions like S_{N1} or in bimolecular reactions like E1cb. The important characteristics of reaction intermediates is that they are real chemical species with finite life time.They are highly reactive and undergo chemical reaction and may occasionally be trapped by suitable reagent or observed spectroscopically. The intervention of reaction intermediates in a mechanism of chemical reaction is represented by a local minimum in potential energy diagram. Activated complex and T.S. are represented by maxima in the reaction coordinate and are intrinsically different from reaction intermediates fig.13.a -b

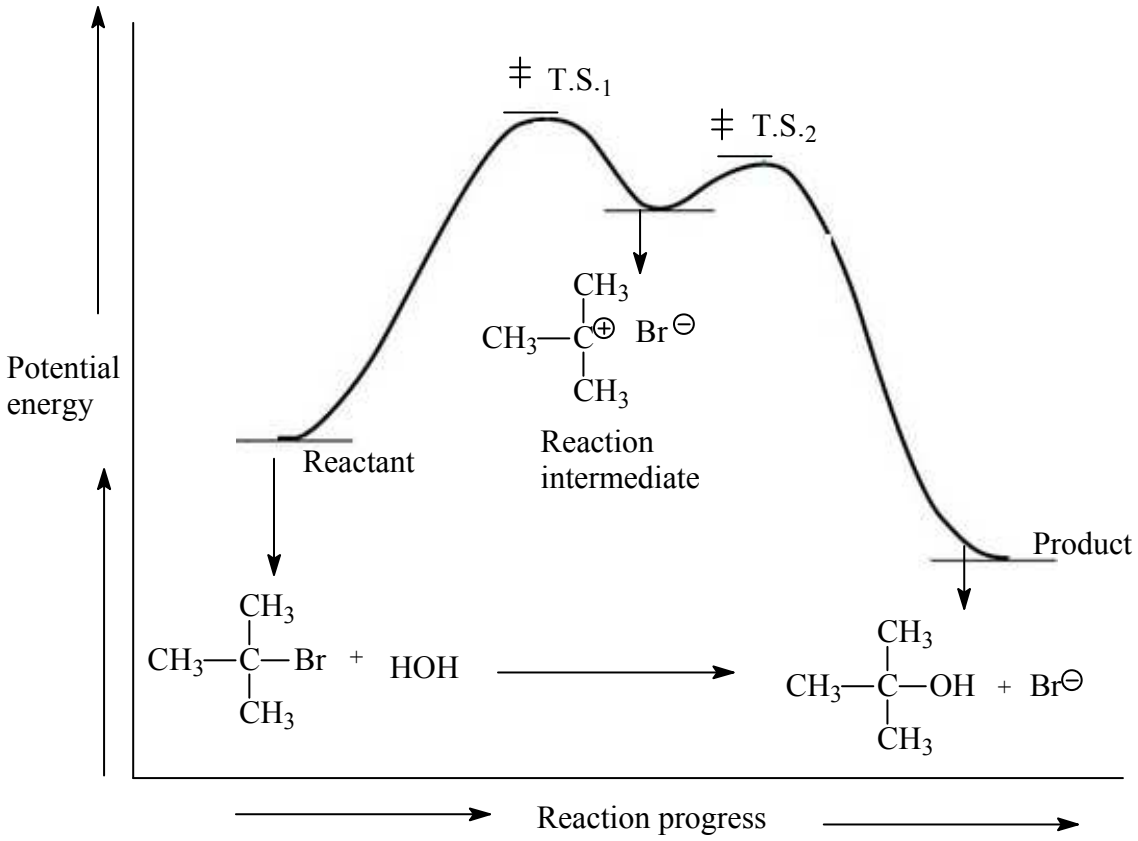


Fig.13. a. reaction coordinate diagram for atwo step reaction (S_{N1})

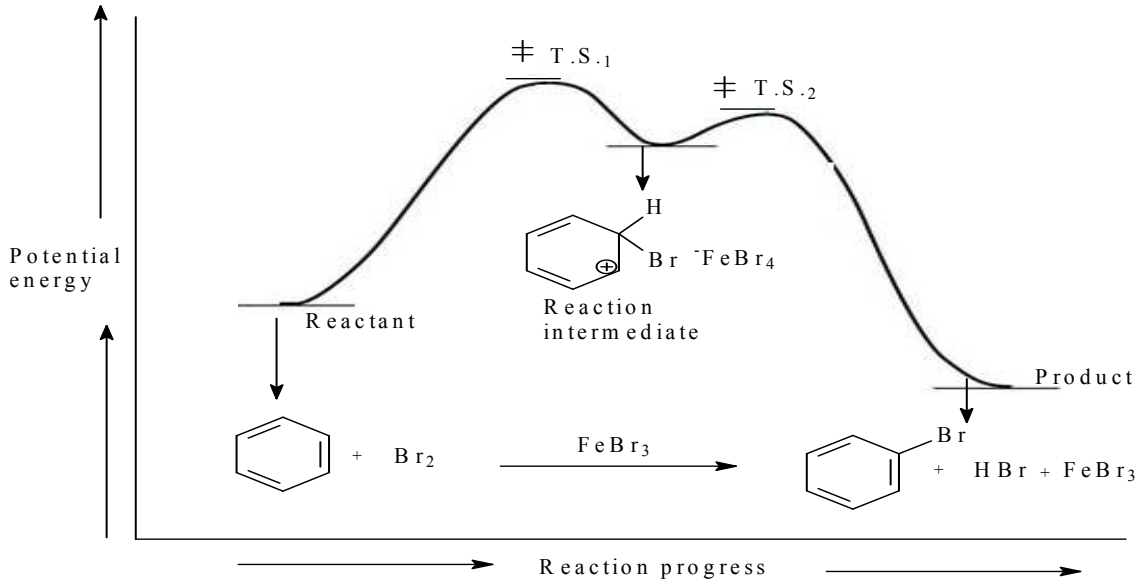


Fig.13. b. reaction coordinate diagram for atwo step reaction (electrophilic substitution)

2.11 METHODS OF DETERMINING MECHANISMS:

There are a number of commonly used methods for determining mechanisms. In most cases, one method is not sufficient and the problem is generally approached from several directions.

1. Identification of products

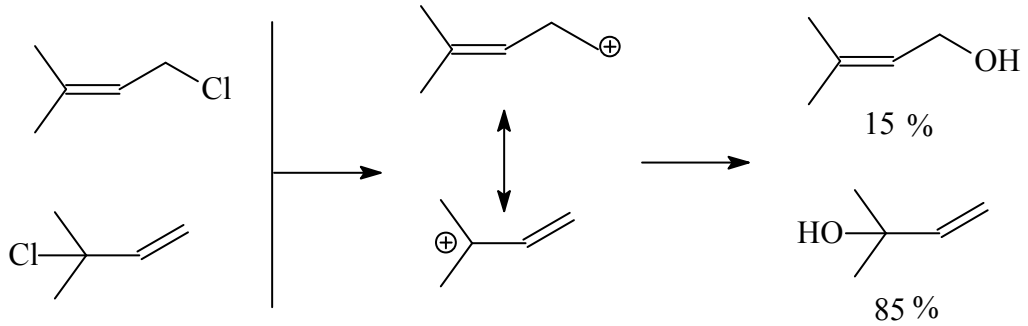
Any mechanism proposed for a reaction must account for all the products obtained and their relative propor tions. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions.Viz; (i) Identification of hydroperoxide hydroperoxide ROOR as a major product of autooxidation of simple hydrocarbons lead to the concept of free radical mechanism.

$$RH + \dot{O}—\dot{O} \longrightarrow \dot{R} + \dot{O}OR$$

$$\dot{R} + \dot{O}—\dot{O} \longrightarrow \dot{O}OR$$

$$RH + \dot{O}OR \longrightarrow R—O—O—R + \dot{R}$$

(ii) Hydrolysis of isomeric allyl chloride (I) and (II) as follow gives 85% of 3^0 alcohol and 15% of 1^0 alcohols. From this reaction it can be inferred that the a common mechanism is being followed as the composition of the products remains the same in either cases



(iii) A little ethane accompanies CH_3Cl when CH_4 is chlorinated in the presence of hv. Hexafluroethane is similarly a by product when flurone reacts with CH_4 Free radical mechanism accounts for these facts readily but ionic mechanism cannot.

$$Cl_2 \xrightarrow{hv} \dot{Cl} + \dot{Cl}$$

$$CH_3—H + \dot{Cl} \longrightarrow \dot{C}H_3 + HCl$$

$$\dot{C}H_3 + Cl_2 \longrightarrow CH_3—Cl + \dot{Cl}$$

$$\dot{C}H_3 + \dot{C}H_3 \longrightarrow CH_3–CH_3$$

$$F_2 \xrightarrow{hv} \dot{F} + \dot{F}$$

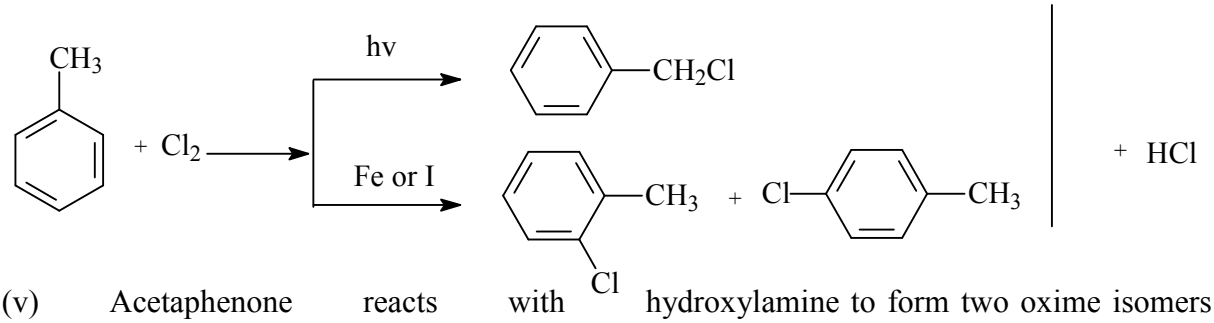
$$CH_3—H + \dot{F} \longrightarrow \dot{C}H_3 + HF$$

$$\dot{C}H_3 + F_2 \longrightarrow CH_3—F + \dot{F}$$

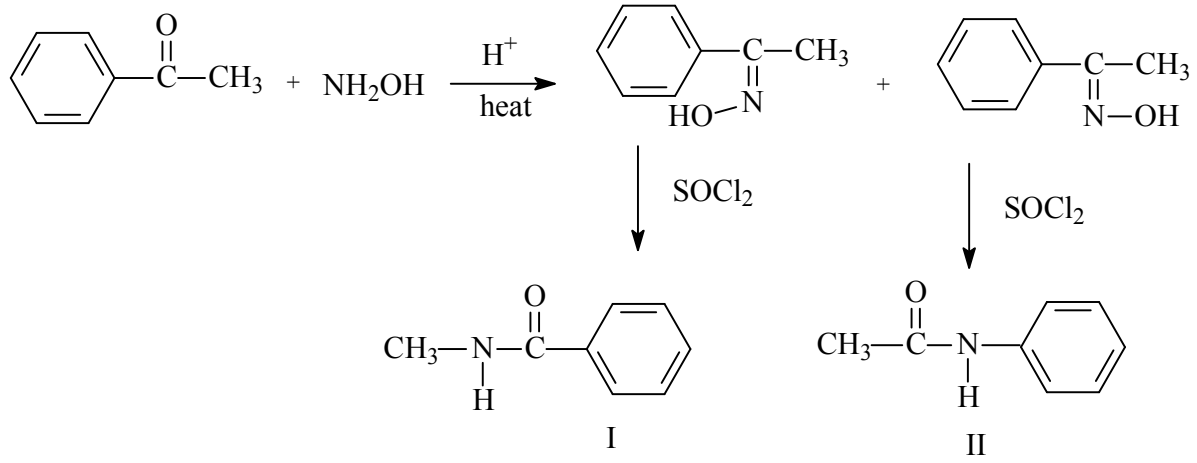
$$\dot{C}F_3 + \dot{C}F_3 \longrightarrow CF_3–CF_3$$

hexafluroethane

(iv) Toluene and chlorine give benzyl chloride in presence of light, but ortho and para-chlorotoluene in presence of iron or iodine at boiling temperature. The different product from the same reactant under different conditions indicates different mechanisms. In fact, the former follows free radical pathway and the latter, an ionic mechanism.

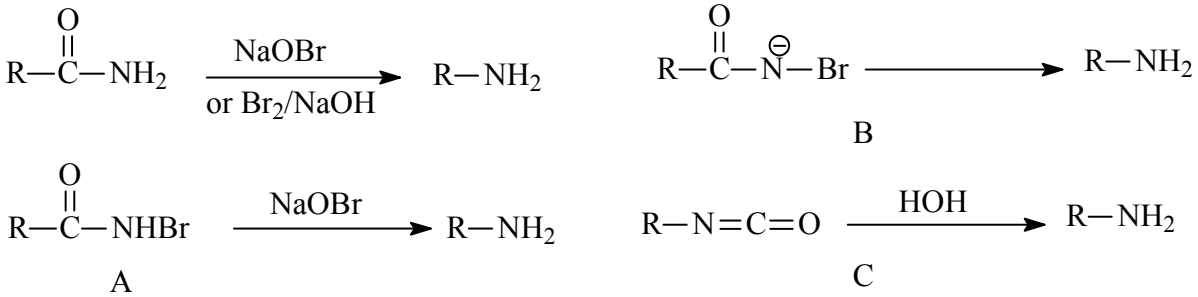


(v) Acetaphenone reacts with hydroxylamine to form two oxime isomers as N-methybezamide I and N-phenylacetamide II in Beckmann rearrangemen (takes place in presence of H_2SO_4/ $SOCl_2$/ PCl_5). This rearrangement reaction indicates that there is atrans migration of the groups with respect to hydroxyl group of the oxime.

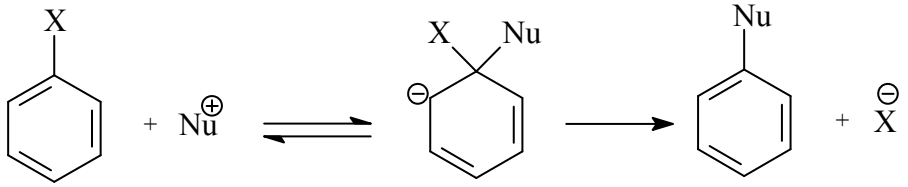


2. Determination of Prescence of an Intermediate: One or more reaction intermediates are formed in complex reactions; they may be detected by physical methods if isolated. Some times the intermediates may be trapped by chemical reaction with an added compound and the compound is known as trapping agent. Reaction kinetics in some cases indicates the formation of an intermediate.

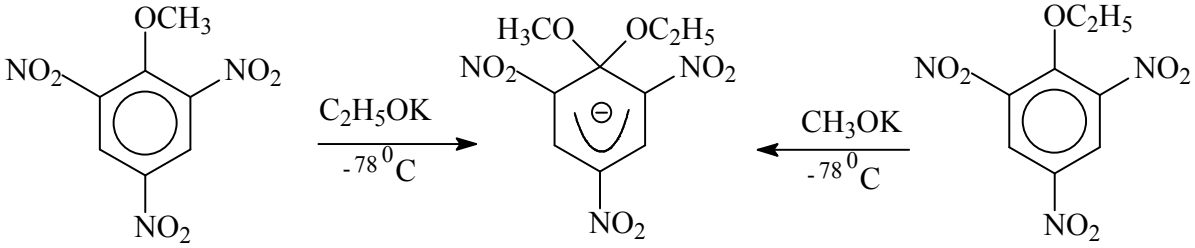
(i) Isolation of an Intermediate: An intermediate can be isolated from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. If the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than the starting compound, this gives strong evidence that the reaction involves that intermediate. Viz; (i) isolation of intermediates N-bromoamide (A) its anion (B) and isocyanate (C) during the formation of primary amine RNH_2 from amide by Hoffmann rearrangement is one of few cases. These can be readily converted into RNH_2. Thus any proposed mechanism for this rearrangement must account for the formation of all these intermediates.



(ii) Biomolecular aromatic nucleophilic substitution reaction takes place by the formation of cyclohexadienylide anion (also known as Meisenheimer complex or σ complex)

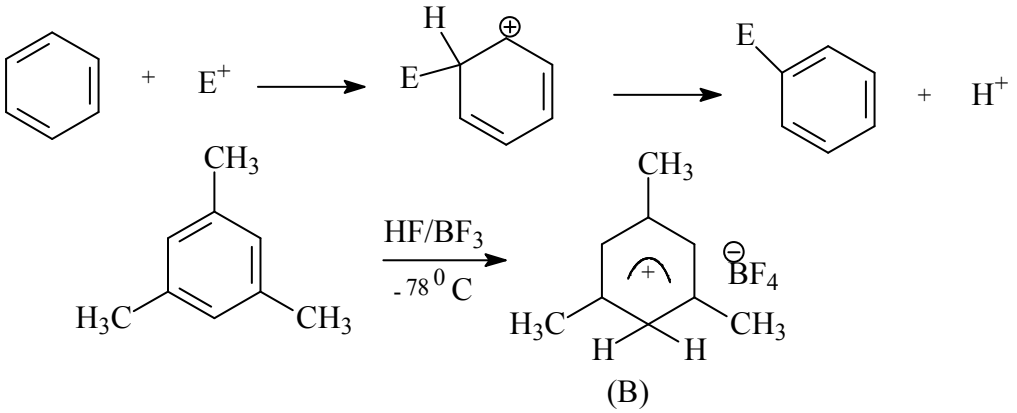


In most of the cases the intermediates have been isolated from the reaction. Viz; the slat (A) formed either by the action of C_2H_5OK on 2, 4, 6-trinitroanisole or CH_3OK on trinitrophenetol

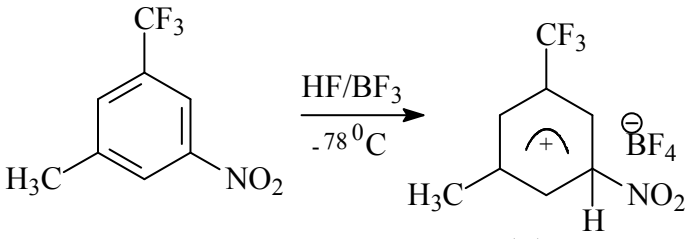


(iii) Biomolecular aromatic E^+ substitution reactions takes place through benzenium ion (σ- complex) formation. Some stable σ- complexes as (B) and (C)

have been isolated from the reaction mixture and also prepared in the form of salts.



(B)

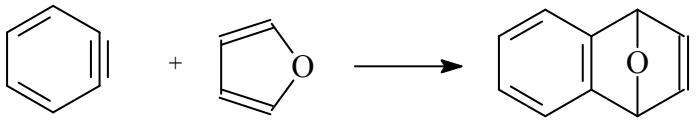


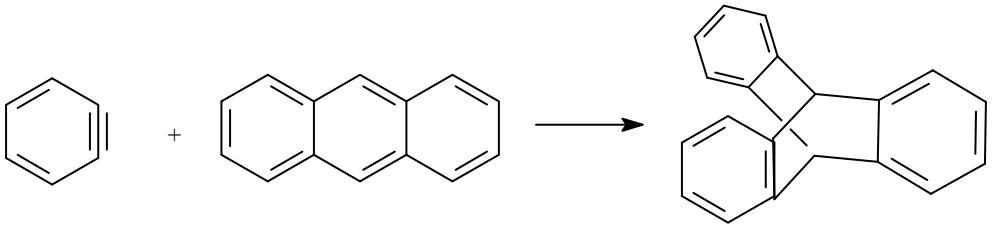
(C)

3. Detection of an intermediate: Intermediates can be detected by IR, NMR, or some other spectra. For example, the detection of NO_2^+ by Raman spectra was regarded as strong evidence that this is an intermediate in the nitration of benzene. Free radicals and triplet intermediates can be detected by ESR and CIDNP (chemically induced dynamic nuclear polarization)

NMR- spectroscopy is a powerfull and versatile tool for detecting organic reaction intermediates. ^{1}H-NMR is most useful because it provides the greatest sensitivity of the nuclei of intrest in organic chemistry. ^{13} C is less sensitive but development high field instruments and the use of FT-methods have greately enhanced the sensitivity so that NMR can be used to detect characteristic signals of reaction intermediates.

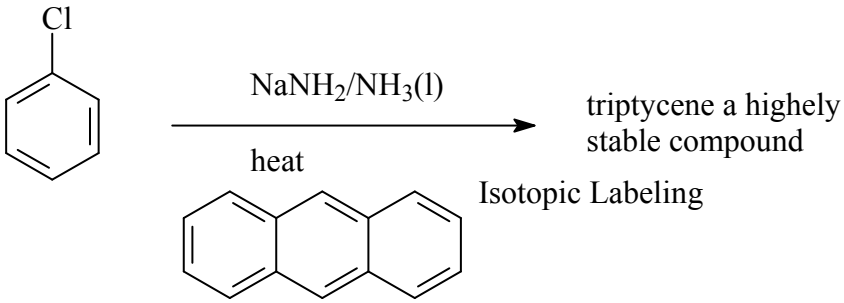
4. Trapping of an intermediate: In some cases, the intermediates may react with a certain compound in a given way. The intermediate can be trapped by running the reaction in the precsence of that compound. For exampe, (i) benzyne react with dienes in the Diels-Alder reaction. The detection of the Diels - Alder adduct indicate that the benzyne was probably present.



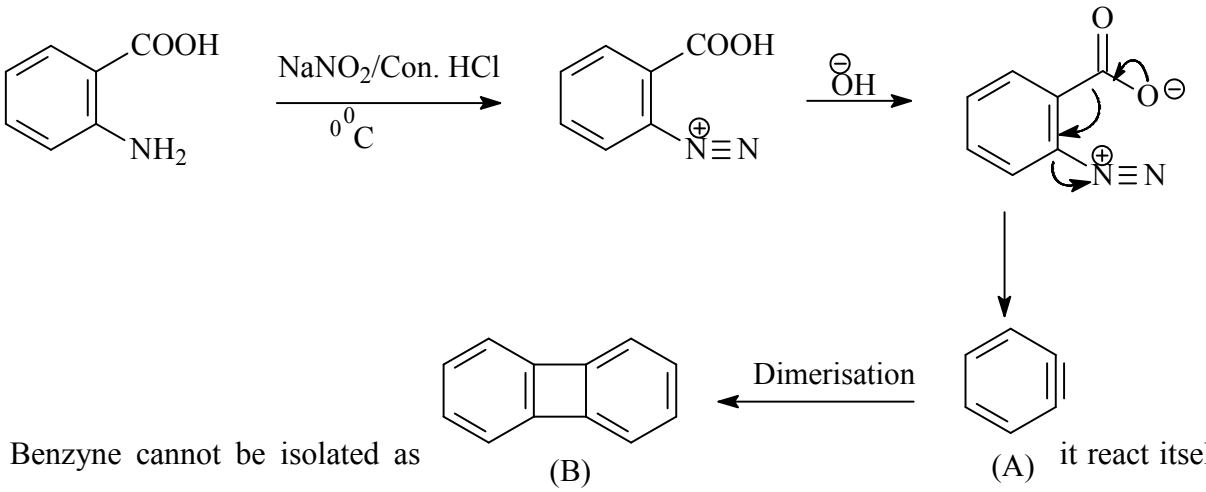


triptycene a highely stable compound

Aromatic Nu^- substitution reaction of chlorobwenzene in the presence of $NaNH_2$ takes place through the formation of benzyne as areaction intermediate. In this reaction formation of benzyne has been confirmed by trapping it with anthracene



Independent existence of benzyne has been confirmed as follow.



(B) (A)

Benzyne cannot be isolated as it react itself to form dimer having a four membered ring between two benzene rings. If the Zwitterion is injected into a mass spectrometer, there is a peak at M/z 152 corresponding for dimer (B) but also astrong

peak at M/z 76 is of benzyne itself (A) fig .14. The lifetime of a particle in MS is about 20 nano-seconds so the benzyne can exist for at least that long time in the gas phase.

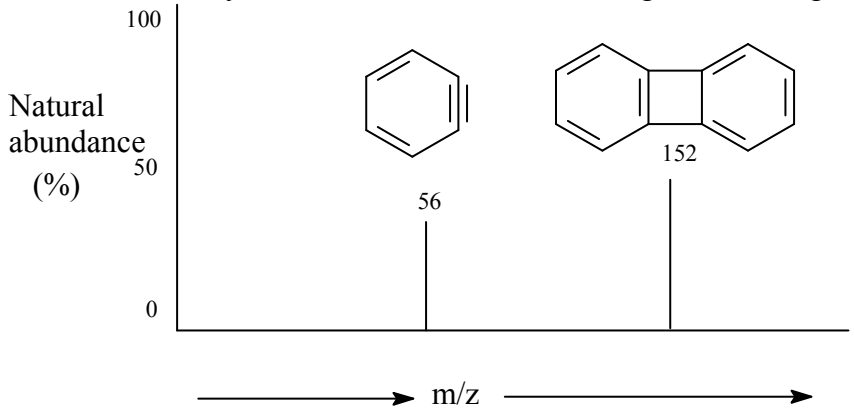
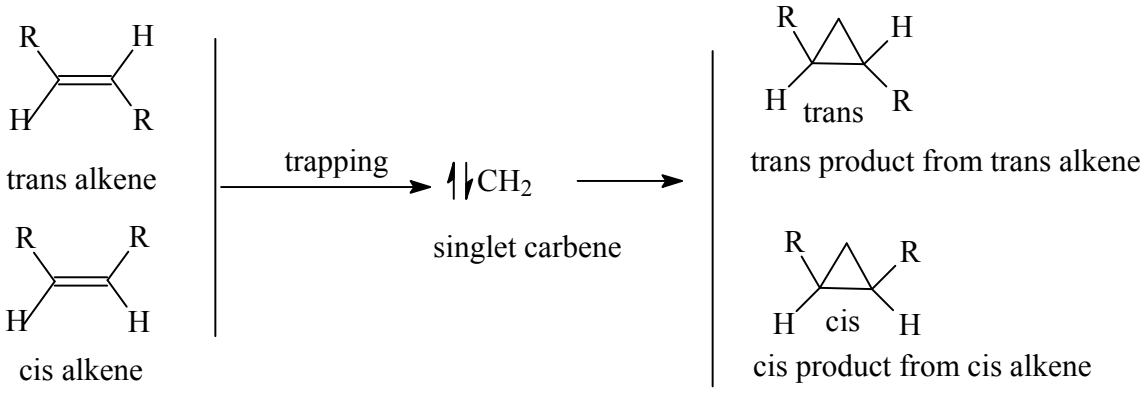
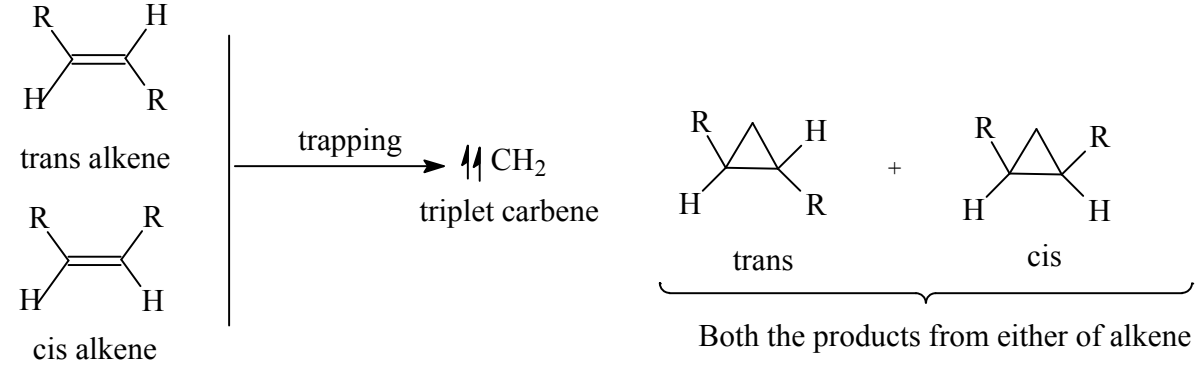


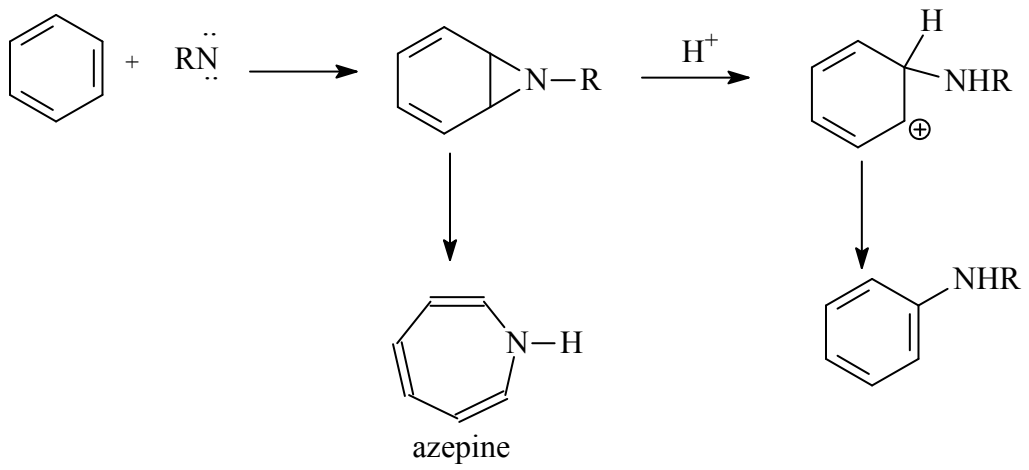
Fig.*14. Representation of mass spec trum of benzyne reaction intermediate*

(ii) Trapping of alkene with carbine inidate the formation of carbine intermediate as when alkenes are treated with carbine, acyclopropane ring is formed. Carbene exists in singlet and triplet form the stereoselective reactions of carbine with alkene is indicative of type of carbine reaction intermediate as follow.



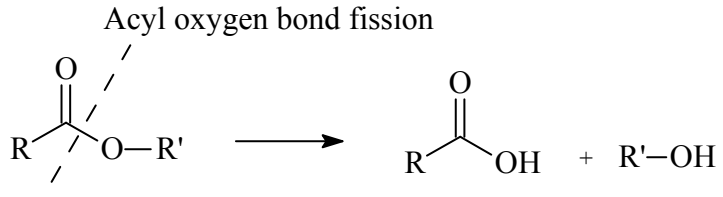


(iii) Trapping reagent of nitrenes is benzene. It react with nitrenes to give ring expended product and/or N-

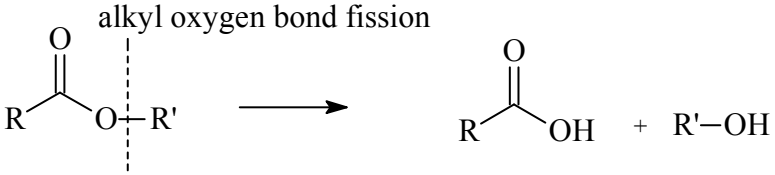


substituted anilines. Both type of products are formed by intial nitrene attack on the π- system of benzene.

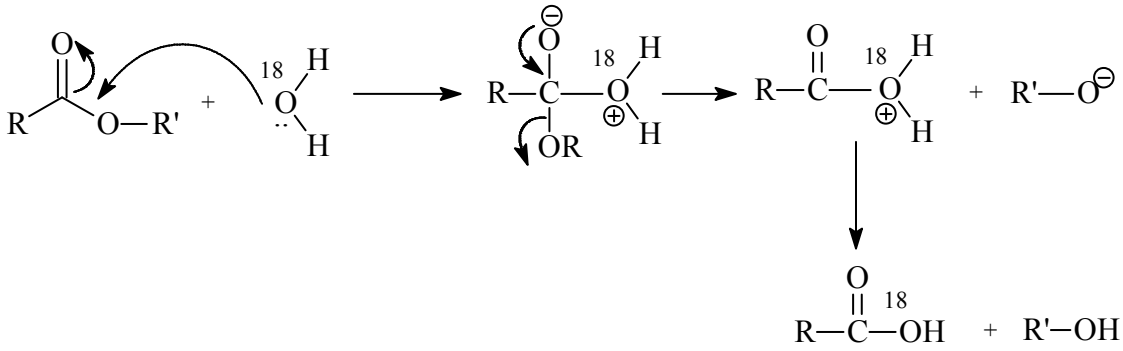
5. Isotopic labeling: Informations about the reaction mechanism can be obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in this way. Radioactive isotopes as well as stable isotopes can be used as tracers.O-18 can be detected by mass spectrometry. D can be determined by IR and NMR spectra when used as a substitute for H. Also, C-13 which is non-radioactive can be detected by C-13 NMR. Viz hydrolysis of carboxylic ester may involve either (A) an acyl-oxygen bond fission or (B) an alkyl-oxygen bond fission



(A)

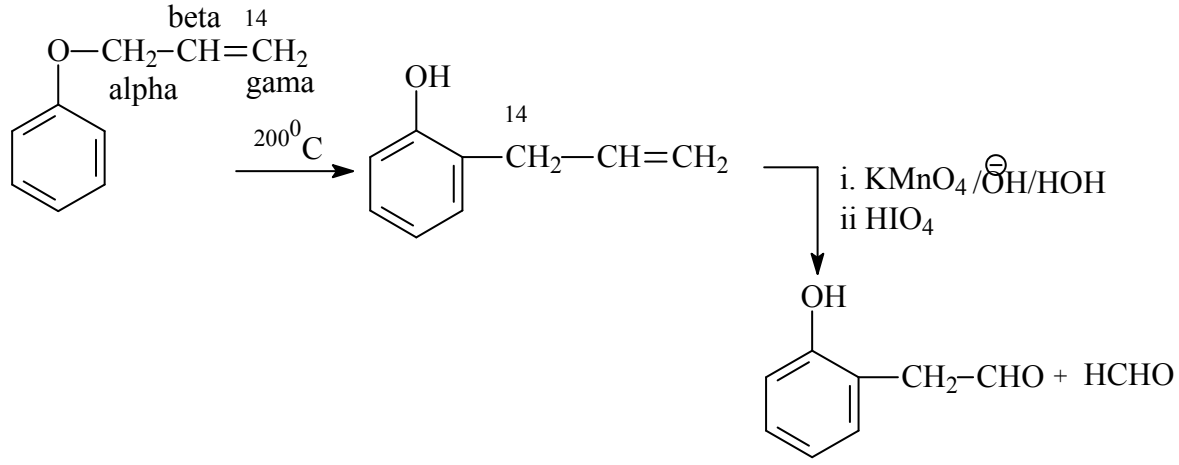


(B)

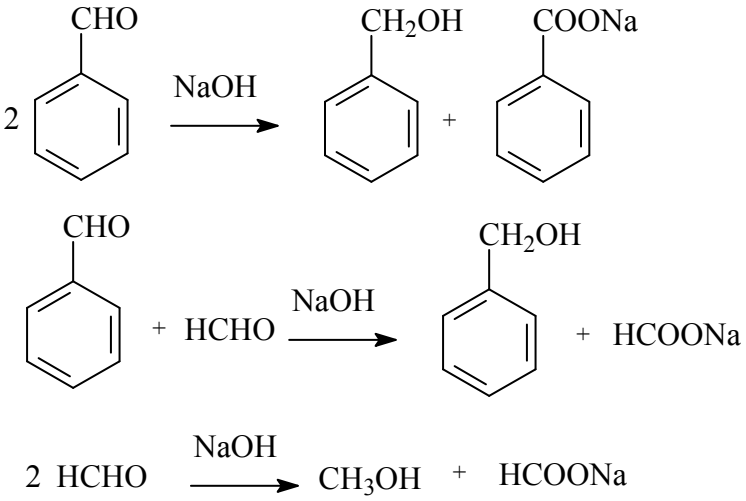


The above mechanism has been solved by hydrolyzing ester in H_2O^{18} . If the acyl –oxygen bond breaks, the labeled oxygen will appear in the acid otherwise it will be in alcohol. The reaction thus confirms that during the course of hydrolysis acyl-oxygen bond breaks.

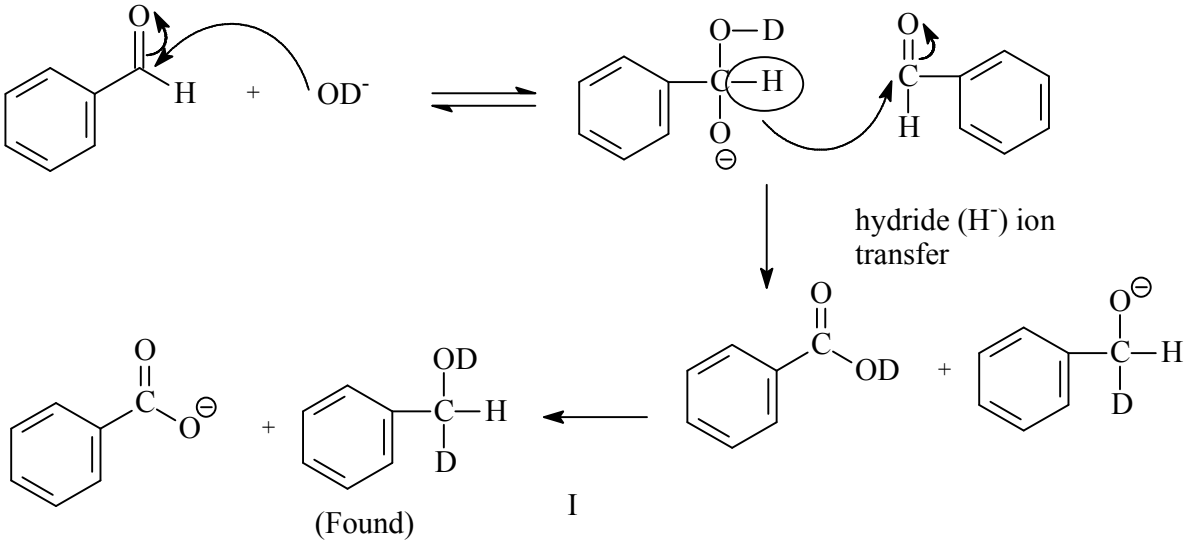
Similarly in the rearrangement of Claisen-reaction the phenyl allyl ether on heating at about 200^0C, undergo inversion. This mechanism has been proofed by labeling the terminal CH_2 (γ)-position with C^{14} isotop. The location of this radioactive isotop bonded as alpha- carbon of the side chain to the o- position is done by oxidation method. The Oxidation of o- allylphenol yields HCHO not $H^{14}CHO$. This result shows that there is inversion of the allyl group.

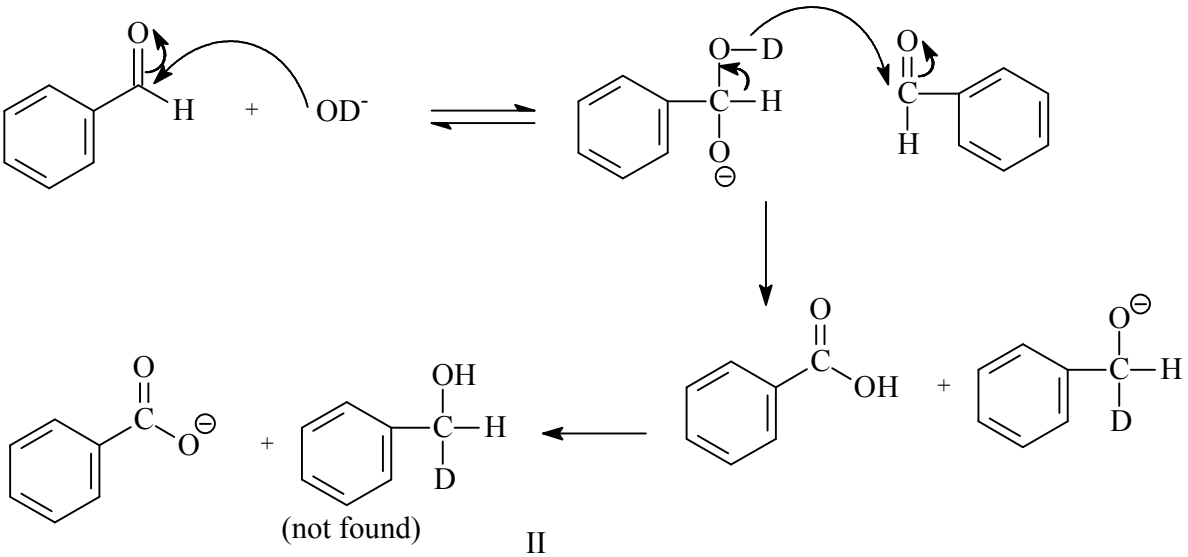


Another evidence is the hydride ion transfer in Cannizzaro reaction in which two molecules of aldehydes devoiding α- hydrogen are condensed in presence of NaOH, a alcohol and sodium slat of corresponding carboxylic acid is formed as follow

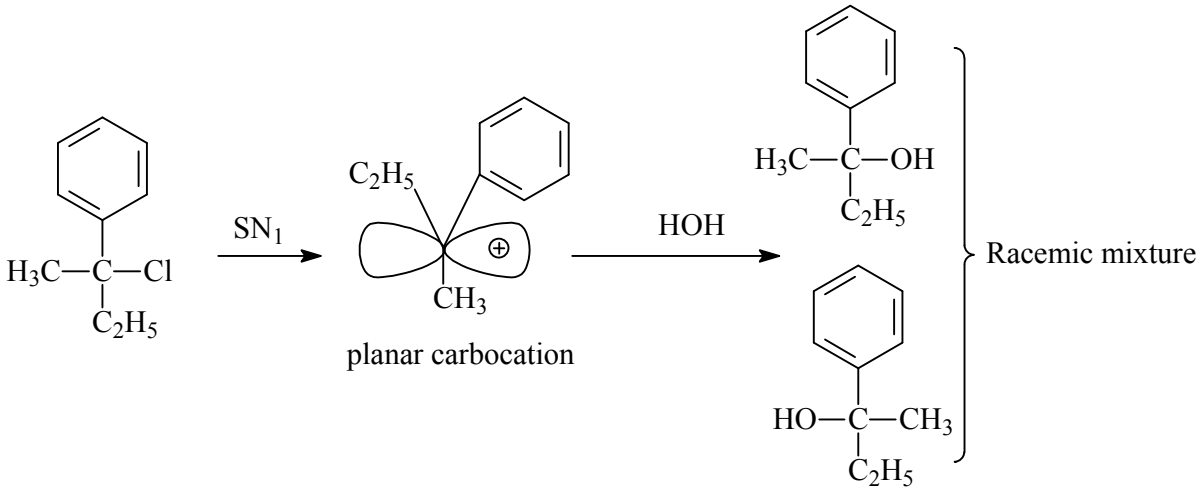


In this reaction second hydrogen in $–CH_2-$ group in alcohol (say benzyl alcohol) may come from either a second molecule of aldehyde (say benzaldehyde) or from the solvent H_2O. By carrying out the reaction in D_2O it has been shown that it comes from another molecule of benzaldehyde by hydride (H^-) ion transfer. Deuterium appeared in the hydroxyl group (as OD) of the alcohol but not as methylene deuterium (-CHD-). This mechanism should be giben as I not as II in following representation.





6. Stereochemistry: Stereochemical evidences If the products of a reaction are capable of



existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, in S_{N1} reaction mechanism formation of racemic mixture indicate that the product formation takes by the formation of planar carbocation as follow.

7. Kinetic evidence: Several types of mechanistic informations can be obtained from kinetic studies such as the order of the reaction, the rate determining step etc. The rate constant obtained from kinetic data is most important since it tells the effect of changes in the structure of the reactants, the solvent, ionic strength, addition of catalyst etc. on the reaction rate.

2.12 ISOTOPE EFFECT

It is basically kinetic isotopic effect (KIE) abd is defined as the change in the reaction rate of a chemical reaction when one of the atoms in the reactants is replaced by one of its isotopes. Formally, it is the ratio of rate constants for the reactions involving the light (K_L) and the heavy (K_H) isotopically substituted reactants:

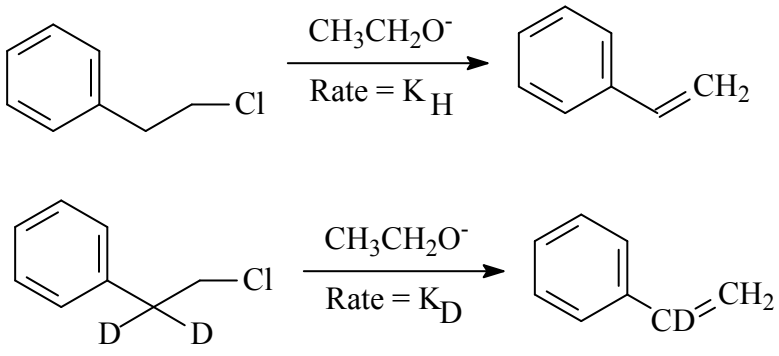
$$KIE = \frac{K_H}{K_D}$$

K_H = rate with substrate containing hydrogen (^1H) and K_D = rate with the substrate containing deuterium (^2H)

The kinetic isotopic effect is of two types:

B. Primary Kinetic Isotope Effect: In this effect bond to isotope is broken in the reaction. The H/D has a large effect and easy to measure.

Changing the H for D can effect the rate of reaction only if that H (or D) is involved in the rate determining step. In this case the K_H/K_D is known as primary kinetic isotope effect. The theoretical maximum is 7 for the reactions taking place at room temperature in which abond H or D is being broken. Viz; compairing the rates of following reactions the K_H/K_D has been found 7.1 at 25^0C



The kinetic isotop effect educates us that the C-H or C-D bond is broken during the rate determining step.

Vibrational frequency of a bond (C-H) is given by following equation.

$$v = \frac{1}{2\pi c}\sqrt{\frac{k\,(m_1 + m_2)}{m_1 m_2}}$$

Where k = the force constant for the bond C-H (or C-D), m_1 =mass of carbon atom, m_2 = mass of hydrogen (or deuterium atom) ,v = vibrational frequency of the bond and c= velocity of light

The bond energy depends upon the vibrational frequency, which in turn depends upon the reduced mass of the two atoms that formed the chemical bond.The energy of H and D in the similar vibrational state are different .Because of large mass of D the vibrational frequency of C-H is greater than that of a C-D bond.So less energy will be required to break a C-H bond than a C-D bond. Since differencies in vibrational energy between C-H and C-D bonds decreases with increasing in temperature, K_H/K_D ratio falls as the temperature of reaction increases. It is 7 at 25^0C, 4.7 at 100^0C and 3.4 at 200^0C. The ratio is much smaller for weakening or partial cleavage of a C-D bond. Very smaller value indicates no primary kinetic isotopic effect.The potential energy diagram for primary kinetic isotop effect if presented in fig. 15.

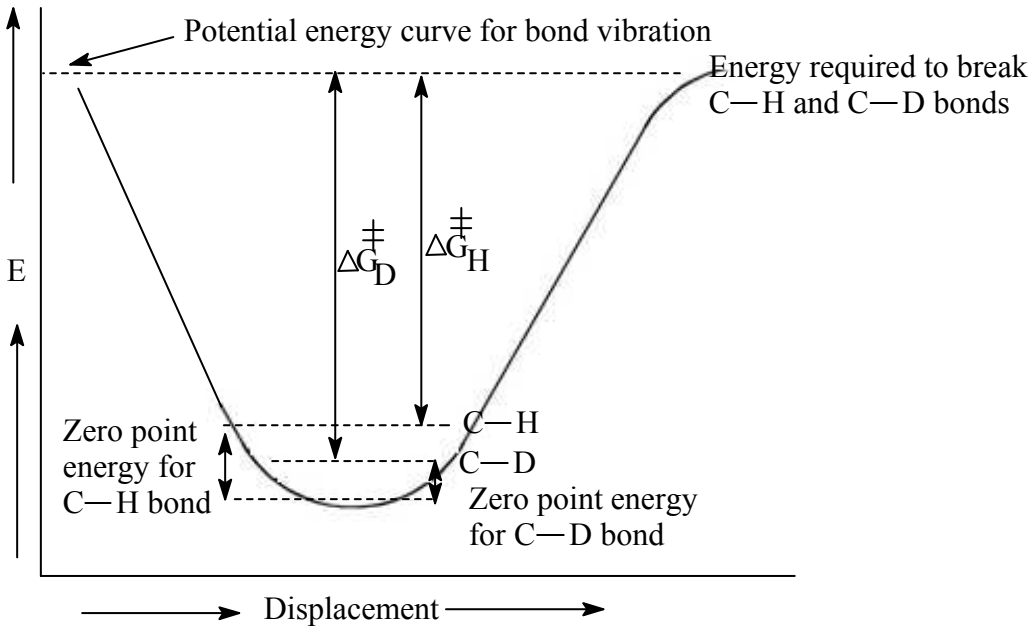


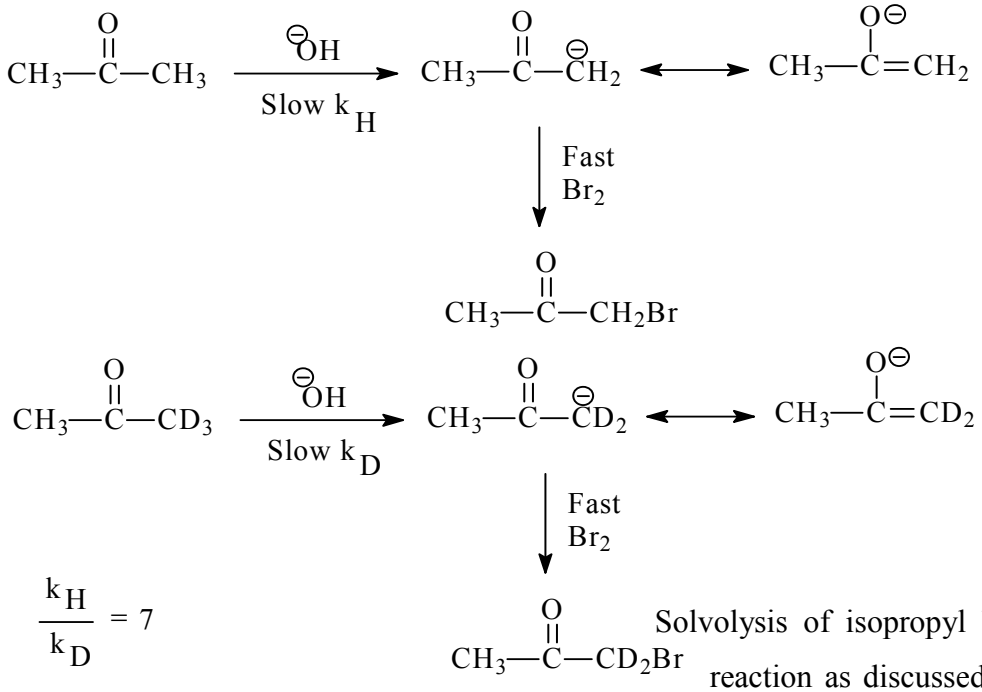
Fig.15. Energy profile diagram for primary kinetic isotop effect

Some of the examples of primary isotop effects are as follow:

B. The base catalysed bromination of acetone is second order reaction, firse order with respect to acetone and first order with respect to $^-$OH but independent to the concentration of

bromine. A primary kinetic isotop effect of about 7 has been observed in bromibation. This indicates that the rate determining step involves removal of hydrogen by catalyst base leading to the formation of the conjugate base of acetone as follow.

C.



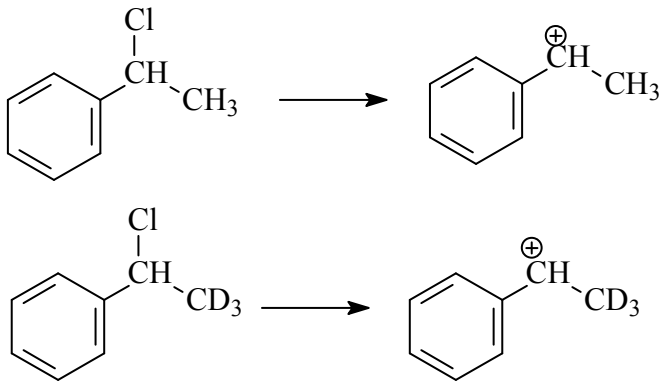
(ii) $\frac{k_H}{k_D} = 7$ Solvolysis of isopropyl bromide: In this reaction as discussed follow this molecule undergoes both S_{N2} and S_{N1} reaction because of its borderline behavior. It also undergoes E_2 reaction. If the deuterated compound CD_3-(CHBr) $–CD_3$ is taken for reactions, primary kinetic effect is observedwith the K_H/K_D ratio of about 6.7. The effect is observed only in elimination reaction because in elimination reaction C-H or C-D bonds are broken.

Carbon-13 isotope effects: Most organic reactions involve the breaking and making of bonds to a carbon; thus, it is reasonable to expect detectable carbon isotope effects. When 13C is used as the label, the change in mass of the isotope is only ~8%, though, which limits the observable kinetic isotope effects to much smaller values than the ones observable with hydrogen isotope effects.

B. Secondary Kinetic Isotope Effect: Secondary kinetic effects arise from rate differences caused by isotopically labeled bonds that are not made or broken in the rate determining step.Secondary deuterium kinetic isotopic effect can be normal or inverse. Generally for deuterium these effects come from change in hybridization and hyperconjugation. The secondary kinetic effects are smaller than primary and are usually in the range of K_H/K_D =0.7 – 1.5. Secondary isotope effects may be normal ($K_H/K_D > 1$) or inverse (($K_H/K_D < 1$). They are also

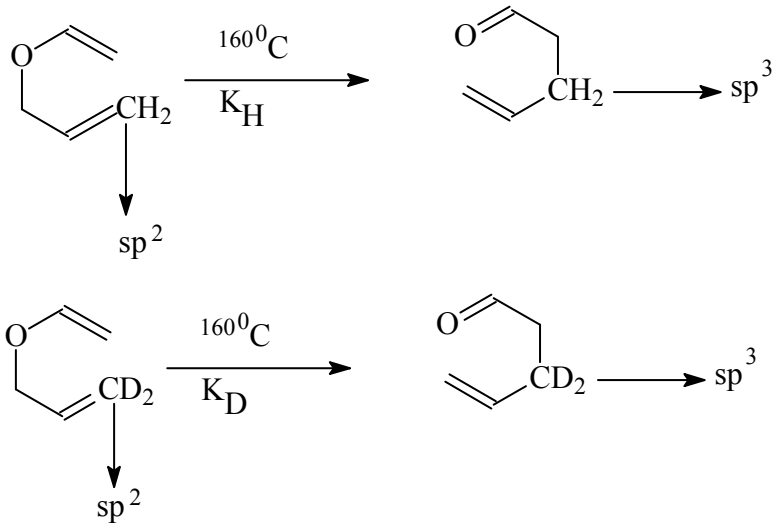
classified as α or β etc.depending ob the location of the isotopic substitution with respect to the reacting carbon. Secondary isotopic effect results from a tightening or loosening of a C-H bond at the T.S. The strength of bond may change because of a hybridization change or change in the extent of hyperconjugation.

Secondary isotope effect at β- position has been especially thoroughly studied in nucleophilic substitution reactions. When carbonium ions are involved as reaction intermediate. Substituted β- isotope effects are observed. This happens because the bo-bond resonance stabilization by β-hydrogens weakens the C-H bond. Viz; $K_H/K_D = 1.5$ for solvolysis of 1 – chloro – 1- phenyl



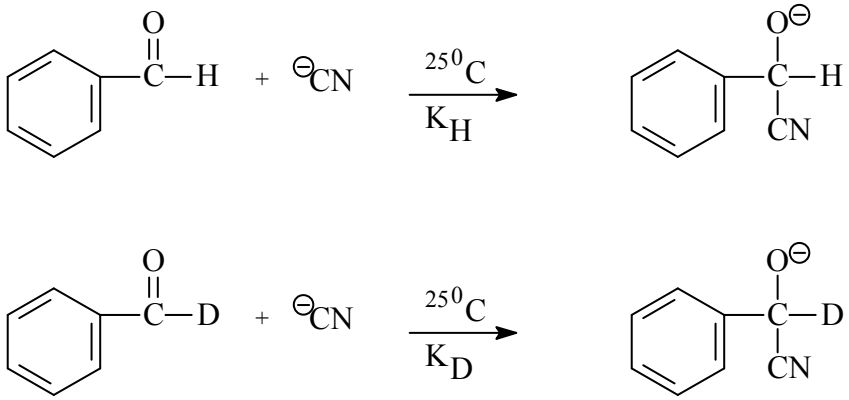
ethane in 50% aqueous ethanol at 25^0C. Here the C-Cl bond breaks to form the carbocation which is stablised by hyperconjugation by H or D. Heavier D stabilize the carbonium ion less effectively than H. hence there is a fall in reaction rate.

In Cope rearrangement secondary deuterium isotope effect is observed due to conversion of sp^2 hybrid carbon into sp^3 hybrid carbon in the T.S.



$$\frac{K_H}{K_D} = 0{\cdot}976$$

Secondary deuterium isotope effect is also observed in Nu^- addition reaction of carbonyl compounds. In these case effect is due to the conversion of sp^2 hybrid into sp^3 hybrid carbon



$$\frac{K_H}{K_D} = 0{\cdot}883$$

In above example when sp^2-hybrid carbon converts into sp^3 hybrid carbon than the value of K_H/K_D is less than 1.0 On the other hand when sp^3 hybrid carbon converts into sp^2 hybrid carbon in the T.S. then the value of K_H/K_D is greater than 1.0

2.13 SUMMARY

This unit describes about the basic concepts which are essential to know prior to study the reaction mechanism. The concepts like type of reactions, their kinetic feasibility and thermodynamic stability and has been described in dtetails with suitable examples. Regarding the thermodynamic study it has been outlined that the thermodynamics is concern only with the finat state of the system, while kinetics of the reaction describes how fast the equilibrium is reached. The thermodynamics stability determines the equilibrium constant, while kinetic stability determines the rate constant. It has also been described in this unit that if $\Delta G^{\ddagger}$ >, the reaction is kinetically stable and if ΔG^0 is negative, the reaction is thermodynamically stable and exothermic in nature while positive value ofΔG^0 indicates the endothermic reaction. For graphical representation of the reaction mechanism the energy coordinate diagrams has been depicted. The Hammonds postulates have been described in detail alongwith their reaction coordinate representations. Reactions intermediates are very important species to understand the reaction mechanism in organic reaction. Evidences of formation of reaction intermediates to speculate the mechanism of the reaction has been exaplained in detail along with their potential energy diagram representation.To know the mechanism of the reaction various methods for determining the mechanism viz, Kinetic evidence, stereochemistry, isotopic labeling, irapping of an intermediate, detection of an intermediate, determination of prescence of an intermediate, identification of products etc have been described with examples. The kinetic isotopic effect is very important tool to understand the mechanism of organic reactions. In this study the isotopes like deuterium, ^{14}C etc are used and the ratio of K_H/K_D is studied which tells us the possible mechanism of the reactions.This concept has bben described with example in present unit

2.14 TERMINAL QUESTIONS

Q.1. MCQs

Tick out the correct options

i. Geometry of methy free radical is:

A. Planar B. Pyramidal

C. Tetradehral D. Linear

ii. Which of the following reaction take place via the formation of carbonium ion as areaction intermediate?

1. SN1 2.E1 3. E2 4.SN2

A. Only 1 B. Only 2

C. 1 and 2 D. 1, 2 and 4

iii. The reaction is said to be kinetically stable if:

A. $\Delta G^{\ddagger}$ value is large B. $\Delta G^{\ddagger}$ value is small

C. $\Delta G^{\ddagger}$ is zero D. ΔG^{0} is (-) ve

iv. For secondary kinetic isotopic effct the responsible factor(s) is/are:

A. Channge in hybridization and stability ob bond between carbon and deuterium

B. Change in hybridization and no-bond resonance

C. Hyperconjugation

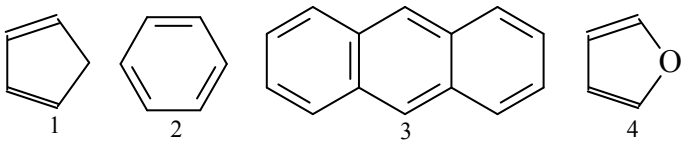
D. D. hybridization

v. Singlet/ triplet carbine reaction intermediate can be studied and distinguished by:

A. Trapping reactions with olifines B. Reactions with benzene

C. Beckmann reaction D. Diels- Alder reaction

vi. Benzyne can be trapped by which of the following



A. Only1 B. Only 3 and 4

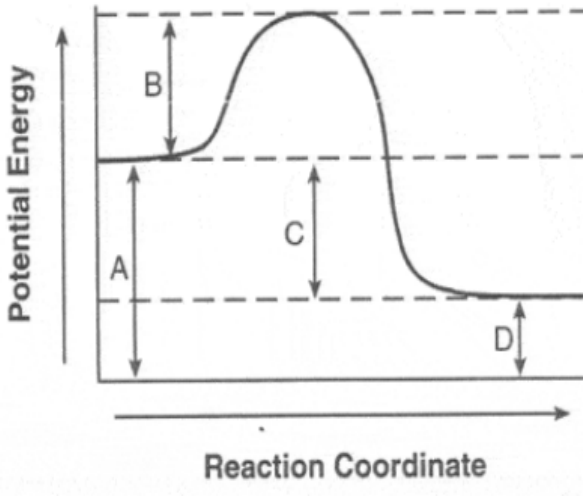
C. 2,3 qnd 4 D. 1,2,3 and 4

vii. Exothermic" processes:

A. Absorb energy B. Give off energy

C. Have no energy change D. It is impossible to predict the energy change of an exothermic process.

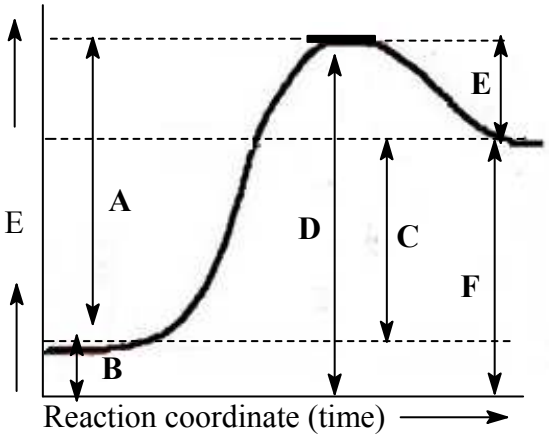
viii. Which of the following phase changes would this type of energy diagram refer to?



A. Melting B. Condensation

C. Evaporation D. Sublimation

ix. What letter represents the activation energy?



A. D B. B

C. A D.C

x. Which of the following reactions will show a significant kinetic isotope effect?

A. $CD_2(=O)-C-OCH_3 \xrightarrow[\text{Heat}]{CH_3ONa}$

B. $CD_3-C(CD_3)(H)-CH_2Br \xrightarrow[\text{Heat}]{CH_3ONa}$

D. $CH_3-CD_2-C(=O)-CH_3 \xrightarrow[\text{Heat}]{CH_3ONa}$

C. All of these ractions show kinetic isotopic effect

Q.2. Write brief notes on:

1. Hammond's postulates
2. Curtin – Hammett principle
3. Kinetically and thermodynamically controlled reactions

Q.3. What is reaction coordinate? How various types of reactions are depicted graphically by using reaction coordinate diagrams? Explain your answer with examples.

Q.4. What different methods for determining the the mechanism of organic reactions. Discuss with suitable reactions.

Q.5. Explain primary and secondary kinetic isotopic effects (KIE) with suitable examples.

Q.6. Discuss that one of the hydrogen in $–CH_2-$ of $-CH_2OH$ (alcohole) in Cannizzaro reaction comes from hydride shift.

Q.7. Discuss with example;

1. Isotopic effect
2. Trapping reactions of benzynes
3. Potential energy diagram

Q.8. Discuss the mechanism of SN1 and E1 reactions using deuterium isotopic displacement.

Q.9. How kinetics and thermodynamics help us to understand the feasibility of reaction ?

Q.10. Discuss the Hammond's postulates in details.

2.15 ANSWERS (MCQs)

i	A	ii	C	iii	A	iv	B	v	A
vi	D	vii	B	viii	B	ix	A	x	A

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UNIT 3: REACTIVE INTERMEDIATES

CONTENTS:

3.1 OBJECTIVES

In the beginning of this chapter, we introduced about reactive intermediates of the organic reaction. We also learn about Generation, structure, stability and reactivity of Reaction Intermediates. Describe the properties of carbocations, carbanions, carbon radicals, carbenes, nitrenes and benzynes including their structure, hybridization, geometry, and reason for reactivity.

3.2 INTRODUCTION

A reactive intermediate is a short-lived, high-energy, highly reactive molecule. When generated in a chemical reaction, it will quickly convert into a more stable molecule. Only in exceptional cases can these compounds be isolated and stored, e.g. low temperatures, matrix isolation. When their existence is indicated, reactive intermediates can help explain how a chemical reaction takes place

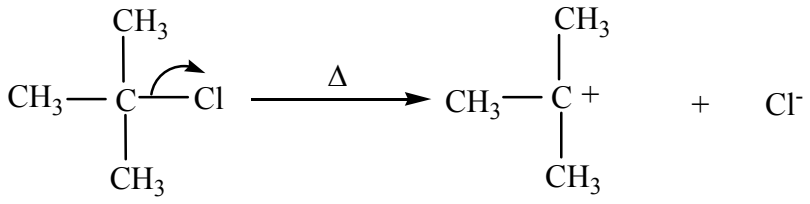
Most chemical reactions take more than one elementary step to complete, and a reactive intermediate is a high-energy, yet stable, product that exists only in one of the intermediate steps. The series of steps together make a reaction mechanism. A reactive intermediate differs from a reactant or product or a simple reaction intermediate only in that it cannot usually be isolated but is sometimes observable only through fast spectroscopic methods. Some important examples of reactive intermediates are: carbocation, carbanions, free radicqals, carbenes, nitrenes and benzyne.

3.3 GENERATION, STRUCTURE, STABILITY AND REACTIVITY OF REACTION INTERMEDIATES

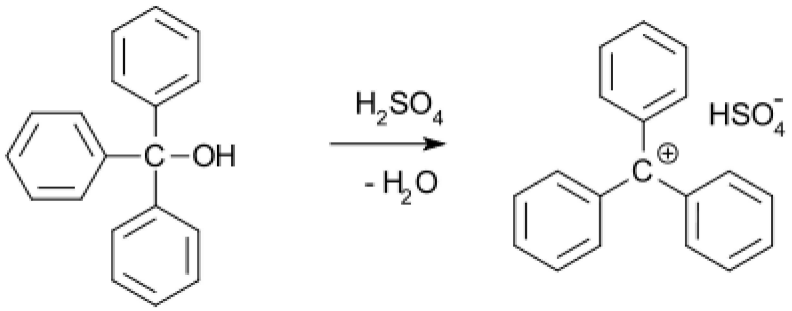
1.3.1 Carbocations:

An Organic species which has a carbon atom containing only six electrons in its outermost shell and has appositive charge is called a carbocation reaction intermediate. The carbon atom of the carbocation is Sp^2 hybridized, it use the three hybrid orbitals for single bonding to three substituents and remaining p- orbital is empty. The carbocations thus has a planner structure having all the three covalent bonds are in plane with the bond angle of 120^0 between them.

Formation of carbocations: These are formed by the heterolytic cleavage of the covalent bonds in which the leaving in which the leaving group takes away with it the shared pair of electrons. For example,



tert-Butyl chloride tert-Butyl carbocation

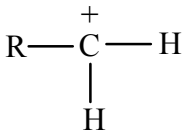


Classification of carbonium ion: Carbocations are classified as primary (1^0), secondary (2^0) and tertiary (3^0) according to the positive charge is present on a primary, secondary and tertiary carbon atom respectively. For examples:

1. **Alkyl Carbonium ion:**

   Like free radical carbinium ion also classified in to three classes-

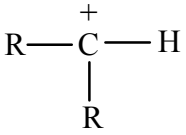
a. Primary carbonium ion: In this type of carbonium ion one carbon atom is attached with the positive carbon atom.



Where R is the alkyl group

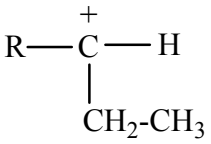
b. Secondary carbonium ion-

In this type of carbonium ion two H atoms are replaced by two alkyl groups from the + charge bearing carbon.



Where R is the alkyl group

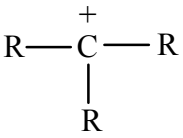
Isopropyl carbonium ion



Where R is the alkyl group

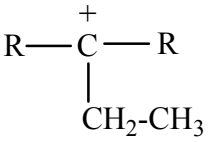
c. Tertary carbonium ion:

In this type of carbonium ion 3 hydrogen atoms are replaced by 3 alkyl groups from the positive charge bearing carbon.



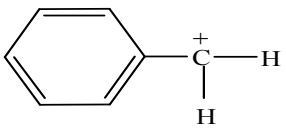
Where R is the alkyl group

tert. Butyl carbonium ion

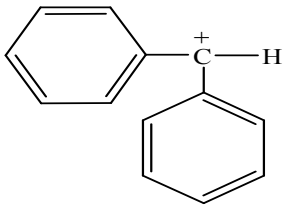


Where R is the alkyl group

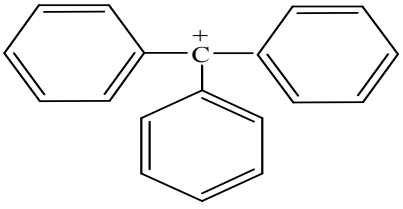
2. Benzylic carbocations:



1^0

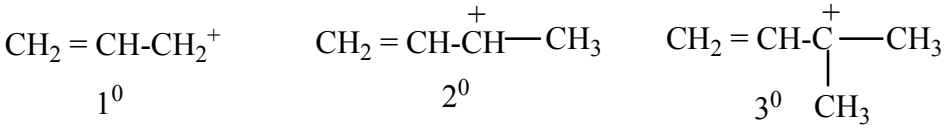


2^0

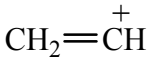


3^0

3. **Allylic carbocations:**



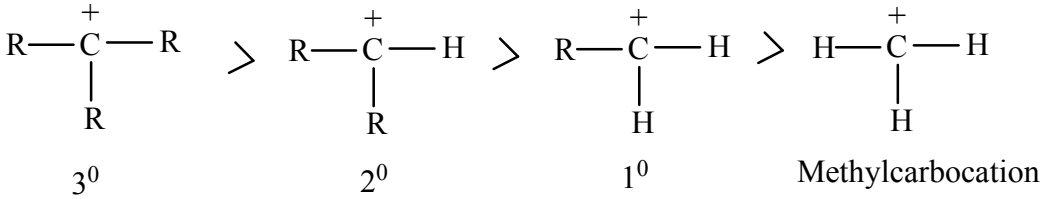
4. **Vinylic carbocation:**



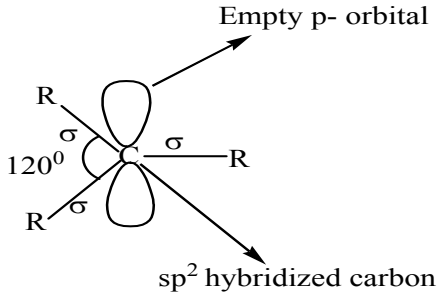
5. **clopropylmethyl carbocation**

Stability of carbonium ion:

The relative stability of carbonium ion is explained with the help of Inductive effect. In the case of 1^0 carbonium ion the CH_3 group contains +I affect, so it release the electron towards the carbon that bearing positive charge. So some charge neutralize and also somewhat positive charge created on the methyl group carbon, so the + charge become dispersed and gives the stability. Hence we can say that greater is the dispersed is the positive charge greater will be the stability. Hence 3^0 carbocation is most stable in compare to 2^0, 1^0 and methyl cabocation.

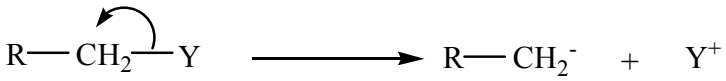


Orbital structure: The carbocations are planner species. The carbon atom carrying the positive charge is sp^2 hybrized. The three sp^2 hybrised orbitals of this carbon form three σ bonds with monovalent atoms or groups which lie in a plane and are inclined to each other at an angle of 120^0. The unhybridized 2p orbital which is perpendicular to the plane of the three σ- bonds is, however, empty which are given as follow:



3.3.2. Carbanaions:

These are chemical species which possess a negatively charged on carbon and possessing eight electrons in its valence shell are called carbanions. Like the Carbocations the Carbanions are also formed by *hetertolytic fission* of covalent C-Y molecules

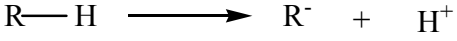


Here Y is an atom which is more electropositive than Carbon. This is why during the heterolytic fission the shared pair of electrons is drawn towards the Carbon atom to develop a negative charge over it.

Generation of carbanions: Carbanions are generated as intermediate in various organic reactions. Some of the methods for the generation of carbanion are given as:

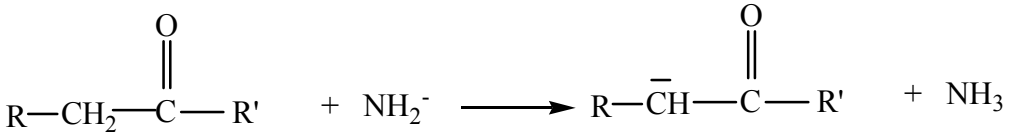
a) Proton abstraction
b) Decarboxylation
c) Addition of nucleophile to alkene
d) Formation of organometallic compounds

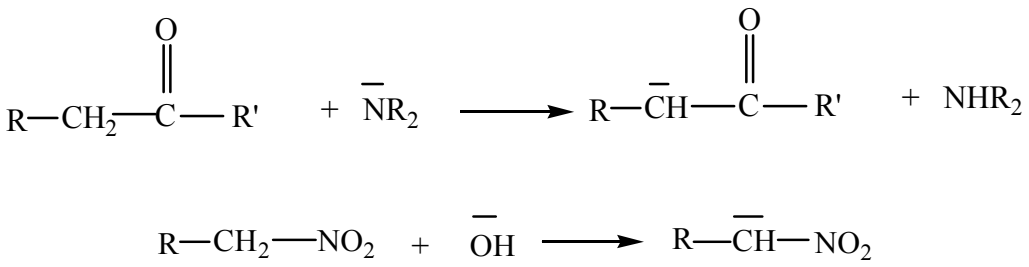
(a) Proton abstraction: When proton is abstracted from a carbon centre then the resulting anion is called a carbanion.



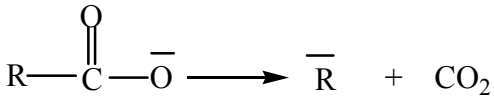
The acidic hydrogen of an organic substrate can be abstracted by an appropriate base. For example carbanion generated from carbonyl compounds.

Here, are some examples showing generation of carbanion by abstraction of the acidic proton using a base (OH^-, NH_2^- and RO^-).

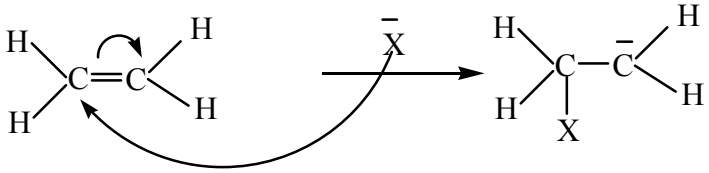




(b) Decarboxylation: Decarboxylation of carboxylates ion to form carbanion intermediate.

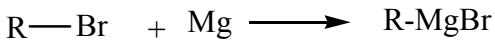


(c) Addition of nucleophile to alkene: Carbanions are generated by the attack of nucleophiles on one of the carbon of an alkene. It results into the development of negative charge on the other carbon atom.



(d) Formation of organometallic compounds: Metals which are less electronegative than carbon (such as magnesium, lithium, potassium, sodium, zinc, mercury, lead, thallium) react with alkyl halides under appropriate conditions to form a carbon-metal bond where the carbon carries negative charge and metal positive charge.

For example, alkyl bromides react with magnesium in the presence of dry diethyl ether to form alkyl magnesium halides also known as Grignard reagent.

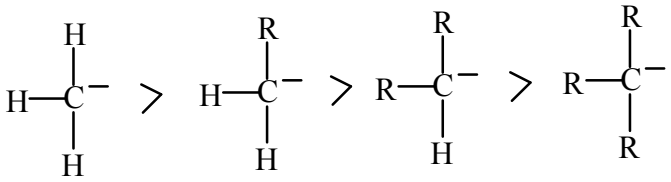


Stability of Carbanion: Factors which can stabilize the negative charge on carbon will stabilize a carbanion. The stability of carbanion depends on the following factors:

a) Inductive effect
b) Extent of conjugation of the anion
c) Hybridization of the charge-bearing atom
d) Aromaticity

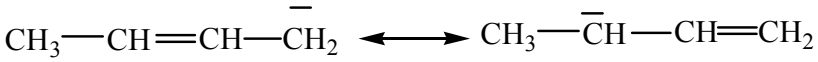
(a) Inductive effect: If the electron donating groups are attached to carbanion they will increase the negative charge on carbon and thus destabilize it. However, electron withdrawing groups adjacent to the negatively charged carbon will stabilize the carbanion.

All alkyl groups are electron donating in nature due to inductive effect (+I effect). More the number of alkyl groups attached lesser will be the stability. Therefore the order of stability order of alkyl carbanion is methyl > 1^o > 2^o > 3^o carbanion.

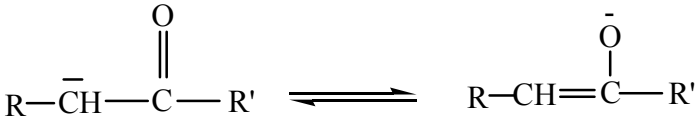


methyal carbanion 1^0 2^2 3^0

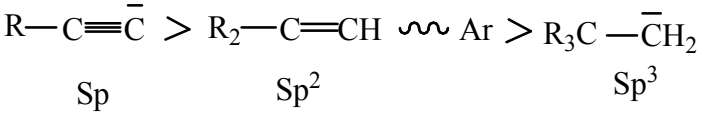
(b) Extent of conjugation of the anion: If negatively charged carbon is in conjugation with a double bond the resonance effects will stabilize the anion by spreading out the charge by rearranging the electron pairs.



Enolate of ester:



(c) Hybridization of the charge bearing atom: Stability of anion will depend upon the s character of carbanion i.e. more the s character, higher will be the stability of anion. The percentage s character in the hybrid orbitals is as follows: sp (50%) > sp^2 (33.33%) > sp^3 (25%).



Sp Sp^2 Sp^3

Explanation of the order of stability:

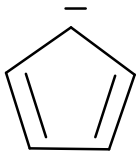
Propargyl anion > propenyl anion > propyl anion

The order of stability can be understood as follows. In propargyl anion, the triply bonded carbon is sp hybridized, in propenyl anion the doubly bonded carbon is sp^2 hybridized while in propyl anion the carbon is sp^3 hybridized. Orbital with greater s character is more close to the nucleus

and having more nuclear charge. The sp hybridized atoms are more electronegative than sp^2 and sp^3. The distance of lone pair and nucleus is less if the lone pair is sp hybridized than in a sp^2 hybrid orbital. Since, it is more favorable for the negative charge of an anion to be in an orbital close to the positively charged nucleus. Therefore sp hybrid anion is more stable than sp^2.

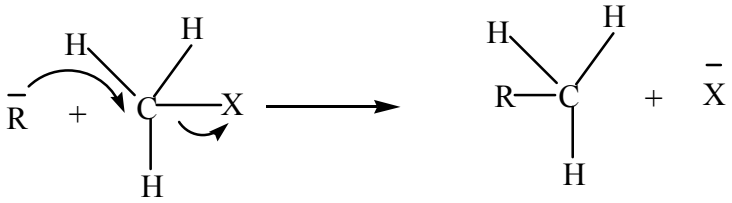
(d) Aromaticity: In some carbanions, the lone pair of electrons of the negative charge is involved in delocalization to add on to the aromatic character of the molecule which gives them extra stability**.**

For example, in cyclopentadienyl anion there are 6π electron and thus it obeys Huckel aromaticity rule, (4n+2)π electron. This anion is stabilized by aromatization.

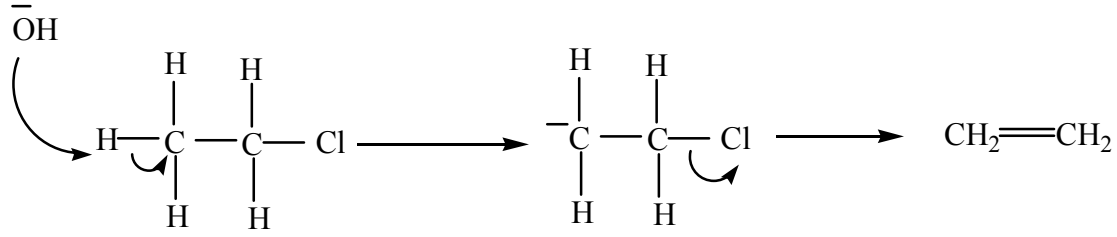


Reactivity of Carbanion: Carbocations are strong Lewis acids while carbanions are strong bases (Lewis and Bronsted bases). Carbanions are part of most of the common reaction types such as displacement, elimination, condensation, addition, rearrangement, polymerisation etc.

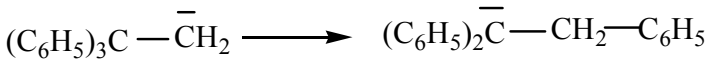
1. Displacement Reaction: Such reactions are nucleophilic substitu (SN^2) reactions observed in alkyl halide.



2. Elimination reaction: In a Conjugate Base Elimination reaction (E_1cb) the C-H bond breaks with formation of carbanion as intermediate. The developed negative charge on carbon assist in the loss of leaving group, leading to the formation of alkene.

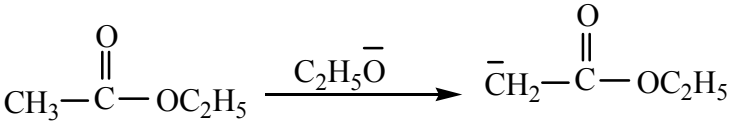


3. Rearrangement reactions: In some cases, carbanions may rearrange to form more stable species. Consider the rearrangement in triphennylmethyl carbanion.



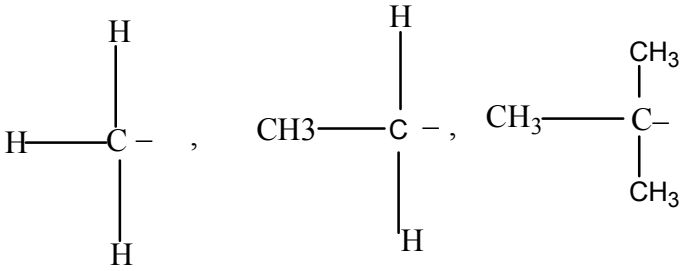
4. Condensation reactions:

Claisen condensation: Formation of β-keto esters from carboxylic esters is known as Clasien ester condensation.



It is generated by heterolytic fission and bearing - ve Charge and the number of valence electrons are 8 in it called carbanion reaction intermediate.

Example:

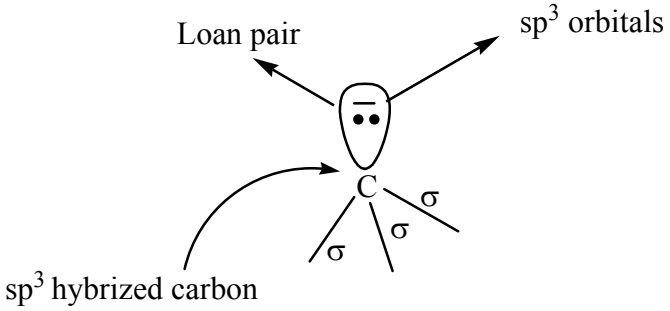


Hybridization in carbanion ion:

The carbanion ion shows SP^3 hybridization with one loan pair of electron. Hence its geometry will be tetrahedral.

E.g.

Structure of Carbanion: The structure of simple carbanion is usually pyramidal just like those of ammonia and amines. The carbon atom carrying the negative charge is sp^3 hybridized. Three of the four sp^3 hybridized orbitals from three σ- bonds with monovalent atoms while the four sp^3 orbital contains the loan pair of electrons.



3.3.3. Carbon Free Radicals:

A free radical (often simply called a radical) may be defined as a species that contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO2), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive. Their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules. Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms persistent and stable are usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not be very stable.

Generation of Free Radicals: Formation of free radicals is favoured by the presence of UV light, heat and organic peroxide. An important characteristic of free radical reactions is that, once initiated, they proceed very fast. The free radicals can be detected by magnetic susceptibility measurement.

$$Cl—Cl \xrightarrow{h\nu} \underset{\text{free radical}}{2Cl^{\bullet}}$$

$$CH_3CO—O—OCOCH_3 \xrightarrow{\text{Thermal}} \underset{\text{free radical}}{2CH_3COO^{\bullet}}$$

Example: CH_3^{o}, CH_3CH_2 ^{o}, H^{o} etc.

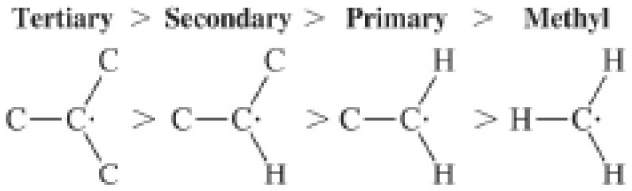
The free radicals are strongly reactive because they have stronger tendency to become paired and their nature is paramagnetic.

Stability of free radicals: The bond dissociation energies give us an idea of the ease with which radicals can form; they can also give us an idea of the stability of those radicals once they have formed. The lower the bond dissociation energy, the higher will be the stability. Alkyl radicals are stabilized by adjacent lone-pair-bearing heteroatom and by the π bonds. The various factors responsible for the stability of free radicals are:

1. Inductive effect
2. Hyperconjugative effect
3. Resonance effect

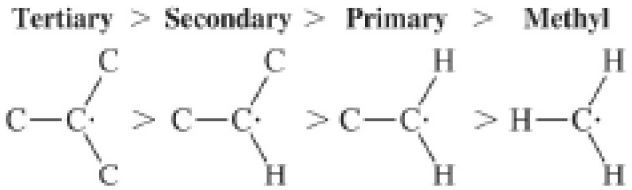
1. Inductive effect: Greater the number of alkyl groups attached to the free radical carbon centre more will be the stability of the radical. This is due to the electron donating inductive effect **(+ I effect)** of the alkyl groups which decrease the electron deficiency of the radical.

The bond dissociation energies, of the C-H bonds for the formation of a free radical of methane, ethane, and other alkanes, clearly shows that radical centres are stabilized by the replacement of one, two, or three of the hydrogens of the methyl radical by alkyl groups.
Thus, the order of stability is $3^{o} > 2^{o} > 1^{o}$.



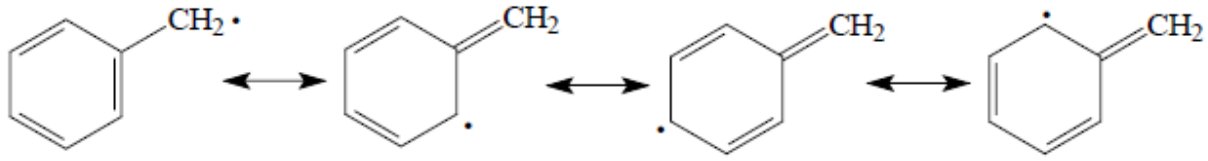
2. Hyperconjugative effect: Hyperconjugative effect also gives stability to free radicals as in the case of carbocations. Thus, Greater the number of hyperconjugative structures more will be the Stability of the radical. The

Stability order of alkyl free radicals is tertiary > secondary > primary > CH_3.



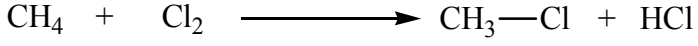
3. Resonance Effect: In the free radicals where the carbon centre is in conjugation to a double bond, the resonance effect leads to stabilisation of these molecules. The stabilising effects of vinyl groups (in allyl radicals) and phenyl groups (in benzyl radicals) are very significant and can be satisfactorily explained by resonance. Allyl and benzyl free radicals are more stable than alkyl free radicals but still have only a transient existence under ordinary conditions.

Resonance in benzyl free radical:



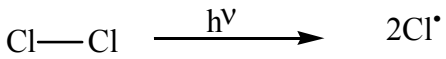
Reactivity of free radical: Some important reactions of free radicals are described below:

1. **Halogenation of aliphatic hydrocarbons:** In the presence of sunlight, halogenation of saturated hydrocarbons like alkane gives haloalkane.

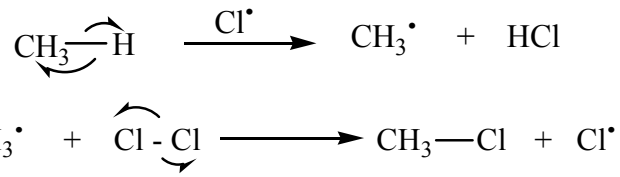


Mechanism of Halogenation: It involves three main steps (i) Initiation (ii) Propagation and (ii) Termination.

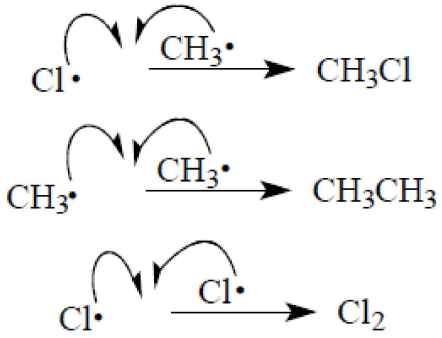
(i) Initiation: In this step, free radicals required for the reaction are generated in situ by irradiation or heating of the reagent or by carrying out the reaction in the presence of an initiator like peroxides. The process is always endothermic.



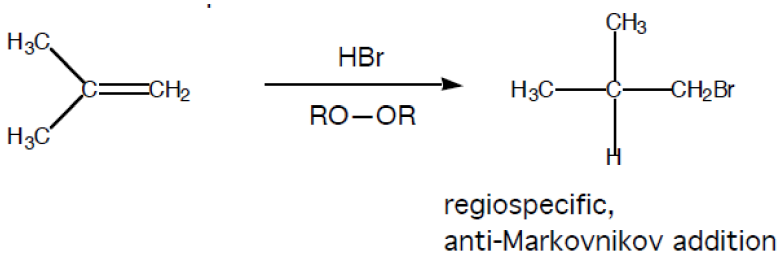
(ii) Chain propagation: Second step is chain propagation. In this step the highly reactive chlorine radicals with unpaired electron reacts further. They are electrophilic, thus each seeks an electron to complete its unfilled shell of electrons. In a reaction with methane, a chlorine atom readily removes hydrogen from the methane. Free radical chain reactions work best when all propagation steps are exothermic.



(iii) Chain termination: The final step is chain termination in which two reactive radicals combine together.

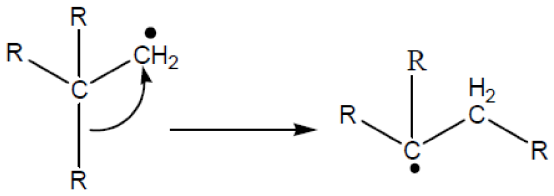


2. **Addition reaction:** The anti-Markovnikov addition of HBr to alkenes was probably the first free radical addition reaction to be discovered.



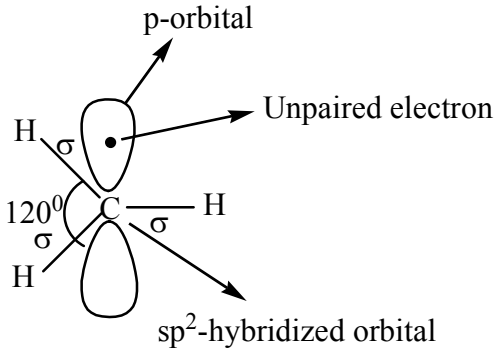
regiospecific,
anti-Markovnikov addition

3. **Rearrangement reaction:** Free radicals may also undergo rearrangement to form a more stable radical and then the final product.



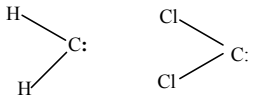
Structure:

Alkyl free radicals like carbocationa are planner species. The only difference being that in carbocations, the unhybridized p- orbital is empty while in free radicals, it contains the odd electron.



3.3.4. Carbene Reaction intermediate:

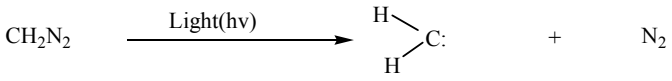
Carbenes are netural, divalent, highly reactive intermediate carbon species. It is defined as a netural reactive divalent species which consist six electrons in its outermost shell is known as Carbene.



Carbenes are highly reactive because they have stronger tendency to complete their octate.

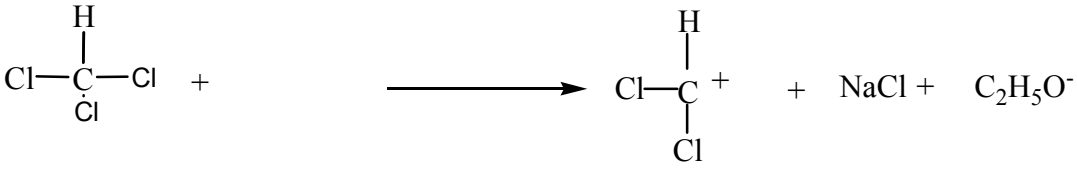
Methods of preparation

1. **From diazomethane:** Diazomethane on decomposition under the action of light gives carbene.

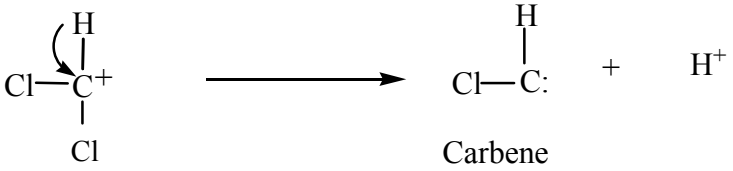


2. **From chlororm:** hloroform on react with sodium ethoxide gives dichloro carbine by releasing C_2H_5OH.

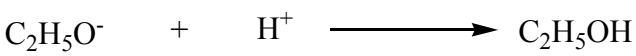
Step 1



Step 2



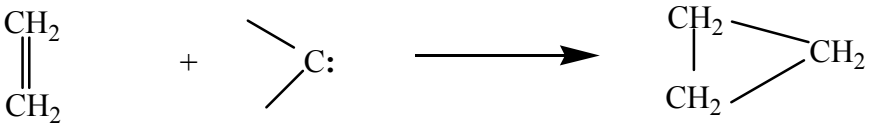
Step 3



Properties of carbine:

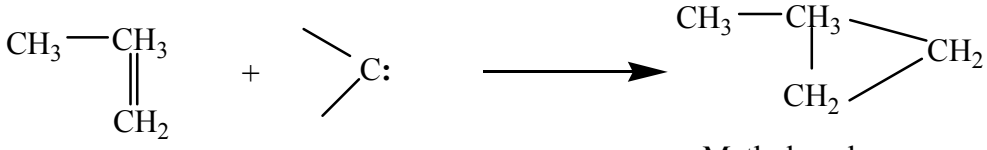
Carbene is ahighly reactivereaction intermediate and it gives easily reaction.

1. **Reaction with Alkene:** carbine on react alkene gives cycloalkanes.



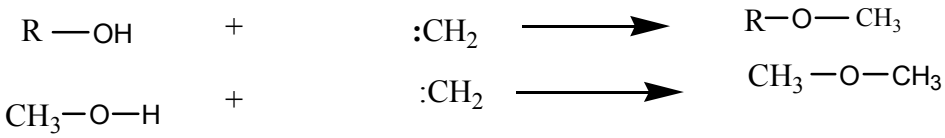
Cyclo propane

e.g.



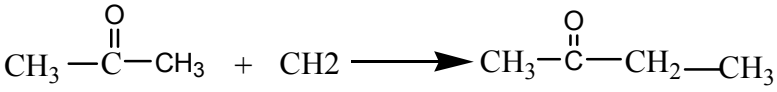
Methyl cyclo propane

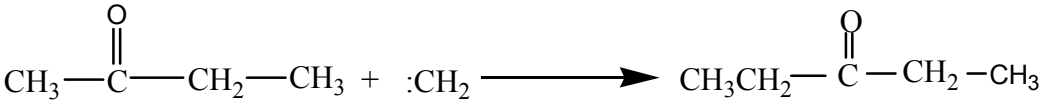
2. **Reaction with alcohol:** Carbene on react with alcohol gives addition compound ether.



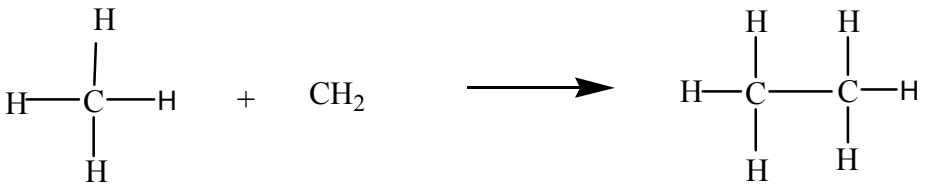
3. **Insertation Reaction:** In this reaction carbine react with those functional groups which are bi-valent and from both sides they are link with another groups undergoes insertation reaction reaction with carbine.

   Note: *ketone on react with carbene gives higher member of ketone.*





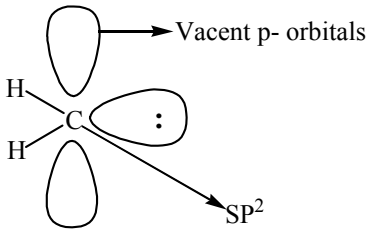
4. **Reaction with alcohol: Alkanes on react with carbene gives higher number of alkane series.**



Classification of caebene: Carbenes are classified in to two classes by name these are-

1. Singlate carbene
2. Triplet carbene

1. Singlet carbene: In this type of carbene SP^2 hybridization is observed and the unshared pair of electron is present in one p- orbital.



Multiplicity = S = 1/2n

(Where n is the number of unpaired electron)

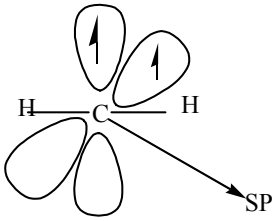
In this case n = 0

Since multiplicity = 2s + 1

= 2 x 0 + 1

= 1 (singlet)

2. Triplet carbene: In this type of carbene the unshared pair of electron is exist in to two unhybridised p- orbital. So they show Sp- hybridization with linear geometry.



S = ½ n

S = ½ x 2

S = 1

Since multiplicity = 2s + 1

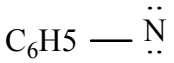
= 2 x1 + 1

= 3 (Triplet)

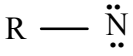
Stability of singlet and triplet carbene: Out of singlet and triplet carbene is more stable because in singlet carbene there is the repulsion between unshared electrons.

3.3.5. Nitrenes:

Nitrenes are defined as "A neutral reactive monovalent species which consist six electron in its outermost shell is known as nitrene". The nomenclature follows that of carbene. Substituted nitrenes are simply named as substituted derivative of carbene. For example:


Phenylnitrene

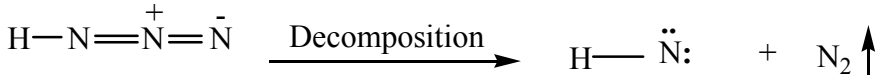

Methanesulphonyl nitrene

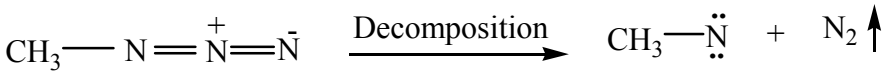

Alkylnitrene

In nitrenes the nitrogen atom N has 1 l.p. of electron and 1 unshared pair of electron.

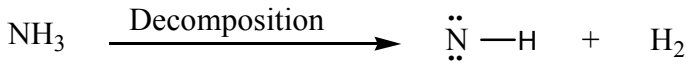
Method of preparation:

1. **From hydrozoic acid-** Hydrozoic acid (HN_3) on decomposition gives nitrene.

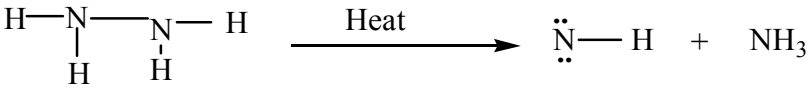




2. **From Ammonia:** Ammonia (NH_3) on decomposition gives nitrene by removing H_2 gas.

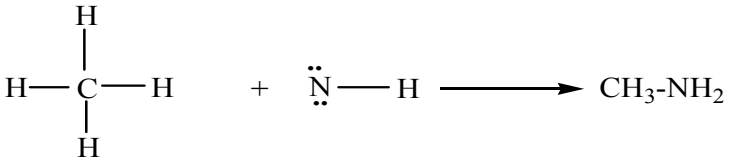


3. **From hydrazen:** Hydrazene on decomposition gives nitrene.



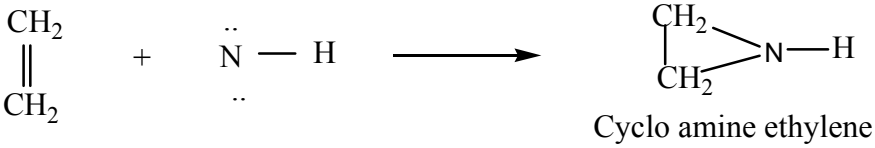
Properties: Nitrenes are highly reactive because they have stronger tendency to complete their octate.

1. **Insertion reaction:** In this type of reaction nitrene react with alkane to give amino derivative compound.



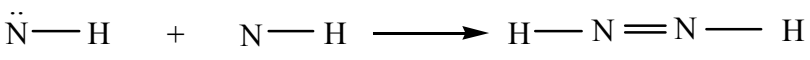
Aminomethane

2. **Reaction with alkene:** Nitrene on react with alkenes gives cyclic amino compounds.



Cyclo amine ethylene

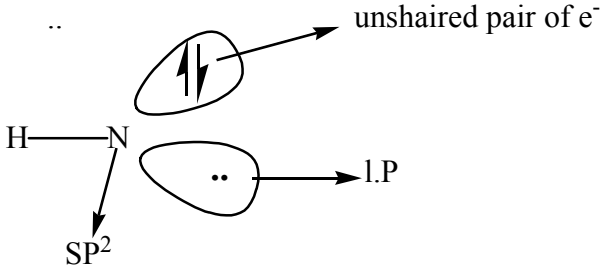
3. **Di- marization reaction:** In this type of reaction two nitrenes are combined together to form the product.



azo hydrogen

Classification of nitrenes: Nitrenes are classified into two classes one is singlet and other is triplet nitene.

1. **Singlet nitrene:** In this type of nitrene the unshared pair of electron is present in one p-orbital and it consist Sp2 hybridization, its geometry is as follow.



For multiplicity:

Unshaired pair of e^- n = 0

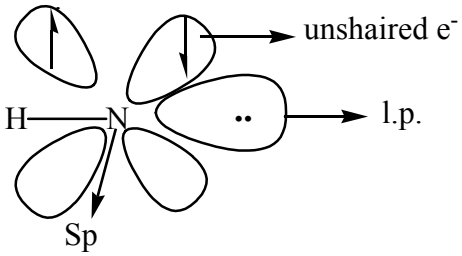
$$S = \frac{1}{2} n = \frac{1}{2} \times 0 = 0$$

Since multiplicity = 2s + 1

$$= 2 \times 0 + 1$$

= 1 (singlet)

2. **Triplet nitrene:** In this type of nitrene N atom shows Sp hybridization and the unshared electron are present in to two different p- orbitals.



For multiplicity: No. of unpaired e^- (n= 2)

s = ½ n= ½ x 2 = 1

So multiplicity = 2s + 1

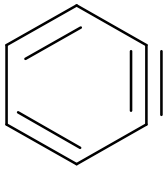
= 2 x1 + 1

= 3 (Triplet)

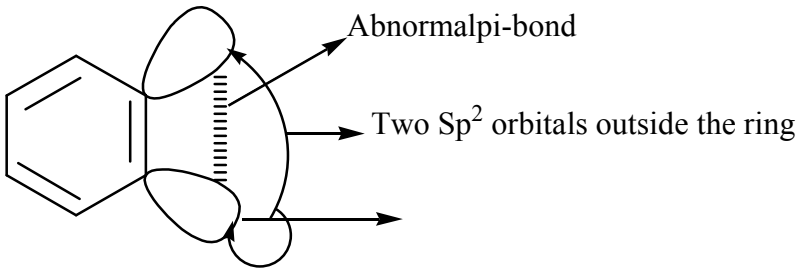
3.3.6. Benzyne:

Benzynes or arynes are highly reactive species derived from an aromatic ring by removal of two ortho substituents. Arynes are usually best described as having a strained triple bond; however, they possess some biradical character as well.

The aryne nomenclature derives from the fact that the C6H4 can be represented as an alkyne, although systematically the species should be named as didehydro aromatic compounds, i.e. 1,2-didehydrobenzene.

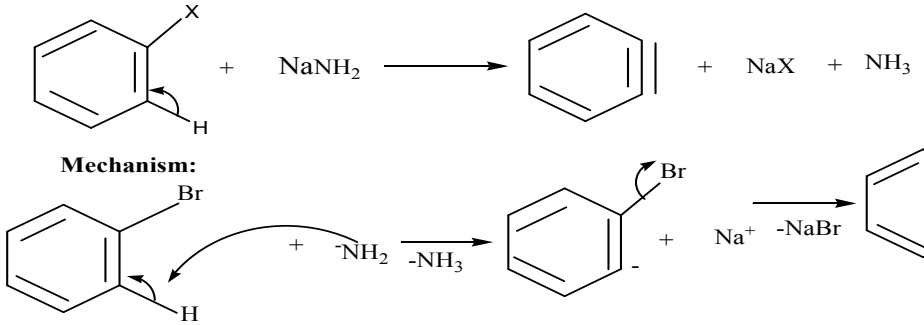


Benzyne can be represented as a singlet molecule with a carbob-carbon triple bond. Although it has triple bond but it is not normal alkyne bond. In benzyne out of two π-bond of triple bond, one π-bondis normal and the other π-bond is abnormal and is formed by overlap of two Sp^2 orbitals outside the ring. This is called external π-bond. It can be represented as follow.

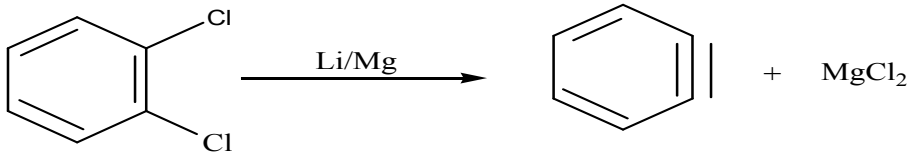


Preparation of benzyne:

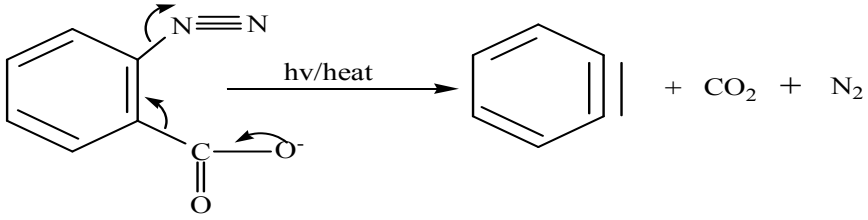
1. **From halobenzene:** When halogbenzene are react with sodamide in liquid ammonia then it gives benzyne.



2. **From 0- dihalobenzene:** When o-dihalobenzene is treated with lithium amalgam or Mg, then it gives benzyne.



3. **From benzenediazonium-2- carboxylic acid:** benzenediazonium-2- carboxylic acid when heated in the presence of heat and sun light then it gives benzynes.



3.4 *QUANTITATIVE RELATIONSHIP BETWEEN MOLECULAR STRUCTURE AND CHEMICAL REACTIVITY*

1.4.1 Hammett equation:

The Hammett equation in organic chemistry describes a linear free-energy relationship relating reaction rates and equilibrium constants for many reactions involving benzoic acid derivatives with meta- and para-substituents to each other with just two parameters: a substituent constant and a reaction constant. This equation was developed and published by Louis Plack Hammett in 1937as a follow-up to qualitative observations in a 1935 publication.

The basic idea is that for any two reactions with two aromatic reactants only differing in the type of substituent, the change in free energy of activation is proportional to the change in Gibbs free energy. This notion does not follow from elemental thermochemistry or chemical kinetics and was introduced by Hammett intuitively.

The basic equation is:

$$log\frac{K}{K_0} = \sigma\rho$$

Relating the equilibrium constant, K, for a given equilibrium reaction with substituent R and the reference K_0 constant when R is a hydrogen atom to the substituent constant σ which depends only on the specific substituent R and the reaction constant ρ which depends only on the type of reaction but not on the substituent used.

The equation also holds for reaction rates k of a series of reactions with substituted benzene derivatives:

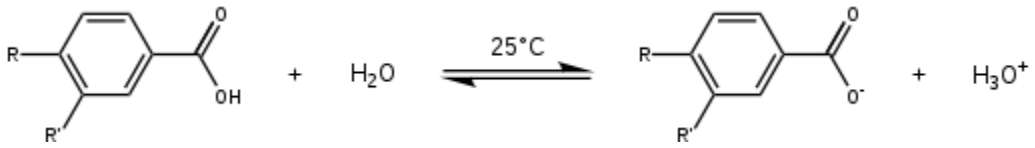
$$log\frac{k}{k_0} = \sigma\rho$$

n this equation k0 is the reference reaction rate of the unsubstituted reactant, and k that of a substituted reactant.

A plot of log (K/K_0) for a given equilibrium versus $\log(k/k_0)$ for a given reaction rate with many differently substituted reactants will give a straight line.

Substituent constants:

The starting point for the collection of the substituent constants is a chemical equilibrium for which both the substituent constant and the reaction constant are arbitrarily set to 1: the ionization of benzoic acid (R and R' both H) in water at 25 °C.

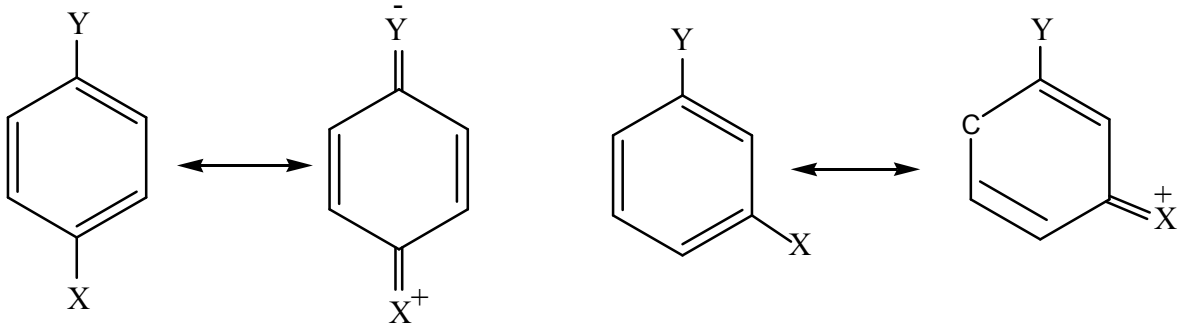


Having obtained a value for K_0, a series of equilibrium constants (K) are now determined based on the same process, but now with variation of the para substituent—for instance, p-hydroxybenzoic acid (R=OH, R'=H) or p-aminobenzoic acid ($R=NH_2$, R'=H). These values, combined in the Hammett equation with K0 and remembering that $\rho = 1$, give the para substituent constants compiled in table 1 for amine, methoxy, ethoxy, dimethylamino, methyl, fluorine, bromine, chlorine, iodine, nitro and cyano substituents. Repeating the process with meta-substituents afford the meta substituent constants. This treatment does not include ortho-substituents, which would introduce steric effects.

The σ values displayed in the Table above reveal certain substituent effects. With $\rho = 1$, the group of substituents with increasing positive values—notably cyano and nitro—cause the equilibrium constant to increase compared to the hydrogen reference, meaning that the acidity of the carboxylic acid (depicted on the left of the equation) has increased. These substituents stabilize the negative charge on the carboxylate oxygen atom by an electron-withdrawing inductive effect (-I) and also by a negative mesomeric effect (-M).

The next set of substituents is the halogens, for which the substituent effect is still positive but much more modest. The reason for this is that while the inductive effect is still negative, the mesomeric effect is positive, causing partial cancellation. The data also show that for these substituents, the meta effect is much larger than the para effect, due to the fact that the mesomeric effect is greatly reduced in a meta substituent. With meta substituents a carbon atom bearing the negative charge is further away from the carboxylic acid group (structure 2b).

This effect is depicted in scheme 3, where, in a para substituted arene 1a, one resonance structure 1b is a quinoid with positive charge on the X substituent, releasing electrons and thus destabilizing the Y substituent. This destabilizing effect is not possible when X has a meta orientation.



Other substituents, like methoxy and ethoxy, can even have opposite signs for the substituent constant as a result of opposing inductive and mesomeric effect. Only alkyl and aryl substituents like methyl are electron-releasing in both respects.

When the sign for the reaction constant is negative, only substituents with a likewise negative substituent constant will increase equilibrium constants.

Determination of ρ- value:

With knowledge of substituent constants it is now possible to obtain reaction constants for a wide range of organic reactions. The archetypal reaction is the alkaline hydrolysis of ethyl benzoate (R=R'=H) in a water/ethanol mixture at 30°C. Measurement of the reaction rate k_0 combined with that of many substituted ethyl benzoates ultimately result in a reaction constant of +2.498.

The reaction constant, or sensitivity constant, ρ, describes the susceptibility of the reaction to substituents, compared to the ionization of benzoic acid. It is equivalent to the slope of the

Hammett plot. Information on the reaction and the associated mechanism can be obtained based on the value obtained for ρ. If the value of:

1. ρ>1, the reaction is more sensitive to substituents than benzoic acid and negative charge is built during the reaction (or positive charge is lost).
2. 0<ρ<1, the reaction is less sensitive to substituents than benzoic acid and negative charge is built (or positive charge is lost).
3. ρ=0, no sensitivity to substituents, and no charge is built or lost.
4. ρ<0, the reaction builds positive charge (or loses negative charge).

These relations can be exploited to elucidate the mechanism of a reaction. As the value of ρ is related to the charge during the rate determining step, mechanisms can be devised based on this information. If the mechanism for the reaction of an aromatic compound is thought to occur through one of two mechanisms, the compound can be modified with substituents with different σ values and kinetic measurements taken. Once these measurements have been made, a Hammett plot can be constructed to determine the value of ρ. If one of these mechanisms involves the formation of charge, this can be verified based on the ρ value. Conversely, if the Hammett plot shows that no charge is developed, i.e. a zero slope, the mechanism involving the building of charge can be discarded.

3.4.2 Taft equation:

The Taft equation is a linear free energy relationship (LFER) used in physical organic chemistry in the study of reaction mechanisms and in the development of quantitative structure activity relationships for organic compounds. It was developed by Robert W. Taft in 1952 as a modification to the Hammett equation. While the Hammett equation accounts for how field, inductive, and resonance effects influence reaction rates, the Taft equation also describes the steric effects of a substituent. The Taft equation is written as:

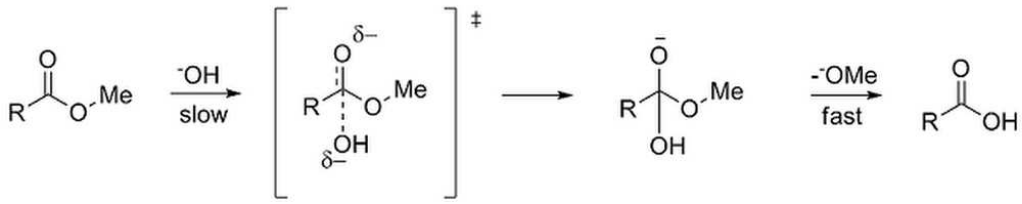
$$\log\left(\frac{k_s}{k_{CH_3}}\right) = \rho^* \sigma^* + \delta E_s$$

Where $\log\left(\frac{k_s}{k_{CH_3}}\right)$ is the ratio of the rate of the substituted reaction compared to the reference reaction, σ* is the polar substituent constant that describes the field and inductive effects of the substituent, Es is the steric substituent constant, ρ* is the sensitivity factor for the reaction to polar effects, and δ is the sensitivity factor for the reaction to steric effects.

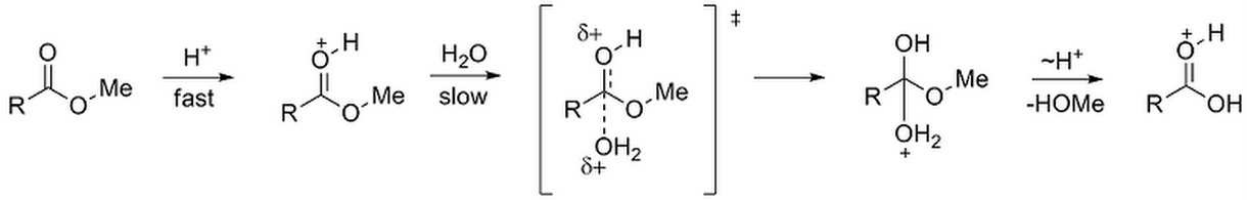
Polar substituent constants, σ*:

Polar substituent constants describe the way a substituent will influence a reaction through polar (inductive, field, and resonance) effects. To determine σ* Taft studied the hydrolysis of methyl esters (RCOOMe). The use of ester hydrolysis rates to study polar effects was first suggested by Ingold in 1930. The hydrolysis of esters can occur through either acid and base catalyzed mechanisms, both of which proceed through a tetrahedral intermediate. In the base catalyzed mechanism the reactant goes from a neutral species to negatively charged intermediate in the rate determining (slow) step, while in the acid catalyzed mechanism a positively charged reactant goes to a positively charged intermediate.

Base Catalyzed Ester Hydrolysis:



Acid Catalyzed Ester Hydrolysis:



Due to the similar tetrahedral intermediates, Taft proposed that under identical conditions any steric factors should be nearly the same for the two mechanisms and therefore would not influence the ratio of the rates. However, because of the difference in charge buildup in the rate determining steps it was proposed that polar effects would only influence the reaction rate of the base catalyzed reaction since a new charge was formed. He defined the polar substituent constant σ* as:

$$\sigma^* = \left(\frac{1}{2.48\rho^*}\right)\left[\log\left(\frac{k_s}{k_{CH_3}}\right)_B - \log\left(\frac{k_s}{k_{CH_3}}\right)_A\right]$$

where log $(k_s/kCH_3)B$ is the ratio of the rate of the base catalyzed reaction compared to the reference reaction, $\log(k_s/kCH_3)A$ is ratio of a rate of the acid catalyzed reaction compared to the reference reaction, and ρ* is a reaction constant that describes the sensitivity of the reaction series. For the definition reaction series, ρ* was set to 1 and R = methyl was defined as the reference reaction (σ* = zero). The factor of 1/2.48 is included to make σ* similar in magnitude to the Hammett σ values.

Steric substituent constants, Es:

Although the acid catalyzed and base catalyzed hydrolysis of esters gives transition states for the rate determining steps that have differing charge densities, their structures differ only by two hydrogen atoms. Taft thus assumed that steric effects would influence both reaction mechanisms equally. Due to this, the steric substituent constant Es was determined from solely the acid catalyzed reaction, as this would not include polar effects. Es was defined as:

$$E_s = \frac{1}{\delta} \log\left(\frac{k_s}{k_{CH_3}}\right)$$

Where k_s is the rate of the studied reaction and k_{CH3} is the rate of the reference reaction (R = methyl). δ is a reaction constant that describes the susceptibility of a reaction series to steric effects. For the definition reaction series δ was set to 1 and Es for the reference reaction was set to zero. This equation is combined with the equation for σ* to give the full Taft equation.

3.5 SUMMARY

In this unit we have discussed the about Reactive intermediates. These species are carbocation, carbanion, carbine, nitrene benzyne and free radical. These species are highly reactive and mostly exist as intermediates in the reactions. Besides these species there is one more species called nitrene which is the nitrogen analog of carbene. In this unit we have also discussed the structure, stability, generation and reactions of these reaction intermediates.

3.6. TERMINAL QUESTIONS

1. What are carbanian? How they are generated? Discuss their stability order.
2. What are Cabenes? How they are generated? Give the structure of Singlet and Triplet carbenes.
3. Discuss some reactions of benzynes.
4. What are benzynes? Give there structure.
5. What are Singlet and Triplet nitrenes.
6. Give the Relative stability of free radicals with the help of hyperconjugation effect.
7. Give the relative stability of the alkyl carbo cations.
8. What are the important factors affecting the stability of carbanions? Discuss the structure of carbanions.
9. How will you distinguish between singlet and triplet carbenes based on their stability and stereochemical bahaviour in addition reactions?
10. Explain the structure and stability of carbon free radicals.
11. Discuss the structure, stability and reactions of carbanions.
12. Write a note on the stability of carbocation and carbanion.
13. What are free radicals? Write the methods of generation of free radicals.

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UNIT 4: STEREOCHEMISTRY 1

CONTENTS

4.1 OBJECTIVES

In this unit learner will be able to:

- Depict various types of isomerism exhibited by organic compounds and their representation
- Analyze the three dimensional depictions of organic compounds and their two dimensional representations.
- Learn Stereogenicity, chirality, enantiomerism, diastereomerism, their relative and absolute configurations
- Learn about the various stereo chemical descriptors such as (cis-trans, E/Z, D/L, d/l, erythro/threo, R/S and syn/anti) given to organic molecules differ
- Describe the stereochemistry of various rigid and complex molecules like spiranes, adamentanes, catenanes, cyclophanes etc.

4.2 INTRODUCTION

In undergraduate level chemistry course we have learn about the fundamental concepts of isomerism and stereochemistry. Isomerism and stereochemistry provides the information about the different kind of depictions for organic compounds with similar structural formulas. Chemical compounds are represented by specific structural formulas. These chemical formulas were first organized by three scientists Kekule, Couper and Butlerov in 1874. The three dimensional representation of depiction of organic molecules were independently suggested by J H van't Hoff and J A LeBel. J H van't Hoff was honored by Nobel Prize for his work in 1901; he was the first recipient of Nobel Prize in Chemistry.

4.3 ISOMERISM

The word isomerism originated from Greek word *isomer* (*iso*= equal; *mers* = part). When two or more organic compounds having similar molecular formula but exhibit differences in their chemical and/or physical properties are called isomers, and the phenomenon is known as isomerism. However, the stereochemistry of an organic compound can be defined as the chemistry of that compound in space and as a function of molecular geometry.

Generally isomerism can be divided in to two categories;

a. Structural (constitutional) Isomerism

b. Stereo (configurational) Isomerism

4.4 STRUCTURAL (CONSTITUTIONAL) ISOMERISM

Structural isomerism is also known as *'constitutional isomerism'*. Structural isomerism arises when a molecule can be represented in to two or more than two different structures. The difference in structure is due to the difference in the arrangement of atoms within the molecules, irrespective of their position in space. In other words, structural isomers are compounds those have identical molecular formulae but different structural formulae; and the phenomenon is called structural isomerism.

Examples 1: Structural isomer of Butane (C_4H_{10}) and Bromobutane (C_4H_9Br)

C_4H_{10} **Butane**

$CH_3CH_2CH_2CH_3$ ***n*-Butane**

CH_3CHCH_3 (with CH_3 branch) **Isobutane**

C_4H_9Br **Bromobutane**

$CH_3CH_2CH_2CH_2Br$ **1-Bromobutane**

$CH_3CHCH_2CH_3$ (with Br) **2-Bromobutane**

Structural isomerism can also be subdivided in to five types.

1) Chain Isomerism
2) Functional Isomerism
3) Position Isomerism
4) Metamerism
5) Tautomerism

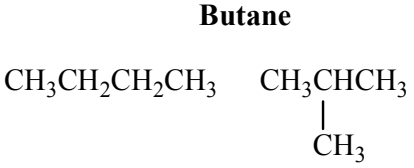
1) Chain Isomerism:

Chain isomers are those isomers having difference in the order in which the carbon atoms are bonded to each other. In other words chain isomers have variable amounts of branching along the hydrocarbon chain.

☞ *If you observe two or more than two molecules having similar molecular formulae, but difference in their hydrocarbon chain length, you should recognize them as chain isomers of each other.*

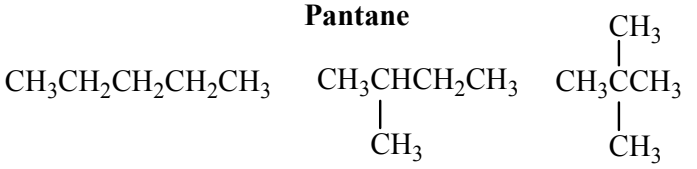
Example 2: Chain isomers of Butane (A) and Pentane (B)

A) C_4H_{10} **Butane**



***n*-Butane** **Isobutane**

B) C_5H_{12} **Pantane**



***n*-Pantane** **Isopetane** **Neopetane**

2) Functional Isomerism:

Two or more than two molecules those having the same molecular formulae but have different functional groups are called functional isomers and the phenomenon is termed as functional isomerism.

☞*If you observe two or more than two molecules having same molecular formulae, but difference in their functional groups, you should understand that these are functional isomers of each other.*

Example 3: Ethyl alcohol and Dimethyl ether

Ethyl alcohol **Dimethyl ether**

Example 4: *n*-Butyl alcohol and Diethyl ether

***n*-Butayl alcohol** **Diethyl ether**

3) Position Isomerism:

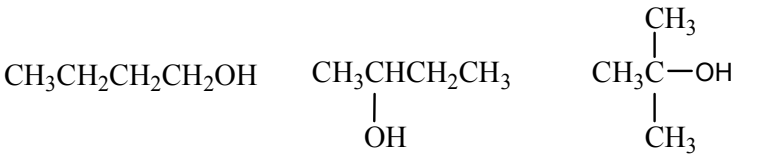
Two or more than two molecules those having same molecular formulae but having difference in the position of functional group on the carbon chain are called position isomers and the phenomenon is called as position isomerism.

☞ *If you observe two or more than two molecules having same molecular formulae, but difference in their functional groups, you should understand that these are functional isomers of each other.*

Example 5: 1-Butene and 2-Butene

1-Butene **2-Butene**

Example 6:1-Butyl alcohol, 2-Butyl alcohol and *t*-Butyl alcohol



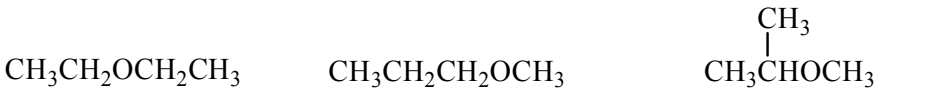
1-Butyl alcohol **2-Butyl alcohol** ***t*-Butyl alcohol**

4) Metamerism:

Two or more than two molecules those having same molecular formulae and functional group but having difference in the distribution of carbon atoms on either side of functional group are called metamers and the phenomenon is called the metamerism.

☞*When you see two or more than two molecule with identical molecular formulae but while structural representation you observe there is a difference in the alkyl group attached to same functional group you should understand these molecules are metamers of each other.*

Example 7: Diethyl ether, Methylpropyl ether and isopropyl methyl ether



Diethyl ether **Methyl propyl ether** **Isopropyl methylether**

Example 8: Diethyl amine, Methylpropyl amine and isopropyl methyl amine

Diethyl amine **Methyl propyl amine** **Isopropyl methylamine**

5) **Tautomerism:**

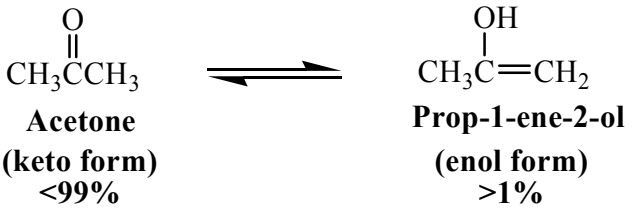
This is a special kind of isomerism where both the isomers are interconvertible and always exist in a dynamic equilibrium to each other. Due to their interconversion change in functional group

takes place that gives two different isomers of an organic compound. This phenomenon is called Tautomerism.

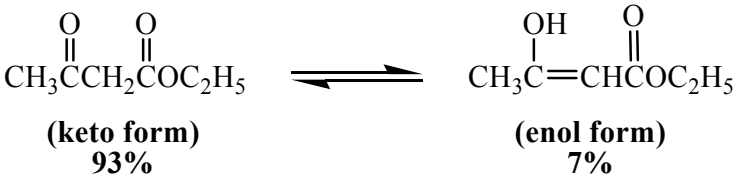
☞*When you observe two different isomeric forms of an organic compound are rapidly interconvertible to each other you should recognize them as tautomer of each other.*

Remember: *Tautomers are not the resonance structure of same compound*

Example 9: Acetone exists in taotomeric equilibrium with Prop-1-en-2-ol



Example 10: Tautomeric forms of Ethyl acetoacetate under taotomeric equilibrium



4.5 STEREO (or CONFIGURATIONAL) ISOMERISM

Stereoisomerism is arises due to the difference in arrangement (configuration) of atoms or groups in space. When two or more than two isomers have the same structural formulae but having difference in the arrangement (configuration) of atoms in space are called stereo isomer and the phenomenon is called stereo isomerism.

Stereo isomerism can be further classified as

i. Geometrical or *cis-trans* isomerism
ii. Optical isomerism

4.5.1 GEOMETRICAL ISOMERISM:

Geometrical isomerism is generally observed in alkenes and cyclic compounds due to their restricted rotation around carbon- carbon bond. The rotation about a double bond in alkene or about a single bond in a cyclic/ring like compound is restricted. Double bonded system consists of a σ (sigma) and a π (pi) bond perpendicular to each other. It is not possible to rotate the molecule about carbon-carbon bond. The rotation will break the π bond as a result the molecule will lose its identity. In some cased the rotation about single bond is also restricted due to steric

hindrance. Geometrical isomerism is shown by various groups of compounds the major class of compounds that exhibit geometrical isomerism are classified as:

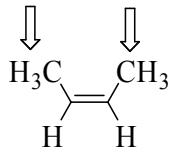
i. Compounds having double bond;

C=C, C=N, N=N

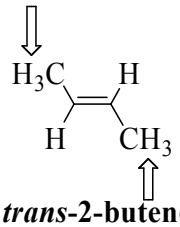
For example *cis*- and *trans*-2-butene have same connection of bond and molecular formulae.

☞ *If you observe two similar groups are on the same side of C=C bond this is called cis- isomer; whereas, if two similar groups are on opposite side of C=C bond this is known as trans- isomer.*

Example 1: *cis*- and *trans*- isomerism in 2-butene



***cis*-2-butene**



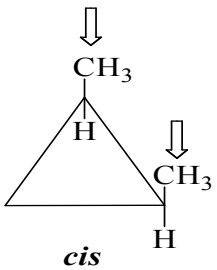
***trans*-2-butene**

☞ *You can understand that due to the presence of one σ (sigma) and one π (pi) bond in carbon–carbon double bond, rotation around C=C bond is not possible. The restricted rotation around C=C bond is responsible for geometrical isomerism in alkenes.*

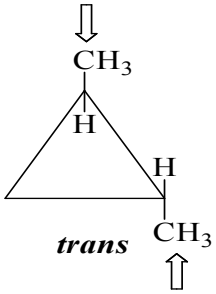
ii. Cyclic compounds like homocyclic, heterocyclic and fused-ring systems

You can easily observe that rotation around C-C bond is also not possible in cyclic compounds as the rotation would break the bonds and break the ring. Thus Geometrical isomerism is also possible in cyclic compounds.

Example 2: *cis*- and *trans*- isomers of 1,2-dimethylcyclopropane



cis



trans

Conditions for geometrical isomerism:

Following two conditions are necessary for any compounds to show geometrical isomerism

a) There should be restricted (not allowed) rotation about a bond in a molecule.
b) Both substituent/atoms on each carbon about which rotation is not allowed should (restricted) be different.

☞ ***Remember*****:** *Geometrical isomers are non-mirror image of each other hence they are called diastereomers. Therefore their physical and chemical properties are different.*

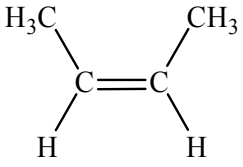
☞ *Triple bonded molecules do not exhibit any kind of stereoisomerism because such molecule shows cylindrical symmetry.*

E & Z system of nomenclature for geometrical isomers:

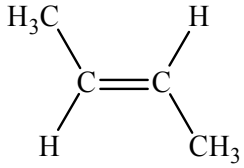
We have already discussed about the *cis*- and *trans*- nomenclature of geometrical isomerism. The *cis*- and *trans*- nomenclature is the oldest and most fundamental nomenclature system for geometrical isomerism. The *cis*- and *trans*- nomenclature system is applicable only for those geometrical isomers in which at least one identical atoms/groups is bonded with each double bonded carbon. If both the identical groups/atoms are on same side of double bond the isomer is called as *cis*- isomer; whereas, if both identical groups/atoms are on opposite side of the double bond the isomer is called as *trans*- isomer (see example 1 of this unit).

The *cis*- and *trans*- nomenclature method is limited to the molecule in which identical groups/atoms are attached to double bonded carbon. If all the atoms/groups on double bonded carbon are different then the configuration of such molecule could not be assigned as *cis*- and *trans*- nomenclature. A more general nomenclature (*i.e.* E/Z nomenclature) was introduced which was based on *Cahn-Ingold-Prelog* system. In E/Z system the configuration is specified by the relative positions of two highest priority groups/atoms on the two carbons of the double bond.

Let us understand the *E/Z* nomenclature system by considering an example which we have already discussed in the beginning of this Unit (example 1).



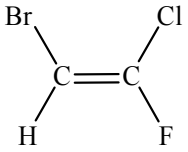
***cis*-2-butene**



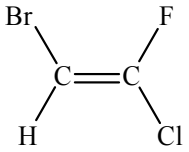
***trans*-2-butene**

You can easily identify which one is *cis*- isomer and which one is *trans*- just by looking the position of similar atoms/groups. It is a simple and visual way of telling the two isomers apart. *So why do we need an alternative system?*

Now consider one another example in which we will change all the atoms/groups in above example by replacing one CH_3- by Br, other CH_3- by Cl, and one H- by F. Now try to predict the nomenclature of these two isomers of **2-bromo-1-chloro-1-fluoroethene (I and II)**. ***Could you name these isomers using cis- and trans- nomenclature?*** The simplest answer is '**NO'**.

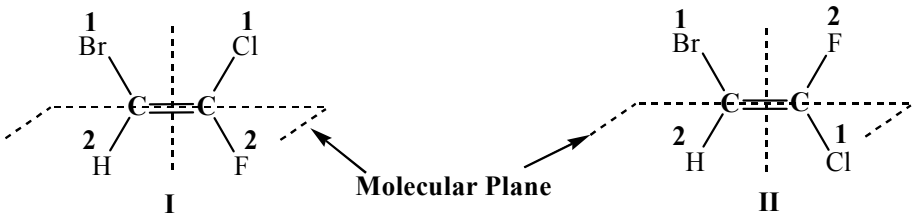


I



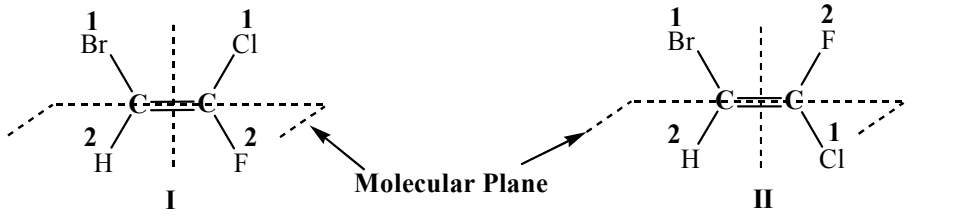
II

Because all four atoms attached to the carbon-carbon double bond are different, therefore it is not so simple that you can predict them as *cis*- and *trans*- to each other. The E/Z system of nomenclature provides the most appropriate solution to above problem. This system is based on the priority of the attached atoms/groups on each double bonded carbon. The priority of the atoms/groups can be assigned as per the 'Sequence Rule' or 'CIP Rule' given by Cahn-Ingold-Prelog. We have discussed the detail about 'Sequence Rule' in later part of this Unit. Now assign priority to atoms/groups attached to each double bonded carbon in above example.



We can easily observe that the both higher priority atoms/groups on each double bonded carbon of isomer **I** are on same side; whereas, the higher priority atoms/groups on each double bonded

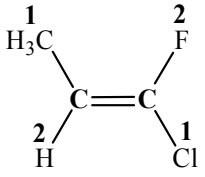
carbon of isomer **II** are on opposite side. If the two groups with the higher priorities are on the same side of the double bond, such isomer is designated as the (*Z*)- isomer. So you would write it as (*Z*)-name of compound. The symbol *Z* comes from a German word *ZUSAMMEN*, which means together. If the two groups with the higher priorities are on opposite sides of the double bond, then such isomer is designated as (*E*)- isomer. *E* comes from the German *ENTGEGEN*, which means opposite. Thus in given example the isomer **I** is having both higher priority groups/atoms are on same side of double bond, hence it is *Z*- isomer; whereas, the isomer **II** is having both higher priority groups/atoms are on opposite side of the double bond, hence it is *E*-isomer.



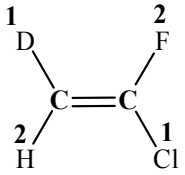
I **II**

(*Z*)-2-bromo-1-chloro-1-fluoroethene **(*E*)-2-bromo-1-chloro-1-fluoroethene**

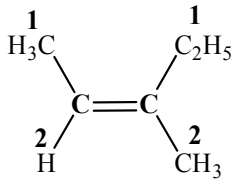
Example 10: Some other examples of geometrical isomers with *E* and *Z* configuration



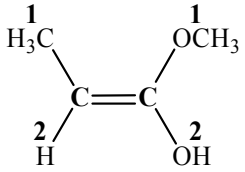
(*E*)-1-chloro-1-fluoroprop-1-ene



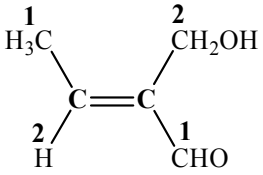
(*E*)-Deuterated1-chloro-1-fluoroprop-1-ene



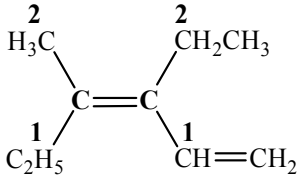
(*Z*)-3-methylpent-2-ene



(*Z*)-1-methoxyprop-1-en-1-ol



(*E*)-2-(hydroxymethyl)but-2-enal



(*Z*)-3-ethyl-4-methylhexa-1,3-diene

Geometrical isomerism in oximes and cyclic compounds:

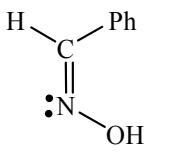
Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are:

(a) Oximes

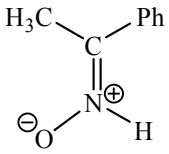
(b) Nitrones

(c) Semicarbazones

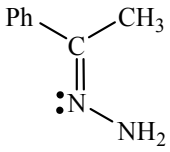
(d) Hydrazones



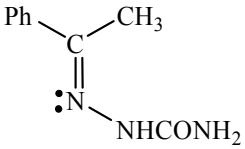
(*Z*)-benzaldehyde oxime



(*E*)-nitrone



(*E*)-1-(1-phenylethylidene) hydrazine

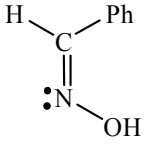


(*E*)-1-(1-phenylethylidene) semicarbazide

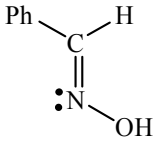
Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism. The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*- isomer.

Example 11:E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime

i)

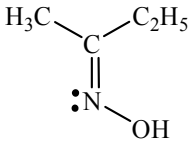


(*Z*)-benzaldehyde oxime

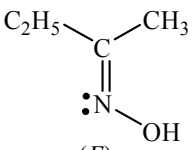


(*E*)-benzaldehyde oxime

ii)

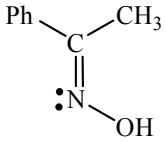


(*Z*)-ethylmethyl ketoxime

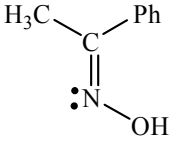


(*E*)-ethylmethyl ketoxime

iii)



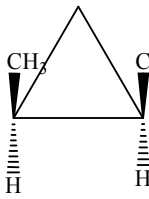
(*E*)-acetophenone oxime



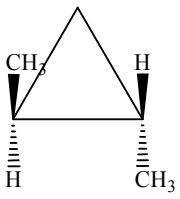
(*Z*)-acetophenone oxime

We have already discussed that the geometrical isomerism is usually arises due to restricted rotation about a bond. Since, there is no rotation possible about the carbon-carbon bond in a cyclic compound or cycloalkanes like cyclopropane, cyclobutane, cyclopantane, cyclohexane, etc. Hence, such molecule also exhibit geometrical isomerism, and can be designated as *cis*- and *trans*- isomer. In a disubstituted cycloalkanes, where the two atoms/groups are bonded on different carbons, can be represented in to two geometrical isomers. The isomer in which the two atoms/groups are located on the same side of the ring is called *cis*-isomer; whereas, the isomer in which the two atoms/groups are located on the opposite side of the ring is called *trans*-isomer.

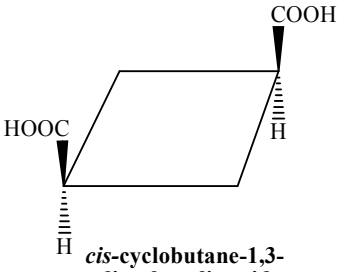
Example 12: Geometrical isomers of disubstituted cyclopropane, cyclobutane, cyclopantane and cyclohexane.



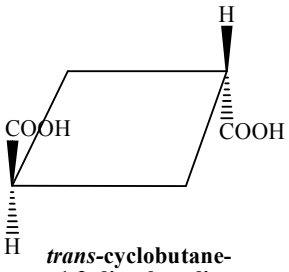
***cis*-1,2-dimethylcyclopropane**



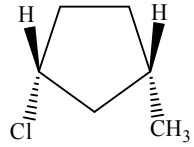
***trans*-1,2-dimethylcyclopropane**



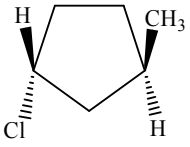
***cis*-cyclobutane-1,3-dicarboxylic acid**



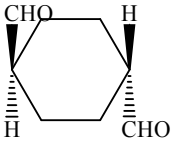
***trans*-cyclobutane-1,3-dicarboxylic acid**



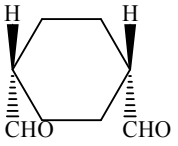
***cis*-1-chloro-3-methylcyclopentane**



***trans*-1-chloro-3-methylcyclopentane**



***trans*-cyclohexane-1,4-dicarbaldehyde**



***cis*-cyclohexane-1,4-dicarbaldehyde**

4.5.2 OPTICAL (CONFIGURATIONAL) ISOMERISM:

Optical isomerism is another class of *stereoisomerism*. The organic compounds that exhibit optical isomerism must have a unique ability to rotate the plane polarized light either towards left or towards right hand directions. This unique ability is generally known as optical activity. Optical activity of any compound is measured by analyzing the sample in an instrument called **Polarimeter.** A solution of known concentration of optically active compound is when exposed to the beam of plane polarized light, the beam of plane polarized light is rotated through a certain number of degrees, either to the clockwise (right) direction or anti-clockwise (left) direction. The compound which rotates the plane polarized light towards clockwise direction is called to be **dextrorotatory** (represented by +); whereas, the compound which rotates the plane polarized light towards anti-clockwise direction is called to be **levorotatory** (represented by -). Figure 1 shows the schematic representation of polarimeter.

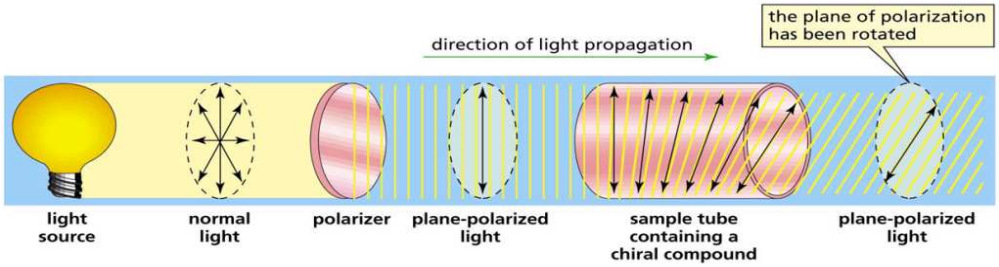


Figure 1. Schematic representation of simple polarimeter

- ☞ *The degree of rotation depends upon the number of the molecules of the compounds falls in the path of beam. To compare the rotating power of different optically active compounds, the specific rotation of each compound is calculated and then comparison should be made.*
- ☞ *Specific rotation is defined as the degree of rotation offered for the given wavelength of plane polarized light at given temperature by a solution of 1g/mL concentration is filled in a 10 cm length sample cell. Specific rotation is represented by* $[\alpha]_{\lambda}^{\xi}$ *and can be calculated as*

$$[\alpha]_{\lambda}^{\xi} = \frac{100\alpha}{lc}$$

Where α is observed angle of rotation; t is the temperature of during experiment; λ is the wavelength of light used; l is the length of the tube in decimeter; and c is the concentration of the compounds per 100 mL of solution.

i. Remember:

Optically active compounds always exist in two isomeric forms which rotates the plane polarized light by equal degrees in opposite directions. The optical isomer which rotates the plane polarized light towards right (clockwise direction) is known as Dextrorotatory Isomer or (+)*-isomer, whereas, the optical isomer which rotates the plane polarized light towards left (anticlockwise direction) is known as Levorotatory Isomer or* (-)*-isomer.*

4.6 ELEMENTS OF SYMMETRY

All optically active molecules/object are chiral and they exhibit enantiomerism (Figure 2). A chiral molecule is that which cannot be superimposed on its mirror image; however, both the non-super imposable isomers are called enantiomers. We will learn more about chirality and enantiomerism in separate section of this unit.

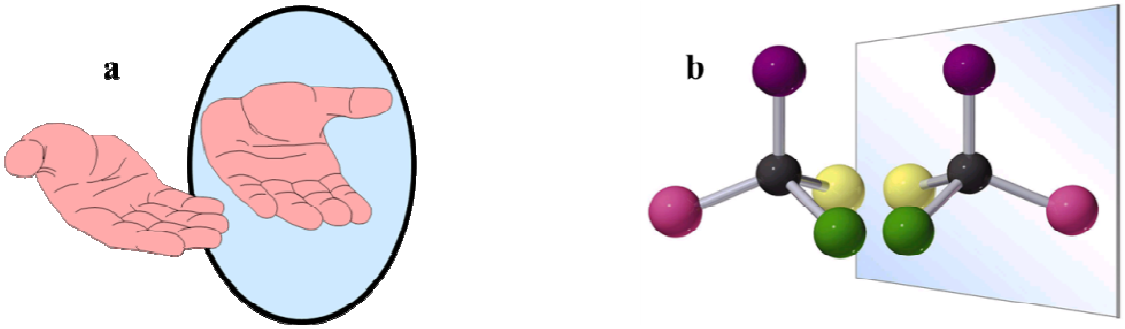


Figure 2. (**a**) Non super imposable mirror image relationship of right and left hands. (**b**) Ball and stick model of tetravalent chiral carbon atom.

Elements of symmetry are a simple tool to identify whether a molecule is chiral or not. The necessary condition for optically active molecule to be chiral is that, the molecule should not possess any kind of symmetry elements. The elements of symmetry are generally categorized as follows:

(i) Simple axis of symmetry (C_n)

(ii) Plane of symmetry (σ)

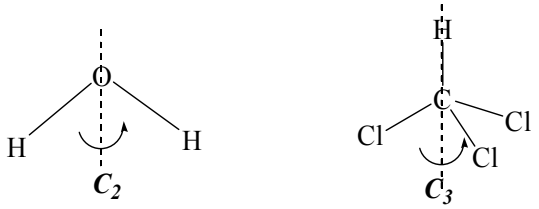
(iii) Centre of symmetry (C_i)

(iv) Alternating axis of symmetry (S_n)

(i) Simple axis of symmetry (C_n):

When a rotation of 360°/n (where n is any integer like 1,2,3…etc.) around the axis of a molecule or object is applied, and the rotated form thus obtained is non-differentiable from the original, then the molecule/object is known to have a *simple axis of symmetry*. It is represented by C_n.

Example 13: Water molecule has C_2 (two fold axis of symmetry) whereas chloroform has C_3 axis of symmetry.



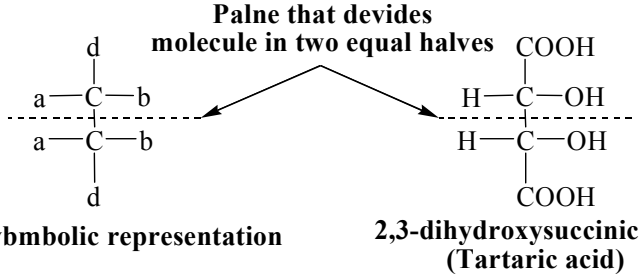
water ***Chloroform***

☞ *From above example you can easily understand that if you rotate the water molecule by 180° (i.e. 360°/2=180°) along its molecular axis you will get the identical (non-differentiable) form of water molecule, hence water molecule has two fold of symmetry. Similarly, if you rotate the chloroform molecule by 120° (i.e. 360°/3=120°) along its molecular axis you will get the identical (non-differentiable) form of chloroform molecule, hence chloroform molecule has three fold of symmetry.*

(ii) Plane of symmetry (σ):

It is defined as 'when a plane that devised a molecule or object in to two equal halves which are related to object and mirror image is known as *plane of symmetry*. It is represented by σ.

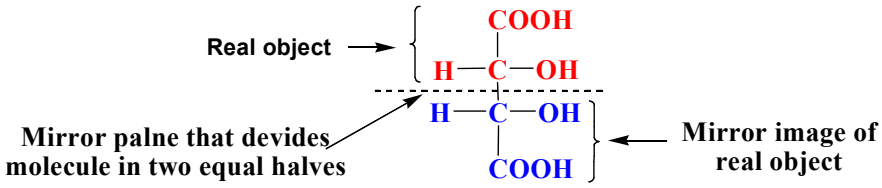
Example 14: Plane of symmetry in Tartaric acid



Sybmbolic representation **2,3-dihydroxysuccinic acid (Tartaric acid)**

☞*From above example you can easily understand that if we put a mirror plane/reflection plane exactly at the centre axis of the molecule/object; you will found that the mirror*

image thus obtained is the complementary of the original and both will give us the appearance of complete molecule/object.

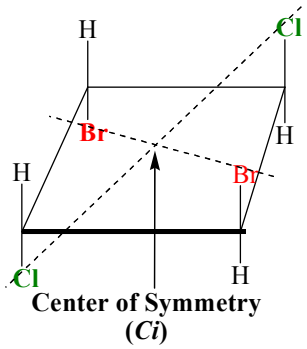


2,3-dihydroxysuccinic acid (Tartaric acid)

(iii) Centre of symmetry (C_i):

A molecule has a centre of symmetry when, for any atom in the molecule, an identical atom exists diametrically (diagonally) opposite to this centre and at equal distance from it.

Example 15: An isomer of 1,3-dichloro-2,4-dibromocyclobutane has a centre of symmetry

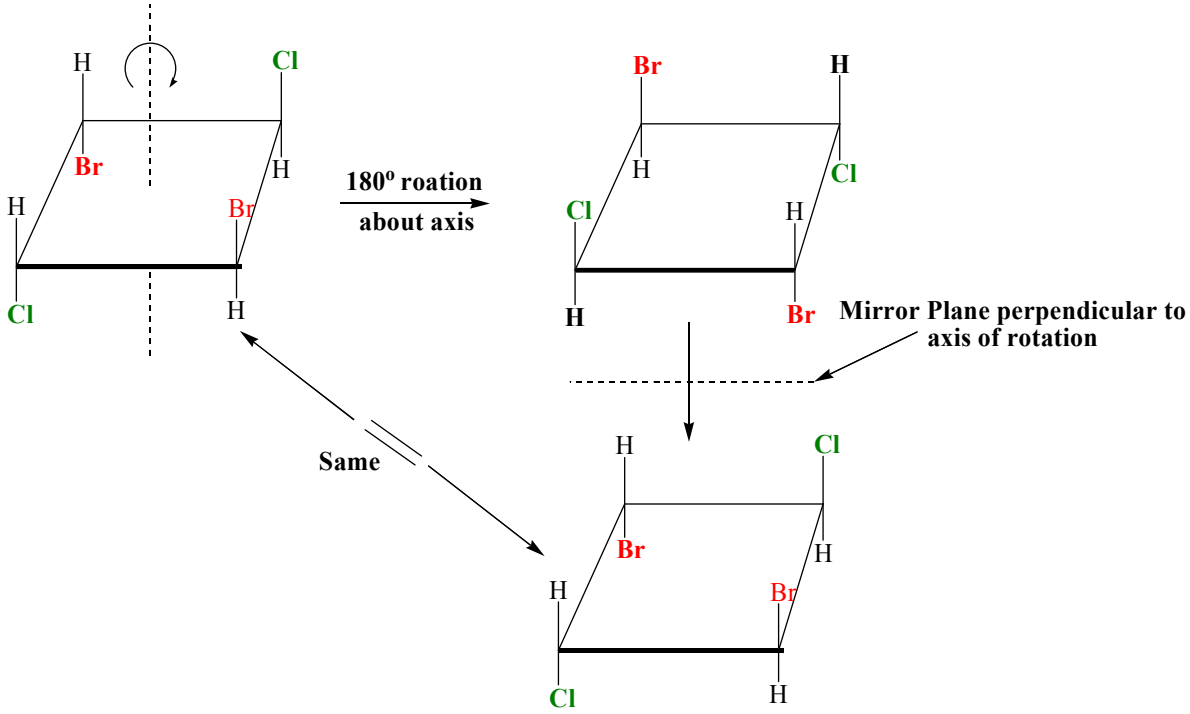


☞*From above example you may understand that all the identical atoms are situated diagonally and at equal distance from the centre. This is called centre of symmetry.*

(iv) Alternating axis of symmetry (S_n):

An alternate axis of symmetry is defined as, when a molecule is rotated by 360°/n degrees about its axis and then a reflection plane is placed exactly at perpendicular to the axis, and the reflection of the molecule thus obtained is identical to the original. It is represented by S_n.

Example 16. An isomer of 1,3-dichloro-2,4-dibromocyclobutane has a 2 fold alternate axis of symmetry

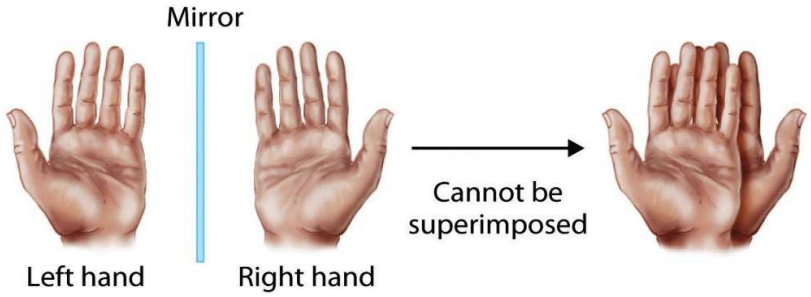


MOLECULAR CHIRALITY, ENANTIOMERISM:

The necessary condition for a molecule to have optical isomerism is that molecule should not have any kind of symmetry elements present in it, in other words the molecule should be dissymmetric. Such molecules are called '*Chiral'* and the property is called '*molecular chirality*'. Optically active chiral molecules which are non-super imposable on their mirror images are called '*enantiomers'* and the phenomenon is known as '*enantiomerism'*. To exhibit optical isomerism an organic compound must have at least one asymmetric carbon atom. An asymmetric carbon atom is that which is bonded to four different atoms or groups.

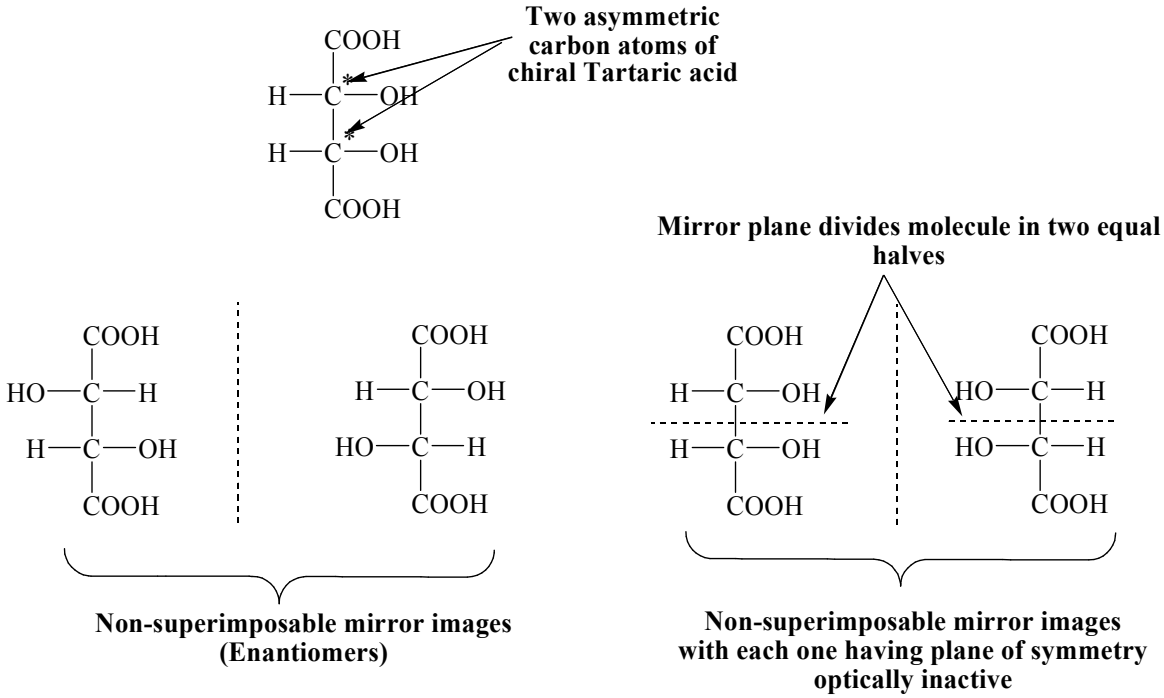
☞*We can easily understand the chirality by comparing our hands (left hand and right hand). Our left hand and right hand are the best example of non-super imposable mirror image of each other. Each hand is therefore considered as chiral.*

ii. Remember: *Our left hand and right hand are non-super imposable mirror image of each other each one of them is chiral.*



iii. Remember: *Chirality is the necessary and sufficient condition for the existence of enantiomers.*

Example 17. Tartaric acid has two asymmetric carbon and it exists in four forms, out of them two form are optically active and two are optically inactive.



4.7 *STEREOGENIC CENTRE (STEREOGENICITY)*

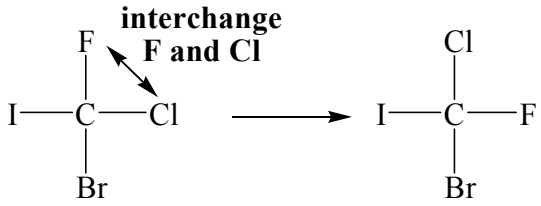
As we discussed in previous section that if a molecule contains one carbon atom which is directly bonded with four different groups or atoms, and the molecule do not have any kind of symmetry element present in it, such molecule is called asymmetric or chiral.

When the interchange of the position of two directly bonded groups or atoms of a centre carbon atom results a new stereoisomer, such chiral centre is called stereo centre or stereogenic centre and the property is called stereogenicity.

If the new stereoisomer is a non-super imposable mirror image of the original molecule such carbon centre is called chiral carbon centre.

iv. Remember: All the chiral centers are stereogenic centers but all stereogenic centers are not chiral centre.

Example 18: Bromochlorofluoroidomethane exhibits chiral carbon centre



Interchange of F and Cl results non-superimposable stereoisomers

4.7.1 OPTICAL ACTIVITY (ENANTIOMERISM):

It is already known to you (from section 4.5) that the optical activity is an ability of a chiral molecule to rotate the plane of plane-polarized light either towards left or right direction. The rotation is measured by an instrument called Polarimeter. When a beam of plane polarized light passes through a sample that can rotate the plane polarized light, the light appears to dim because it no longer passes straight through the polarizing filters. The amount of rotation is quantified as the number of degrees that the analyzing lens must be rotated to observe the no dimming of light appears. Optical rotation can be measured by using the following formulae

$$[\alpha]_{\lambda}^{t} = \frac{100\alpha}{lc}$$

Where α is observed angle of rotation; t is the temperature of during experiment; λ is the wavelength of light used; l is the length of the tube in decimeter; and c is the concentration of the compounds per 100 mL of solution.

Optically active chiral compounds that are non-super imposable mirror image of each other are called enantiomers.

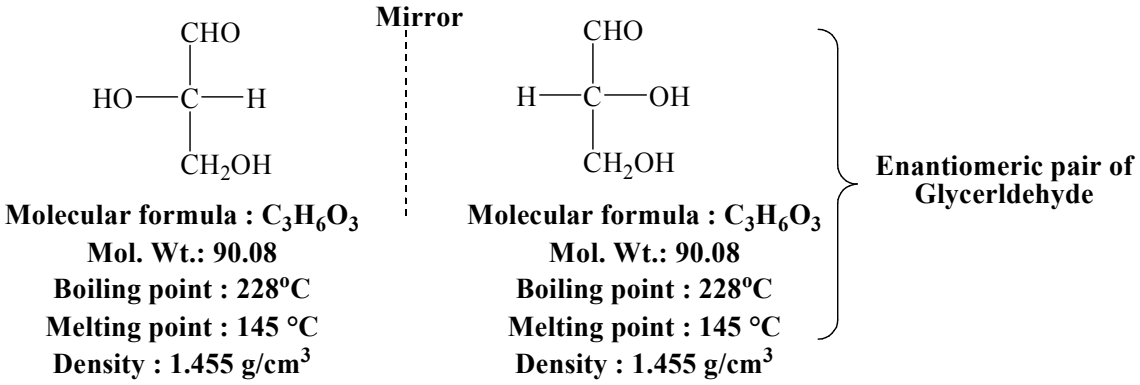
4.7.2 Properties of enantiomers:

The main properties of enantiomers are given as follow

- Enantiomers always exist in pair
- Enantiomers are non-super imposable mirror image to each other

- Enantiomers have same physical properties (like boiling point, melting point, solubility, density, viscosity, refractive index etc.)and chemical properties in achiral environment
- Each enantiomers have opposite behavior with respect to plane polarized light, if one of them will rotate the plane polarized light towards right hand direction then definitely the other will rotate the plane polarized light towards left hand direction.
- Each enantiomers shows the same chemical reactivity with achiral reagent; however they have different reactivity with chiral reagent.

Example 19: Glyceraldehyde molecule is a chiral molecule. It has a pair of enantiomers with same physical properties except their behavior towards plane polarized light



Molecular formula : $C_3H_6O_3$
Mol. Wt.: 90.08
Boiling point : 228°C
Melting point : 145 °C
Density : 1.455 g/cm^3

Molecular formula : $C_3H_6O_3$
Mol. Wt.: 90.08
Boiling point : 228°C
Melting point : 145 °C
Density : 1.455 g/cm^3

☞*You can see that the glyceraldehyde molecule can exists in two enantiomeric forms which differ only in the arrangement of bonded atoms around the centre chiral carbon. The physical properties (like molecular formula, molecular weight, melting point, boiling point and density etc.) of both the isomers are same. But if one isomer will rotate the plane polarized light towards right hand direction (dextrorotatory) then the other one will rotate the plane polarized light towards left hand direction (levorotatory).*

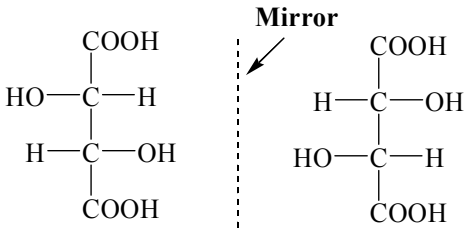
4.7.3 CHIRAL AND ACHIRAL MOLECULES WITH TWO STEREOGENIC CENTRES:

As we have discussed earlier in this unit *(sec. 4.6)* that chiral molecules are those in which the centre carbon atom is bonded directly through four different atoms/groups and do not have any kind of symmetry element present in it and the molecule has non-super imposable mirror image. However, those molecule in which centre carbon atom is directly bonded through four different

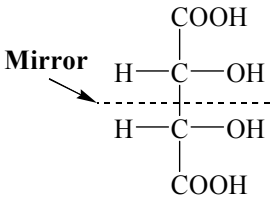
atoms of groups and it satisfied any kind of symmetry elements are called achiral molecule. Achiral molecules have super imposable mirror images.

Let us consider the stereoisomers of Tartaric acid which has two stereo centers with identical atoms/groups attached to both the stereo centers. The tartaric acid have two stereo centers and can have four stereoisomers out of which two stereoisomers are non-super imposable mirror image of each other called enantiomers and chiral; and rest two are identical to each other and also have plane of symmetry hence it can be divided in to two equal halves, therefore are achiral.

Example 20: Tartaric acid has two stereo centers with three stereoisomers (two are chiral and one achiral stereoisomer)



Chiral Tartaric acid

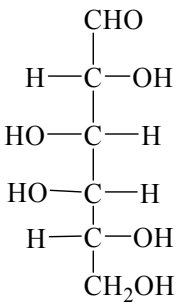


Achiral Tartaric acid

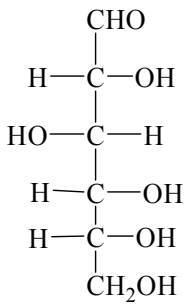
4.7.4 DIASTEREOMERS:

Diastereomers are those stereoisomers that are not mirror image of each other, in other words you can understand the diastereomers are stereoisomers that are not enantiomers. Diastereomers are non-enantiomeric stereoisomers with two or more stereo centers. The pair of stereoisomer that differs in the arrangement of atoms/groups bonded with at least one stereo centre is called diastereomers.

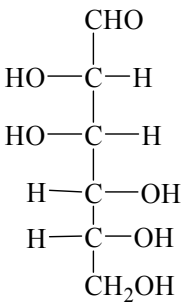
Example 21: D-Galactose, D-Glucose and D-Mannose are the non-mirror image stereoisomer of each other. Therefore are called diastereomers.



D-Galactose

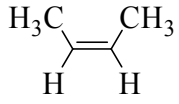


D-Glucose

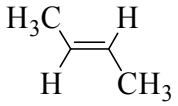


D-Mannose

Example 22: *cis*- and *trans*-2-butenes are non-mirror image stereoisomers of each other hence are called diastereomers.



***cis*-2-butene**



***trans*-2-butene**

4.7.5 PROPERTIES OF DIASTEREOMERS:

The main properties of diastereomers are given as follows:

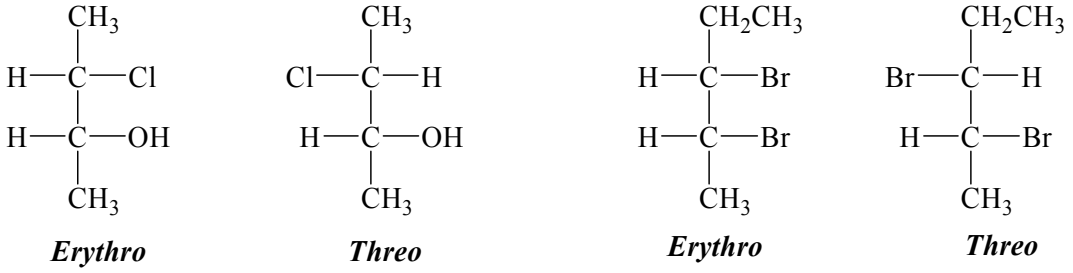
- All the stereoisomers except enantiomers are diastereomers.
- Diastereomers have different physical properties like boiling point, melting point, density, solubility, density, viscosity, refractive index etc.
- Diastereomers have different chemical properties like rates of reactions, reactivity even in achiral reaction medium.
- This difference in physical and chemical properties of diastereomers is very useful in the separation of enantiomers from their mixture.

4.7.6 ERYTHRO (*SYN*) AND THREO (*ANTI*) DIASTEREOMERS:

Threo and *erythro* nomenclature method is designated by organic chemists to assign appropriate name to diastereomers. The *threo* and *erythro* naming is given only to those diastereomers having two adjacent stereocentres. The nomenclature is applicable to these diastereomers if there are two common atoms/groups bonded to each adjacent stereo centre. In other words the terms *erythro* and *threo* are generally applied only to those molecules which do not have symmetric ends. However, when the ends are symmetric then instead of *erythro* and *threo* the *meso* and *dl* nomenclature is preferred. We will discuss separately about *meso* and *dl* in this unit.

If the similar groups/atoms on adjacent stereocentres of diastereomer are on same (*syn*) side it is designated as *erythro*, whereas if the similar groups/atoms on adjacent stereocentres of diastereomer are on opposite (*anti*) side the diastereomer is designated as *threo.*

Example 23: You can easily understand the erythro and threo nomenclature by taking examples of 3-bromo-2-butanol and 2,3-dibromo pentane.



3-Chloro-2-butanol **2,3-Dibromopentane**

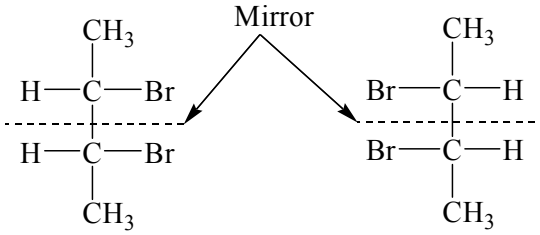
☞*You can see if both the hydrogen atom on two adjacent stereocentres of 3-chloro-2butanol lies on same (syn) side the isomer is called erythro, whereas, when both the hydrogen atoms on two adjacent stereocentres of 3-chloro-2butanol lies on opposite (anti) side the isomer is called threo. Similarly you can find the same observation with 2,3-dibromopentane and designate the isomers as erythro and threo.*

☞*You must also remember that the each erythro and threo stereo isomer can have their non-super imposable mirror image (enantiomers). Thus there will be always one enantiomeric pair of erythro and one enantiomeric pair of threo stereoisomer exists for a stereoisomer with two similar atoms on adjacent stereocentres.*

4.7.7 *MESO* COMPOUNDS:

A compound with two or more carbon stereo centre but also having a plane of symmetry is called *meso* compounds. All the carbon centers have four different atoms/groups but the compound can be divided in to two equal halves which are super imposable mirror image.

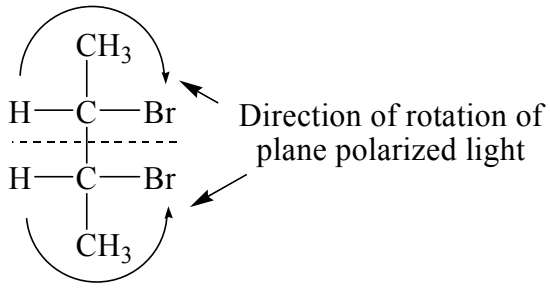
Example 24: 2,3-dibromobutane have two stereocentres, but the molecule have two symmetric ends therefore it can be divided in to two equal halves. In other words the molecule have plane of symmetry.



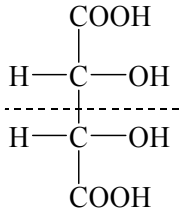
2,3-Dibromobutane

☞*We can see that even the 2,3-dibromobutane have non super imposable mirror image but this molecule have an internal plane of symmetry hence this molecule is optically*

inactive or achiral. This molecule will not be able to rotate the plane polarized light in any direction. If one half of the molecule will rotate the plane polarized light towards right hand direction with some degrees; the other half will rotate the plane polarized light towards left hand direction with same degrees of rotation. Thus the net rotation of the plane polarized light is zero. Such molecules are called meso compounds.



Example 25: Another example of meso compound is one of the stereo isomeric forms of Tartaric acid (2, 3-dihydroxysuccinic acid). The molecule is optically inactive because it has internal plane of symmetry.



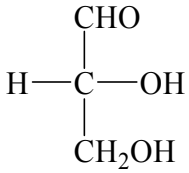
meso-Tartaric acid

4.8 RELATIVE AND ABSOLUTE CONFIGURATION

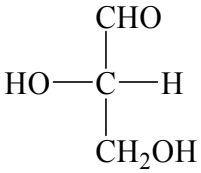
Relative and absolute configuration of a compound discusses about the spatial arrangement of atoms/groups around the centre chiral atom. Relative configuration is a comparison of the spatial arrangement of attached atoms/groups of two different chiral centers. Relative configuration is a geometrical property which do not changes on reflection; whereas, the absolute configuration is the precise arrangement of atoms in three dimensional space. The *D/L* system is usually known as relative configuration whereas, the *R/S* stereo descriptor or nomenclature system for chiral molecules is known as absolute configuration. The absolute configuration is a topographic property which changes on reflection.

4.8.1 *D/L* NOMENCLATURE:

The *D/L* nomenclature is the oldest nomenclature system for enantiomers. In this nomenclature system the configuration of all the compounds were given with respect to glyceraldehyde molecule, where the configuration of glyceraldehyde molecule is taken as an arbitrary standard. According to this nomenclature if in glyceraldehyde molecule the –OH group on right and –H on left, the –CHO and $–CH_2OH$ groups being on top and bottom, respectively the molecule is designated as (+) Glyceraldehyde and it was arbitrary given the configuration symbol *D*. The mirror image of this compound (-) glyceraldehyde was given the configuration *L*.



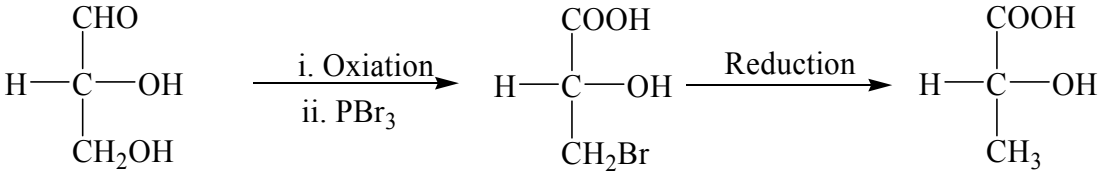
***D*-(+)-glyceraldehyde**



***L*-(+)-glyceraldehyde**

Any compound that can be prepared, or converted in to *D*-(+)-glyceraldehyde will belong to *D* series (relative configuration), whereas, any compound that can be prepared, or converted in to *L*-(+)-glyceraldehyde will belong to *L* series.

Example 26: Lactic acid obtained from *D*-(+)-glyceraldehyde and hence assigned D configuration



***D*-(+)-glyceraldehyde** ***D*-(+)-Lactic acid**

Remember:

- *There is no correlation between the D and L designation and the sign of rotation. D form of isomer may be levorotatory, and L form of isomer may be dextrorotatory and vice versa.*
- *The D/L nomenclature is limited to the compound that can pe prepared or converted from the glyceraldehyde.*
- *It is limited to only one chiral atom.*

4.8.2 *R/S* NOMENCLATURE:

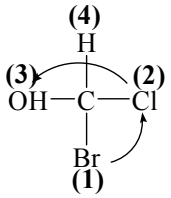
Since you have been noted from the above discussion on D/L configuration, there are several drawbacks associated with the D/L nomenclature system. Hence a definite and universally applicable nomenclature system was needed to specifying the absolute configuration of each chiral centre in a molecule. Cahn and coworkers (1956, 1966) have proposed a new and universally applicable nomenclature pattern for the determination of absolute configuration of any chiral molecule. This is known as the R/S system or *Cahn-Ingold-Prelog* (CIP) nomenclature. It involves following two steps.

- In first step we need to assign the priority to the four different atoms/groups attached to a chiral centre.
- Priorities to the groups/atoms can be assigned as per the **sequence rule**.
- After assigning the priority to the atoms/groups attached to the chiral centre, the molecule is oriented in such a way that the lowest priority group is directed away to the observer.
- Now the arrangement of the remaining atoms/groups is viewed by following deceasing order of priorities from highest priority to lowest priority.
- While viewing the atoms/groups in their decreasing order if your eyes follow the clockwise direction then the chiral centre will have *R* configuration; whereas if your eyes follow anticlockwise direction the chiral centre will have *S* configuration.
- When a molecule has two or more than two chiral centers then the same process should be followed to assign their configuration.

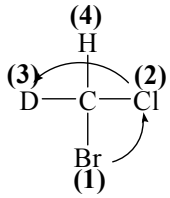
4.8.3 SEQUENCE RULE:

To assign the priorities to all four different groups/atoms attached with the chiral centre following sequence rule should be followed. The sequence rule is given by the three scientists *Cahn-Ingold-Prelog* therefore it is also called the CIP rule. The sequence rules are arbitrary but consistent. The main observations of sequence rules are listed below.

1. If all the atoms directly attached to the chiral centre are different, the sequence of priorities is determined by their atomic number. The atom with higher atomic number is given higher priority. If two atoms are isotopes of same element, the isotope with higher mass number has the higher priority.



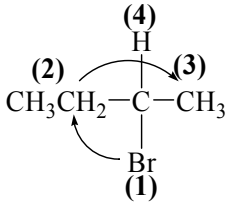
Bromochloromethanol
1-2-3 order is anticlockwise
the configuration is *S*



Deuterio bromochloromethane
1-2-3 order is anticlockwise
the configuration is *S*

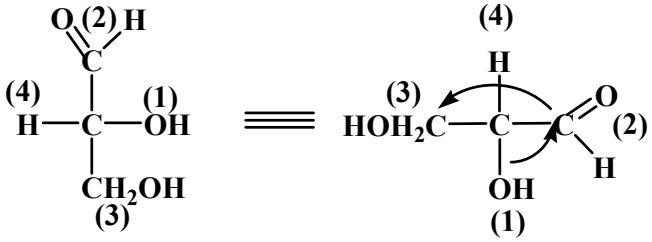
Deuterium (D) is an isotope of Hydrogen with mass number 2 hence get higher priority than H

2. If two or more atoms attached to the chiral centre having same atomic number, the priorities are assigned by comparing the atomic numbers of the next atoms attached to each group/atom.



2-bromobutane
1-2-3 order is clockwise
configuration is *R*

3. If the atoms or groups attached to the centre atom are further linked with some other atoms via double and triple bonds. Then the double or triple bonded atoms are considered to be duplicate or triplicate. As per sequence rule the triple bond gets priority over double bond, similarly double bond gets priority over single bond.



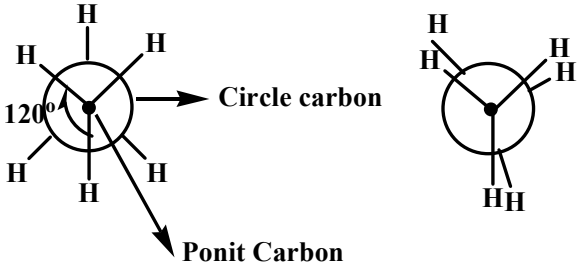
2,3-dihydroxypropanal
1-2-3 order is anticlockwise
configuration is *S*

4.9 NEWMAN AND SAWHORSE PROJECTION FORMULA

The different spatial arrangements of atoms in a molecule which is readily interconvertible by rotation about single bonds are called ***conformations***. The study of various preferred conformations of a molecule and the correlation of physical and chemical properties to the most

preferred conformer is called conformational analysis. Due to rapid interchange of the spatial positions of groups/atoms these conformers are non-separable under normal conditions. Since, different conformations arises because of the rotation about single bonds, hence, they are also called the rotamers. The conformational and configurational isomerisms are related to energy barrier for interconversions of different spatial arrangements of atoms in a molecule. If the energy barrier for interconversion of different spatial arrangements is between 0.6 kcal/mol-16.0 kcal/mol; it result the conformational isomers or conformers; whereas, if this energy barrier is more than or equal to 16 kcal/mol than the configurational isomers are obtained.

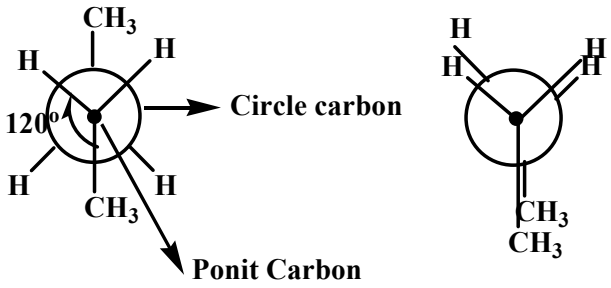
The Newman representation formula: Newman Projections are used mainly for determining conformational relationships. Recall that, conformers are molecules that can be converted into one another by a rotation around a single bond. Newman Projections are also useful when studying a reaction involving prochiral molecules that have a double bond, in which the addition of a new group creates a new stereocenter.In this notation, you are actually viewing a molecule by looking down a particular carbon-carbon bond. The Newman representation formula is a planar representation of the sawhorse formula. The molecule is viewed along the axis of a carbon-carbon bond. The carbon atom in front of the viewer is represented by a dot (●), whereas the carbon atom away to the viewer is represented by circle. The rest of the atoms/groups are located on each carbon atoms at +120° or -120° angles to each other as shown below:



Newman representation formula of ethane

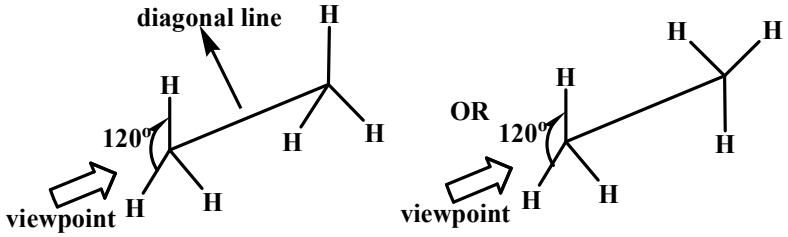
Addition of more carbons makes Newman Projections more complicated. For example, Newman Projections can be made for butane, such that it's eclipsed, gauche, and anti-conformations can be seen. (Recall that these three forms of butane are conformational isomers of one another.) In this case, the front dot represents the second carbon in the butane chain, and the back circle

represents the third carbon in the butane chain. The Newman Projection condenses the bond between these two carbons.



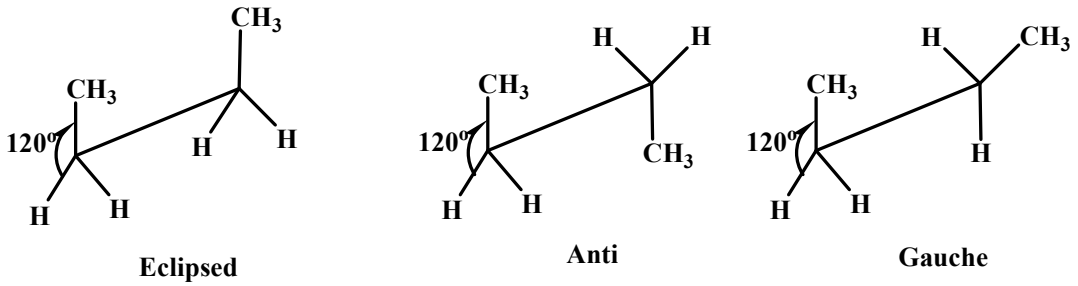
Newman representation formula of butane

The Sawhorse representation formula: Sawhorse Projections are very similar to Newman Projections, but are used more often because the carbon-carbon bond that is compressed in a Newman Projection is fully drawn out in a Sawhorse Projection. When properly laid-out, Sawhorse Projections are useful for determining enantiomeric or diastereomeric relationships between two molecules, because the mirror image or superimposibility relationships are clearer. Like with Newman Projections, a Sawhorse Projection is a view of a molecule down a particular carbon-carbon bond, and groups connected to both the front and back carbons are drawn using sticks at 120 degree angles. Sawhorse Projections can also be drawn so that the groups on the front carbon are staggered (60 degrees apart) or eclipsed (directly overlapping) with the groups on the back carbon. Below are two Sawhorse Projections of ethane. The structure on the left is staggered, and the structure on the right is eclipsed. These are the simplest Sawhorse Projections because they have only two carbons, and all of the groups on the front and back carbons are identical. The sawhorse representation formula is the spatial arrangement of all the atoms/groups on two adjacent carbon atoms. The bond between adjacent carbon atoms is represented by a diagonal line and rest of the atoms are located on each carbon at +120° or -120° angles to each other. The sawhorse representation is shown as:



Sawhorse representation formula of ethane

Addition of more carbons makes Sawhorse Projections slightly more complicated. Similar to Newman Projections, Sawhorse Projections can also be made for butane, such that it's eclipsed, gauche, and anti-conformations can be seen. (Recall that these three forms of butane are conformational isomers of one another).

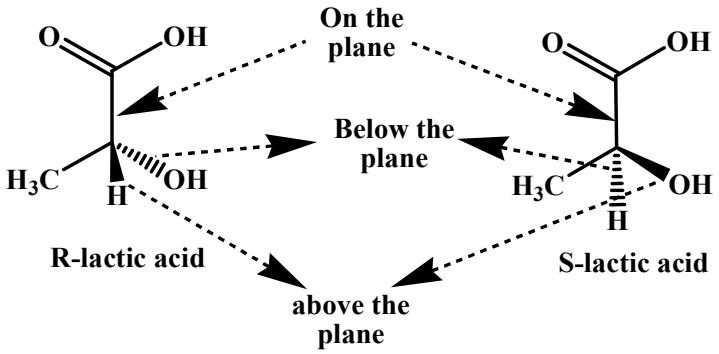


Sawhorse representation formula of butane

4.10 FISCHER AND FLYING WEDGE FORMULA

The sp^3 hybridized tetrahedral carbon is three dimensional in nature. Generally it is very difficult to represent a three dimensional structure in a two dimensional plane paper. There are many methods have been developed for two dimensional representation of a three dimensional structure. Out of them the flying-wedge and Fischer representation methods are most commonly used for two dimensional representation of a three dimensional structure.

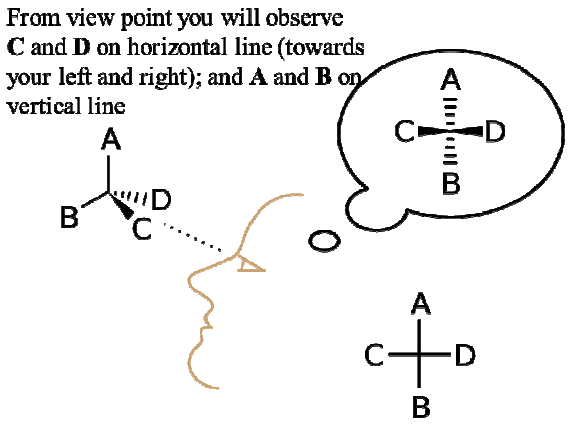
The flying-wedge: This is the most commonly used model for the two dimensional representation of a three dimensional molecule. In this model the bonds are presented in continuous, solid thick and dashed lines. A solid this line represents a bond projecting above the plane of the paper; it is considered that the bond with solid thick line is pointing towards observer. A dashed line represents a bond below the plane of the paper; it is considered that the bond with dashed line is pointing away to the observer. The bonds with continuous lines represent the bonds in the plane of paper. Let us consider an example of *R*-Lactic acid and *S*-Lactic acid.



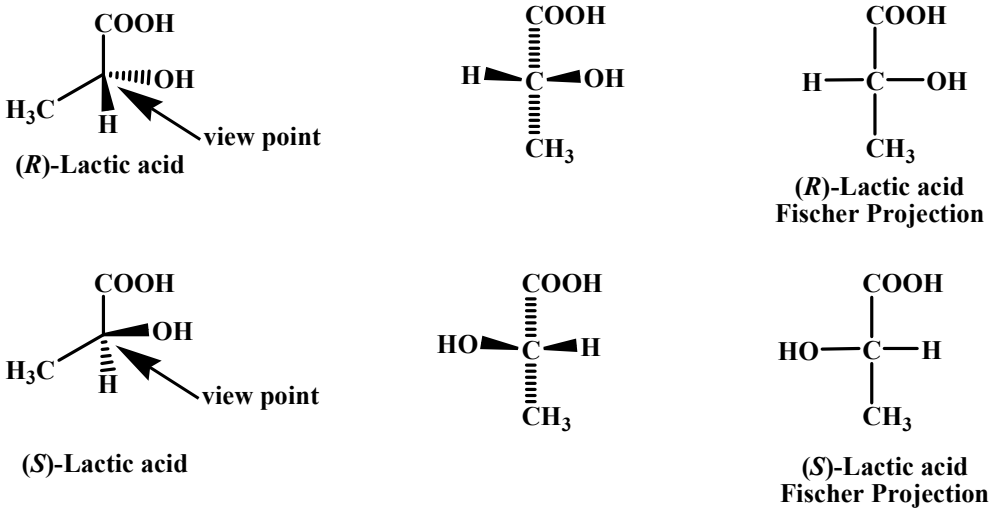
Flying-wedge representation of *R*- and *S*-Lactic acid

Fischer projection formula: It is a simplification of flying-wedge representation, in Fischer projection formula all bonds are drawn as solid lines in a plane paper. Fischer Projections are used often in drawing sugars and hydrocarbons, because the carbon backbone is drawn as a straight vertical line, making them very easy to draw. When properly laid-out, Fischer Projections are useful for determining enantiomeric or diastereomeric relationships between two molecules, because the mirror image relationship is very clear. In a Fischer Projection, each place where the horizontal and vertical lines cross represents a carbon. The vertical lines are actually oriented away from you (similar to dashes in the Wedge-Dash Notation) and the horizontal lines are oriented toward you (similar to wedges in the Wedge-Dash Notation).

Fischer projection is not as demonstrative as flying –wedge representation. It does not represent the actual shape of the molecule. Usually the Fischer projection formula is drawn so that the longest carbon chain in the molecule is vertical with the highly oxidized group on the top.



Let us consider an example for conversion of flying-wedge formula to Fischer projection formula for *R*- and *S*- Lactic acid.



Conversion of flying wedge to Fischer projection formula for Lactic acid

4.11 RACEMIC MIXTURE (RACEMATES)

A Racemic mixture is an equimolar mixture of a pair of enantiomers. The racemic mixture or racemates are optically inactive due to mutual or external compensation of two enantiomeric constituents. Racemic mixture in liquid and vapor phase shows physical properties (like boiling points, density, refractive index etc.) identical to those of pure enantiomers. However, the solid phase enantiomeric mixtures have some properties different from the pure enantiomers.

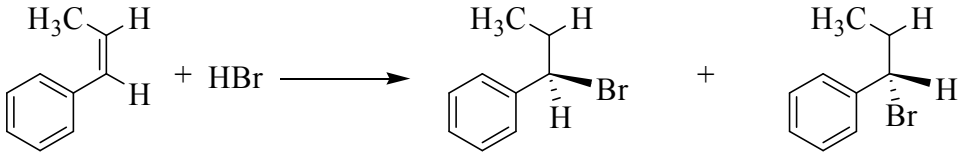
i. ***Remember:*** *Racemic mixture is not a meso compound; since both are optically inactive. The racemic mixture is an equimolar mixture of two enantiomers whereas meso is a single compound. Meso compounds are optically inactive because of the internal compensation; however, the racemic mixtures (racemates) are optically inactive because of the external compensation.*

You might have aware with that the enantiomerically pure compounds are of great importance in chemical and pharmaceutical areas. But during the synthesis of optically active compounds using achiral reaction condition and achiral reagents, it always gives racemic mixture (racemates). Therefore to obtain the pure enantiomers we must have to separate the racemic mixture in to corresponding pure enantiomers. Thus, the separation process of a racemic mixture in to its pure

individual enantiomeric constituents is called resolution of racemic mixtures (resolution of enantiomers).Since enantiomers have identical physical properties(like solubility, boiling point, melting point, density, refractive index etc.),therefore, they cannot be separated by common physical techniques such as direct crystallization, distillation or basic chromatography. There are four general methods that are extensively being used for the resolution of racemic mixtures.

i. Mechanical separation (crystallization method) method
ii. Diastereomer formation method
iii. Chromatographic method
iv. Biochemical/enzymatic methods

Example 27: The addition of HBr on *beta*-Methyl styrene gives an equimolar mixture of enantiomers.

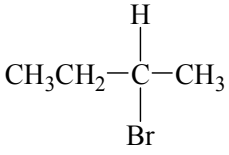


beta-Methyl styrene | 50% *S* enantiomer | 50% *R* enantiomer

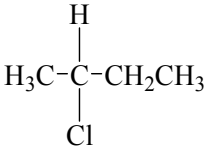
4.12 QUASI-ENANTIOMERS

Quasi enantiomers are defined as, two different chemical compounds those are closely related to the sense of chirality. Although chemically different, they are sterically similar (isosteric) and are still able to form a racemic crystalline phase. One of the compound have a property to rotate the plane polarized light towards left hand direction; whereas, the other have a tendency to rotate the plane polarized light towards right hand direction. The first quasi-enantiomeric pair was studied by Pasteur in 1853.

Example 28: (*R*)-2-bromobutane is a quasi-enantiomer of (*S*)-2-chlorobutane.



(R)-2-Bromobutane

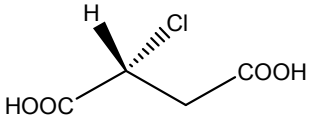


(S)-2-Chlorobutane

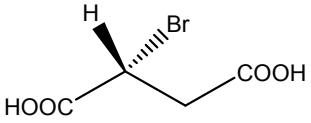
4.13 QUASI-RACEMATE

Quasi-racemate is defined as a 1:1 mixture of quasi-enantiomers that may form a compound, a eutectic mixture, or a solid solution and shows typical compound behaviour in the phase diagram.

Example 29: Equimolar mixture of (+)-Chlorosuccinic acid and (+)-Bromosuccinic acid form a quasi-racemate and shows eutectic behaviour similar to that of a conglomerate.



(*R*)-2-chlorosuccinic acid



(*R*)-2-bromosuccinic acid

4.14 STEREOCHEMISTRY OF ALLENES, SPIRANES; BIPHENYLS, ANSA COMPOUNDS CYCLOPHANES AND RELATED COMPOUNDS

In above sections of this unit we have discussed about the compounds containing one or more stereocentres and their chirality is specified at these centres. However, there are a class of compounds with nonsuperimposable mirror images it is not possible to identify a stereocentre, then to predict the stereochemistry of such compounds it becomes necessary to focus our attention on other aspects of the molecule. Thus, the presence of stereocentre is not a necessary and sufficient condition for molecular dissymmetry. The overall chirality of a molecule can be categorised in to three elements; i) stereocentres; ii) stereoaxes; and iii) stereoplanes, one other element of chirality is still there and called helicity.

Chirality due to axes (Axial chirality): Such type of chirality is produced in a molecule when there is no chiral centre present in the molecule. As discussed, in order to produce chirality it is not necessary for all of the substituents to be different. However, it is sufficient to have each substituent different from its nearest neighbour.

When four atoms/groups attached to a central atom are located on the corners of tetrahedron the central atom is termed as chiral centre. If the chiral centre is replaced by a linear grouping like C-C or C=C=C, the tetrahedron geometry get extended along the axis of the grouping and thus generates a chiral axis. Depending on the nature of groups attached with the carbon atoms, some examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes, adamentanes etc.; are shown below (Figure 3).

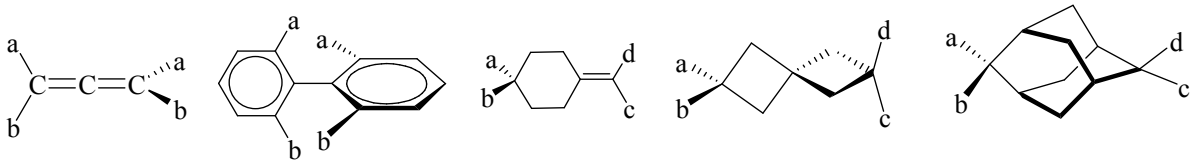


Figure: 3 examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes and adamentane

Allenes: Allenes are compounds with two or more double bonds side-by-side. Such bonds are called *cumulated double bonds.* The central carbon of allene forms two sigma bonds and two pi bonds. The central carbon is *sp*-hybridized and the two terminal carbons are sp^2-hybridized. The two π-bonds attached to the central carbon are perpendicular to each other. The geometry of the π-bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes (Figure 4). The bond angle formed by the three carbons is 180°, indicating linear geometry for the carbons of allene.

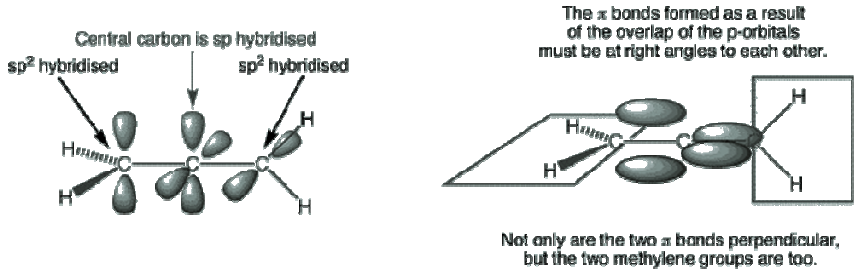
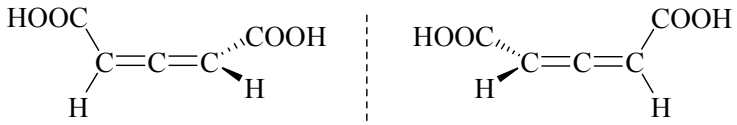


Figure 4: Planar depiction of allene molecule

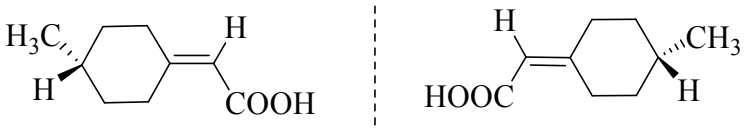
Stereochemistry of Allenes: When three or more adjacent carbon atoms in a molecule are bonded by double bonds, the compounds is called cumulene or said to have cumulative double

bonds. Allene is the simplest example of this class. Allenes are chiral and they have nonsuperimposable mirror images and exist as enantiomers although they have no chiral centre.



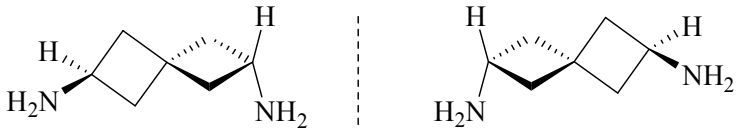
Nonsuperimposable Mirror images
(Enantiomeric Pair)

Stereochemistry of Alkylidenecycloalkanes: The replacement of double bonds in allene by a cycloalkane ring gives the alkylidenecycloalkane; such replacement does not change the basic geometry of the molecule. The suitably substituted alkylidenecycloalkanes also exhibit enantiomerism. The enantiomerism in such compounds is also due to the presence of chiral axis. For example, 4-methylcyclohexyldene acetic acid has been resolved into two enantiomers.



4-methylcyclohexyldene acetic acid

Stereochemistry of Spiranes: When both the double bonds in allenes are replaced with the ring system the resulting compounds are known as *spiranes* or *spiro* compounds. The conditions for chirality in spiranes are similar to those of allenes. The two rings of spiranes are perpendicular to each other; therefore, proper substitution on the terminal carbon will make the molecule chiral and thus exhibit enantiomerism. The chirality in the spiranes is also due to the presence of chiral axis. For example, Diaminospiroheptane can be resolved in to its enantiomers.



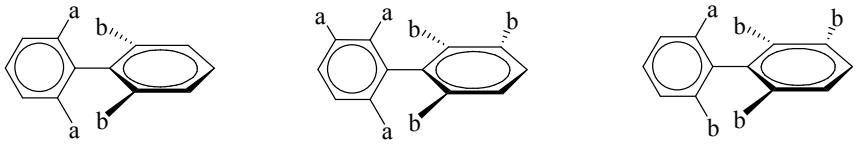
Diaminospiroheptane

Stereochemistry of Biphenyls: Stereoisomers obtained due to the restricted rotation about carbon-carbon single bond are called atropisomers and the phenomenon is called atropisomerism. Such compounds also have the chirality due to the axis. Suitably substituted biphenyls exhibit enantiomerism due to the presence of chiral axis. This enantiomerism arises

due to atropisomerism *i.e.* restricted rotation around C-C bond between two phenyl rings. This steric hindrance of substituents at *ortho*- position of the each ring is responsible for such restricted rotation. To maintain the maximum stability, molecule orients itself in such a manner so that both the *ortho*- substituted phenyl rings lie in different plane.

Biphenyl shows the enantiomerism when the molecule has the following properties.

a) Each ring must be unsymmetrically substituted. Each of the rings should not contain any kind of symmetry element.



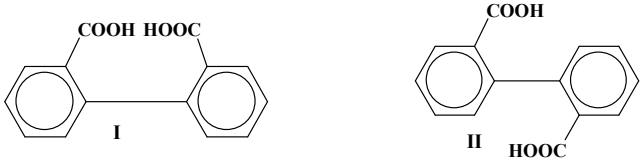
nonresolvable Biphenyl (optically inactive due to plane of symmetry)

resolvable Biphenyls (optically active due to absence of symmetry elements)

b) Suitable substitution (at least one substitution) at *ortho*- position must be there at each rings.

c) *othro*- substituents must be larger in size (-Cl, -Br, -I, -COOH, -NO_2, -$NHCOCH_3$, -SO_3H, -R groups etc.).

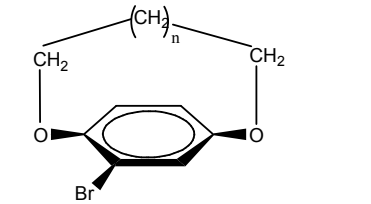
The smaller groups at *othro*- position make the compounds planar in nature and thus do not exhibit atropisomerism.



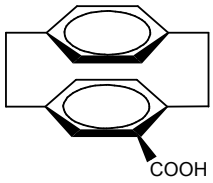
nonresolvable Biphenyl (optically inactive due to plane of symmetry)

nonresolvable Biphenyl (optically inactive due to centre of symmetry)

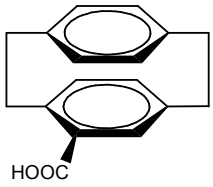
Chirality due to Plane (Planar Chirality): Chirality shown by a molecule due to the asymmetry in molecular plane is called chirality due to plane. The chirality is particularly due to the out of the plane arrangement of atoms or groups in the molecule with respect to reference plane, hence called chiral plane. The most important example of the molecule with chiral plane is cyclophanes. Other examples are trans-cyclooctene, bridged annulenes and metallocenes etc.



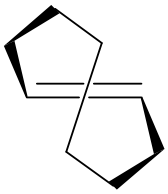
Polymethylene ether of hydroquinone



paracyclophane (*S*)-



paracyclophane (*R*)-



***trans*-cyclooctene**

The polymethylene bridge is perpendicular to the plane of the benzene ring; the substituent Br restricts the rotation of the benzene nucleus inside the methyl bridge, that makes the molecule chiral. Similarly the simple paracyclophane can be resolved because the benzene ring cannot rotate in such a way that the carboxylic passes through the acyclic ring. The plane of both the aromatic rings is approximately parallel to each other. Similarly the *trans*-cyclooctene also exhibits the chirality due to the presence of chiral plane.

4.15 SUMMARY

- The stereochemistry, determines many chemical, physical and biochemical properties of the compounds.
- The types of stereo-chemical situations are divided into classes called geometrical isomers, conformational isomers and configurational isomers.
- All of the isomers are studied as a way to understand the shapes and properties of organic compounds.
- Alkenes and cyclic compounds display geometrical isomers.
- In alkenes, geometrical isomers are labeled as *cis*- or *trans*- for the longest chain in the alkene, or as *E* and *Z* for substituents of higher priority attached to the alkene.
- Cyclic alkanes are designated only as *cis*- or *trans*-.
- Stereochemistry is all about the 3Dimensional spatial aspects of chemistry.
- Molecules that differ only in the arrangement of bonds in 3Dimensional space are called "stereoisomers"

- Many objects (including molecules) are non-differentiable from their mirror images, but other objects, such as your left and right hands, are differentiable. An object that has a non-superimposable mirror image is said to be "chiral" (Greek = "handedness") and one that has a superimposable mirror image is called "achiral".
- Pairs of molecules that are non-superimposable mirror images of each other are called "enantiomers"
- The most common type of "chirality" is observed when a carbon atom has four different groups attached to it. This carbon atom is then described as a chiral or asymmetric or stereogenic center. This later term can also be contracted to a stereocenter.
- Enantiomers have the same chemical and physical properties (melting points, boiling points, heat of combustion etc.), except for their interaction with plane polarized light or with other chiral molecules (reagents, solvents, catalysts, etc). (Think about how your feet feel if you put them in the wrong shoes).
- Diastereomers are stereoisomers that are not enantiomers.
- The differing interaction with plane polarized light gives rise to optical activity. Enantiomers cause the plane of polarized light to rotate in opposite directions, but to the same extent (clockwise = +ve, counterclockwise = -ve). This can be measured using a polarimeter. An achiral molecule is optically inactive.
- A 50:50 mixture of a pair of enantiomers is called a racemic mixture. This is optically inactive since the rotations produced by each of the enantiomers must cancel each other out.
- If there is more of one enantiomer than the other, then the optical purity of a sample can be determined by measuring the rotation and comparing it to that of a pure enantiomer. This can be used to establish the enantiomeric excess (ee) of the mixture.
- Despite what one may observe, most molecules are not 2D objects, they are 3D as a result of the spatial arrangement of the atoms, groups and bonds. The interaction of molecules (reactions) which occur as the result of collisions between these 3D objects in 3D spacecan therefore also have 3D requirements and characteristics. Stereochemistry is all about the 3D properties of molecules and reactions.

4.16 TERMINAL QUESTION

1. What do you understand by Isomerism? Give its types.
2. What is chirality? Explain the necessary condition for a molecule to be chiral.
3. What do you understand by optical activity? How is it measured?
4. What are enantiomers and diastereomers?
5. What are symmetry elements? How they affect optical isomerism?
6. Explain relative and absolute configuration.
7. What is racemization?

4.17 ANSWERS

Ans.1. When two or more compounds having the same molecular formula but difference in their chemical and/or physical properties are called isomers and the phenomenon is known as isomerism. Isomerism has following types:

a. Structural (constitutional) Isomerism
b. Stereo (configurational) Isomerism

Ans. 2. An organic compound with four different atoms/groups attached to center carbon and have non-superimposable mirror image is called chiral compound and the phenomenon is called chirality. The presence of four different atoms/groups attached to center carbon and absence of any kind of element of symmetry are the necessary condition for a molecule to be chiral.

Ans. 3. The tendency of an organic compound to rotate the plane polarized light towards left or right hand direction is called optical activity. Optical activity of any compound is measured by analyzing the sample in an instrument called **Polarimeter.** A solution of known concentration of optically active compound is when exposed to the beam of plane polarized light, the beam of plane polarized light is rotated through a certain number of degrees, either to the clockwise (right) direction or anti-clockwise (left) direction. The compound which rotates the plane polarized light towards clockwise direction is called to be **dextrorotatory** (represented by +);whereas, the compound which rotates the plane polarized light towards anti-clockwise direction is called to be **levorotatory** (represented by -).

Ans. 4. Optically active chiral compounds that are non-superimposable mirror image of each other are called enantiomers. Whereas, optically active compounds which are non-mirror image of each other are called diastereomers.

Ans. 5. Elements of symmetry are a simple tool to identify whether a molecule is chiral or not. The necessary condition for optically active molecule to be chiral is that, the molecule should not possess any kind of symmetry elements. The elements of symmetry are generally categorized as follows:

(i) Simple axis of symmetry (C_n)
(ii) Plane of symmetry (σ)
(iii) Centre of symmetry (C_i)
(iv) Alternating axis of symmetry (S_n)

Optically active compound should not have any kind of symmetry elements.

Ans.6. Relative and absolute configuration of a compound discusses about the spatial arrangement of atoms/groups around the centre chiral atom. Relative configuration is a comparison of the spatial arrangement of attached atoms/groupsof two different chiral centres. Relative configuration is a geometrical property which do not changes on reflection. The absolute configuration is the precise arrangement of atoms in space. The *D/L* system is usually known as relative configuration whereas, the *R/S* stereo descriptor or nomenclature system for chiral molecules is known as absolute configuration. The absolute configuration is a topographic property which changes on reflection.

Ans.7. The process of conversion of an optically active compound in to the racemic mixture/racemate is called *racemization*. The racemization process may take place under the influence of temperature, light or chemical reagents.

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Following books are referred for compiling the material of present unit.

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2. Organic Chemistry by T. W. Graham Solomons, Published by John Wiley; ISBN-10: 1118133579.
3. Stereochemistry of Organic Compounds by Ernest L. Eliel; Published by John Wiley; ISBN- 0-471-01670-5
4. Organic Chemistry by Leroy G. Wade. Published by Pearson Education; ISBN-9780321768414
5. Stereochemistry: Conformation and Mechanism by P. S. Kalsi. Published by New Age International Publication. **ISBN**-10: 8122435645;**ISBN**-13: 978-8122435641
6. Stereochemistry of Organic Compounds: Principles and Applications by D Nasipuri, Published by New Academic Science ISBN-10: 190657491X; ISBN-13: 978-1906574918

UNIT 5: STEREOCHEMISTRY-II

CONTENTS

5.1 OBJECTIVES

In this unit learner will be able to

- Define prochiral property of an achiral molecule
- Differentiate between two similar atoms or groups attached with a prochiral center
- Learn about the homotopic, heterotopic, enantiotopic and diastereotopic ligands and faces
- Define stereospecific and stereoselective synthesis
- Learn about the principle of asymmetric synthesis
- Learn about the various conformations of cyclohexanes and decalins
- Know about the stereochemistry of compounds containing N, P and S

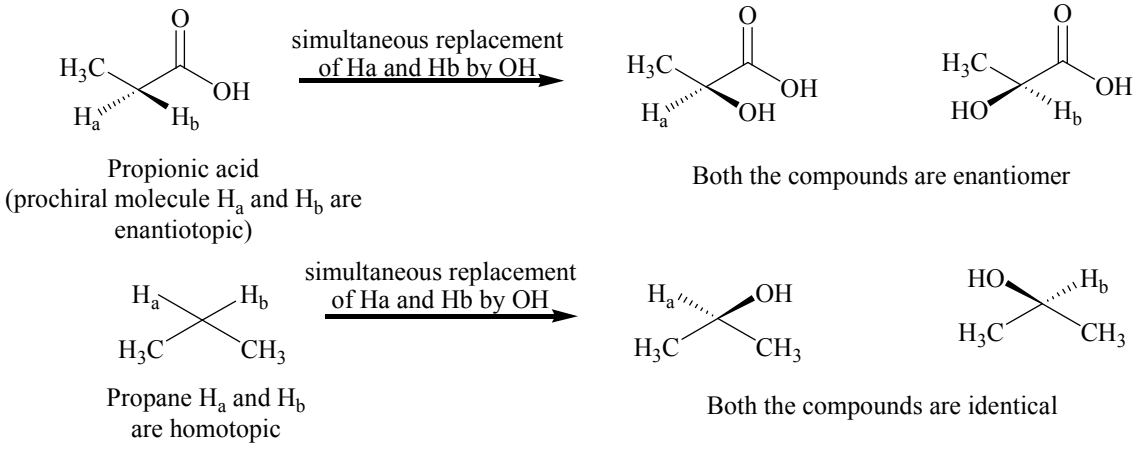
5.2 INTRODUCTION

Stereochemistry is a sub-discipline of chemistry that involves the study of the relative spatial arrangement of atoms. The study of stereochemistry focuses on stereoisomers, which by definition have the same molecular formula and sequence of bonded atoms (constitution), but differ in the three-dimensional orientations of their atoms in space. For this reason, it is also known as 3D chemistry-the prefix "*stereo*-" means "*three-dimensionality*". Stereochemistry includes methods for determining and describing these relationships; the effect on the physical or biological properties these relationships impart upon the molecules in question, and the manner in which these relationships influence the reactivity of the molecules in question (dynamic stereochemistry). Thus stereochemistry is all about the 3D properties of molecules and reactions and has its own language and terms that need to be appreciated.

5.3 *TOPOCITY*

Stereo-chemical relationships between individual atoms or groups within a single molecule can be defined in terms of topicity. Thus, two atoms equated by a mirror reflection of the molecule are enantiotopic and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are homotopic. Two protons placed in diastereomeric positions by a mirror reflection are in diastereotopic environments.

Examples 1: Propane has homotopic ligands; however, propionic acid has enantiotopic ligands

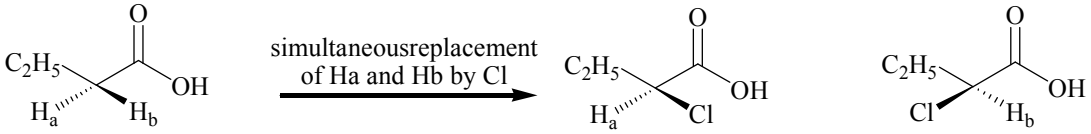


5.3.1 PROCHIRAL CENTER AND PROCHIRAL MOLECULE:

As we discussed in Unit 4 (Stereochemistry I) of this module; a tetrahedrally bonded atom with four different atoms or groups (**Cabcd**) is called a chiral molecule. However, a tetrahedrally bonded atom with two identical atoms or groups (**Cabbc**) is called an achiral molecule.

If replacement of one of the identical groups in an achiral molecule of type **Cabbc** with a different group when gives an asymmetric molecule then the achiral center is called prochiral center and the molecule is called prochiral molecule. This property is called prochirality.

Example 2: Propionic acid is a prochiral molecule with centre carbon atom as prochiral centre. Replacement of one of the hydrogen atom by a different group gives the optically active compound.



Butanoic acid
(prochiral molecule H_a and H_b are enantiotopic)

Both the compounds are enantiomer

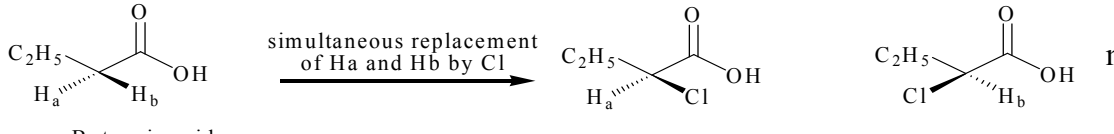
5.3.2 HOMOMORPHIC LIGANDS:

Two apparently identical atoms/groups of a prochiral centre are called homomorphic atoms/groups. These are also known as homomorphic ligands. Homomorphic is a Greek name where *homos* meaning similar and *morphe* meaning form. Thus two homomorphic ligands are indistinguishable during their isolation. Two hydrogen atoms of Propionic acid are apparently identical groups *i.e.* H atoms of methylene group are called homomorphic atoms or ligands.

5.3.2 STEREOHETEROTOPIC LIGANDS:

Consider two molecules, Butanoic acid in which two identical hydrogen atoms attached with methylene carbon, and 2-butanol in which two identical hydrogen atoms of methylene carbon. Replacement of any one of the homomorphic ligands in butanoic acid will give a pair of enantiomer; however, replacement of any one of the homomorphic ligands in 2-butanol will give the formation of two diastereomers. Since enantiomers and diastereomers are stereoisomers therefore the homomorphic groups or ligands are also called stereoheterotopic groups or ligands.

Example 3: Stereoheterotopic ligands (H_a and H_b) of **butanoic acid** and **2-butanol**. Simultaneous replacement of H_a and H_b in both the compounds leads the formation stereoisomers.



Butanoic acid
(prochiral molecule H_a and H_b are enantiotopic)

Both the compounds are enantiomer

2-butanol

Both the compounds are diastereomers

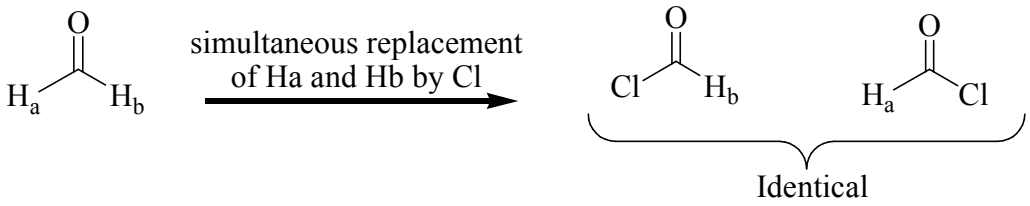
5.3.4 PROCHIRALITY:

It is the property of some molecules due to which these molecules can be converted in to stereoisomers (enantiomers or diastereomers) by replacing one of the identical atoms or groups by a different atom or group. It is also known as '*prostereoisomerism'* more specifically. If the replacement of such atoms or groups leads the formation of enantiomer the atoms or groups are called enantiotopic; whereas, if such replacement lead the formation of diastereomers the atoms or groups are termed as diastereotopic.

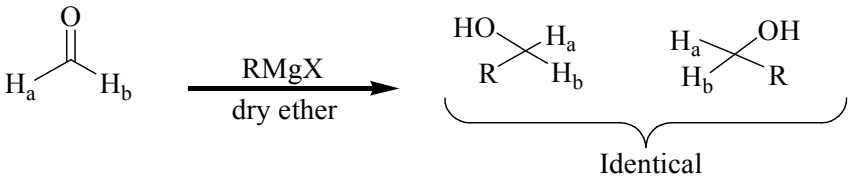
5.3.5 HOMOTOPIC LIGANDS AND FACES:

When replacement of two H atom in a methylene carbon of a molecule generates two identical compounds instead of stereoisomers, these two hydrogen atoms are called homotopic ligands.

Example 4: Let us consider the case of formaldehyde, the two hydrogen atoms of formaldehyde when replaced with a different atom or group generates two identical compounds hence both the hydrogen atom of formaldehyde molecules are homotopic atoms or homotopic groups.

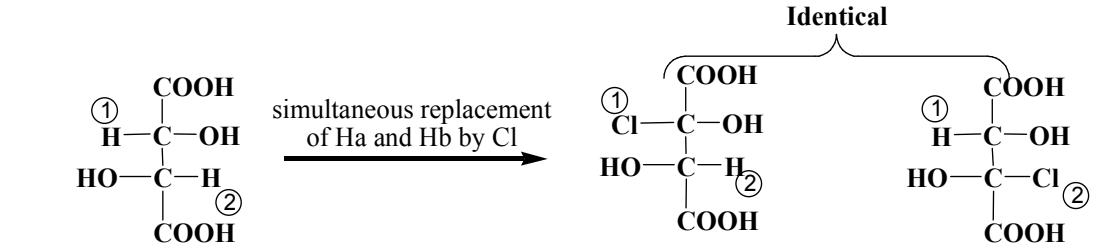


Example 5: Similarly there is no way to differentiate between the two faces of formaldehyde molecule. The addition of Grignard reagent RMgX to either faces gives the identical compound ethanol. Hence, two faces of formaldehyde are also homotopic faces.

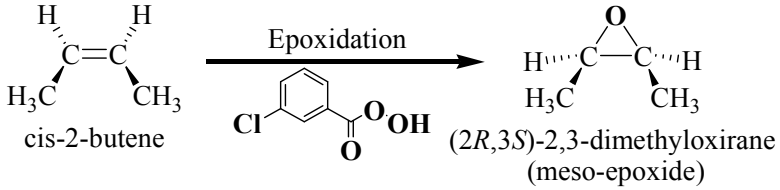


Substitution/addition and symmetry are the two key criteria to determine the topicity of homomorphic ligands and faces. Two homomorphic ligands are called homotopic if replacement of each one of them by another atom or group leads to the identical structure. Thus we can consider three hydrogen atom of acetic acid as homotopic hydrogen, similarly three hydrogen of toluene are also called homotopic hydrogen, because replacement of each one of them will lead the same structure.

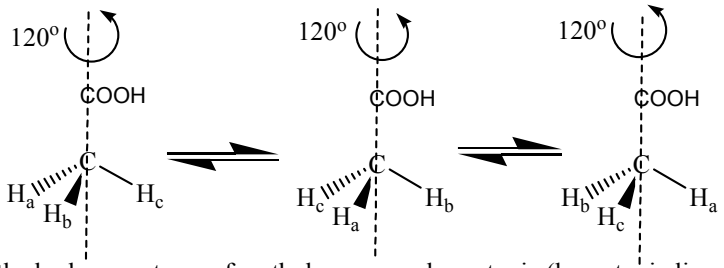
Example 6: In (2*R,3R*)-2,3-dihydroxytartaric acid two homotopic hydrogen atoms are present; replacement of each one of them by a different atom gives identical compounds.



Example 7: In a double bonded compound like cis-2-butene, two faces of double bond are homotopic since addition on either faces gives the same product. The epoxidation of double bond on either face gives meso product [(*2R,3S*)-2,3-dimethyloxirane].

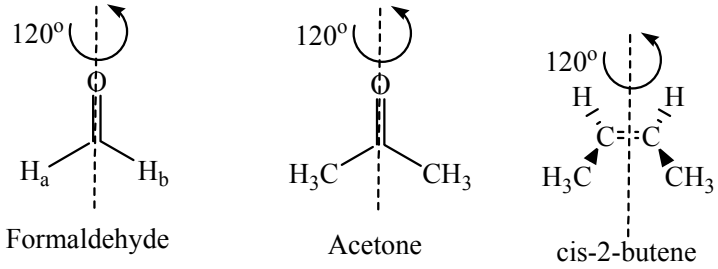


Homotopic ligands and faces can also be determined by employing symmetry operations on the molecule. Let us consider an example of acetic acid, in which all three hydrogen atom of methyl group are homotopic. Two successive rotation of methyl group around its C_3 axis (with the rotation angle of 120°) allow each hydrogen atom to occupy the position of either of the other two hydrogen atoms without effecting any structural changes. As we know that hydrogen atom of methyl group interchanges their position rapidly in 3 dimensional planes, due to this rapid interchange of hydrogen atoms of methyl group leads the formation of indistinguishable structure, that's why these hydrogen atoms are called homotopic hydrogen (homotopic ligands).



All the hydrogen atoms of methyl group are homotopic (homotopic ligands)

Similarly, both the faces of cis-2-butene, formaldehyde and symmetrical ketones are homotopic, hence called homotopic faces.



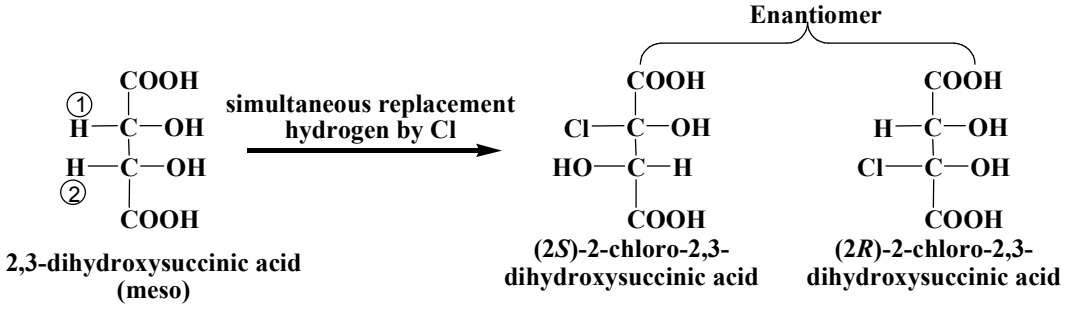
Homotopic Faces

☞ ***Remember:*** *A molecule contains two equivalent atoms/groups they would not be homotopic if the other two groups are different. Such molecules are known as prochiral molecule.*

5.3.6 ENANTIOTOPIC LIGANDS AND FACES:

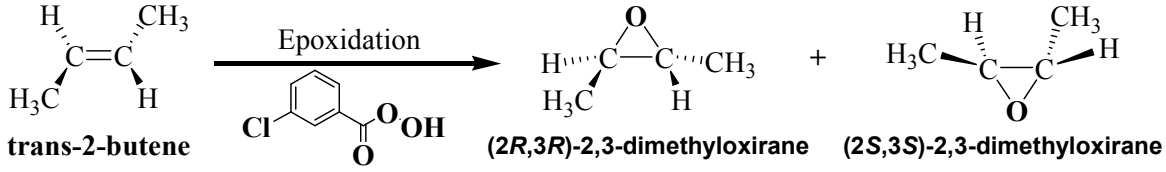
When the replacement of each equivalent atom or groups by a different atom given enantiomeric products, such equivalent atoms or groups are called enantiotopic atoms or enantiotopic ligands.

Example 8: For example, two hydrogen atoms of meso-tartaric acid are enantiotopic since the replacement of each one of them by a different atom or group gives the enantiomeric pair of (*2S*)-2-chloro-2,3-dihydroxysuccinic acid and (*2R*)-2-chloro-2,3-dihydroxysuccinic acid.

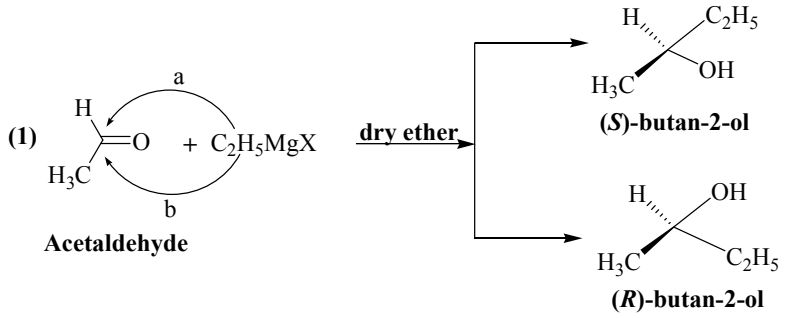


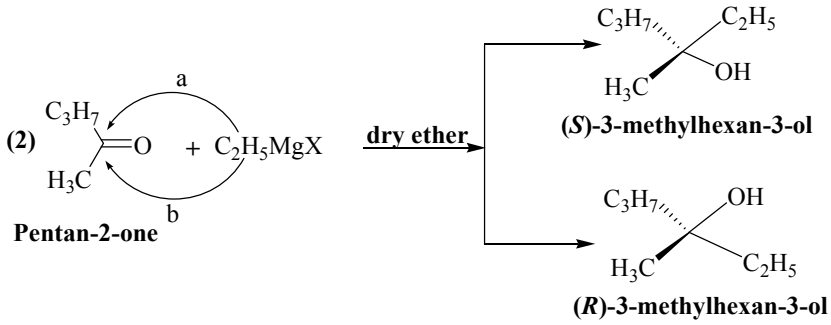
Similarly, when two faces of a double bond gives enantiomers on addition of suitable reagents, such faces are called enantiotopic faces. For example, trans-2-butene and unsymmetrical ketones have enantiotopic faces since they also give enantiomers on addition of suitable reagents.

Example 9: Epoxidation of trans-2-butene on either face of double bonds gives the enantiomeric pair of (*2R,3R*)-2,3-dimethyloxirane and (*2S,3S*)-2,3-dimethyloxirane.



Example 10: Similarly, addition of the Grignard reagent (RMgX; R=C_2H_5) or other organometallic reagents on either faces of unsymmetrical carbonyl compounds gives enantiomers. Hence, faces 'a' and 'b' of acetaldehyde **(1)** and Pentan-2-one **(2)** are called enantiotopic faces.



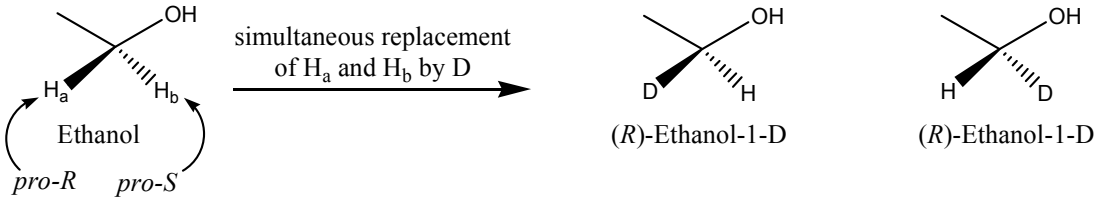


Unlike homotopic ligands and faces, enantiotopic ligands and faces cannot be interchanged by a simple axis of symmetry (C_n). However, they can be interchanged by plane of symmetry, center of symmetry (i) and alternative axis of symmetry (S_n).

5.3.7 NOMENCLATURE OF ENANTIOTOPIC LIGANDS AND FACES:

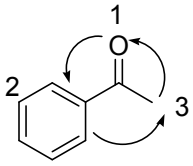
Naming of enantiotopic ligands and faces is based on the CIP sequence rule by arbitrarily assigning priority to the homomorphic groups/ligands/faces.

Example 11: Let us consider ethanol with two homomorphic ligands (H_a and H_b). If H_a is arbitrarily preferred over H_b in the sequence rule, the priority order of the attached groups at central carbon will be OH>CH_3> H_a> H_b and the hypothetical configuration of the stereocenter will be R, thus H_a is designated as *pro-R* and H_b is designated as *pro-S.* Similarly, if H_b was arbitrarily given higher priority over H_a in that case according to sequence rule priority order would have been OH>CH_3> H_b> H_a and the hypothetical configuration of ethanol would be S, thus H_b is designated as *pro-S* and H_a is designated as *pro-R.* Replacement of H_a by deuterium 'D' gives (*R*)-ethanol-1-*D*, hence, H_a is *pro-R;* similarly, replacement of H_b by D gives (*S*)-ethanol-1-*D*, hence, H_b is *pro-S*.

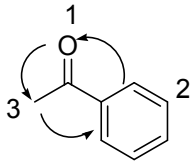


Similalry, two faces of carbonyl carbon are termed as enantiotopic faces. These faces can be designated as *Re-Si* nomenclature. The groups around the carbonyl group are given priorities as

per CIP sequence rule for R and S nomenclature. While going from the highest priority group to the lowest priority group around the faces of carbonyl group, if the path followed is clockwise the faces is *Re* and if it is anticlockwise, the face is *Si*.



Si-face

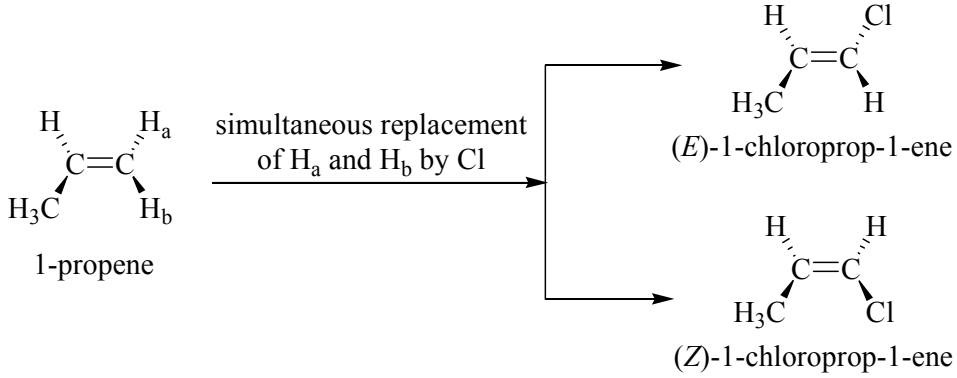


Re-face

5.3.8 DIASTEREOTOPIC LIGANDS AND FACES:

When the replacement of either of two homomorphic ligands or atoms of a molecule by a different atom generates diastereomers, such homomorphic ligands or atoms are called diastereotopic ligands or atoms.

Example 12: Let us consider an example of propene in which two homomorphic hydrogen are present. Replacement of one of the homomorphic hydrogen with a hetero atom Cl gives *Z*-alkene ((*Z*)-1-chloroprop-1-ene) while replacement of other homomorphic hydrogen atom by Cl generates *E*-alkene ((*E*)-1-chloroprop-1-ene). Both, (*Z*)-1-chloroprop-1-ene and (*E*)-1-chloroprop-1-ene are stereoisomer but non mirror image of each other, hence are called diastereomer. Thus, two hydrogen atoms (*i.e.* H_a and H_b) of 1-propene are diastereotopic.



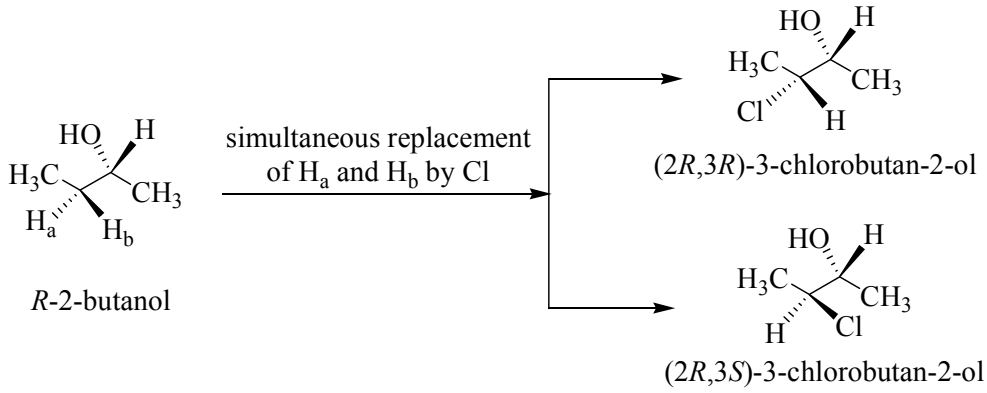
1-propene

(*E*)-1-chloroprop-1-ene

(*Z*)-1-chloroprop-1-ene

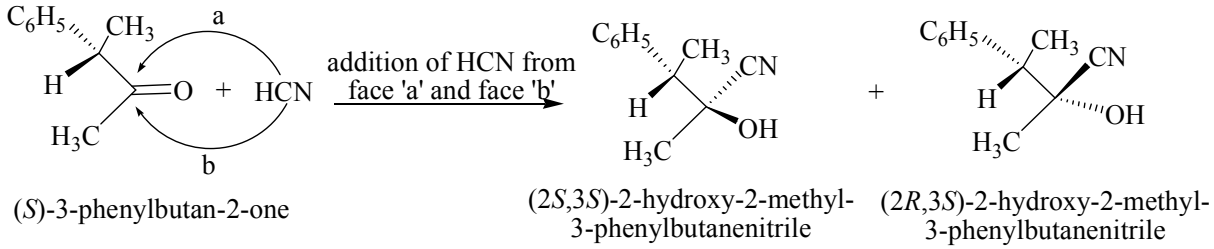
Example 13: Consider another interesting example of *R*-2-butanol with a stereocenter at C1 and two homomorphic hydrogen atoms (H_a and H_b) at C2. Replacement of H_a leads to the formation

of (*2R,3R*)-3-chlorobutan-2-ol, and replacement of H_b leads the formation of (*2R,3S*)-3-chlorobutan-2-ol. Therefore, these two products are diastereomers, and the two protons (H_a and H_b) of *R*-2-butanol are diastereotopic.

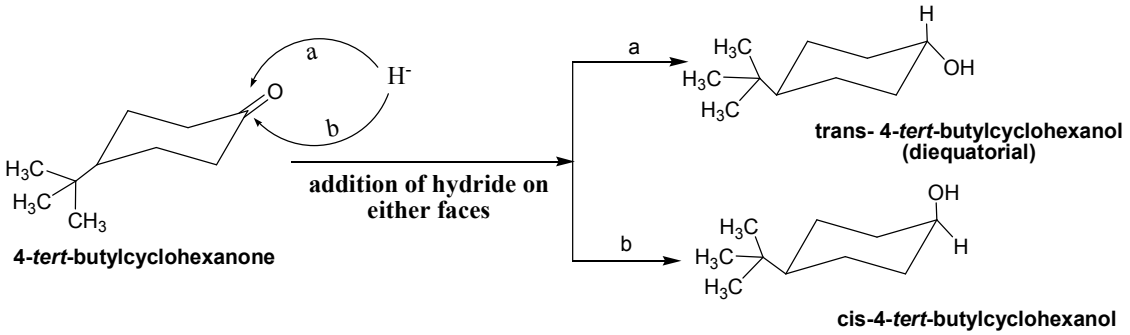


The two faces of carbonyl group next to a stereocenter are diastereotopic. Since, addition of reagents (like HCN, RMgX, HCl etc.) from either faces gives diastereomers. Thus, two faces of such carbonyl group are termed as diastereotopic faces.

Example 14: For example, let us consider addition of HCN to the either faces of carbonyl group of (*S*)-3-phenylbutan-2-one leads to the formation of, (*2S,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile and (*2R,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile, a pair of diastereomers.



Example 15: Similarly, consider another example of 4-*t*-butylcyclohexanone in which addition of hydride on either faces of carbonyl group leads the formation of *trans*- and *cis*- 4-*t*-butylcyclohexanol (diastereomers). Thus two faces of 4-*t*-butylcyclohexanone are diastereotopic faces.



The addition of hydride on either faces of 4-*t*-butylcyclohexanone gives two diastereomers (achiral) products. Hence, the carbonyl carbon is considered as prostereo center rather than prochiral center.

5.4 *ASYMMETRIC INDUCTION*

Before 1940, the optically active compounds could be obtained in stereoisomerically pure form only by isolation of racemic mixture of optically active compounds from natural products and their subsequent enzymatic resolution. Since, equimolar amount of enantiomers (racemic mixture) is obtained when a prochiral molecule undergoes reaction in the absence of chiral environment. As we know the physical and chemical properties of enantiomers are always same in the absence of a chiral environment. However, enantiomers have entirely different reactivities in biological system.

Asymmetric induction is a stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment. This is also known as asymmetric synthesis. The chiral agent must play an active part in the asymmetric induction. Such chiral agent has an important role in the formation of transition state.

The direct synthesis of an optically active substance from optically inactive compound with or without the use of any optically active compound is called asymmetric synthesis. In general asymmetric synthesis can also be defined as *the synthesis which converts a prochiral unit in to a chiral unit and formation of unequal amount of stereoisomers.*

5.4.1 PRINCIPLE OF ASYMMETRIC SYNTHESIS:

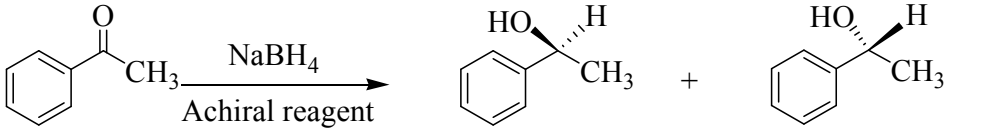
There are three principle of asymmetric synthesis

a) The substrate molecule must be prochiral *i.e.* the substrate must have either enantiotopic or diastereotopic ligands or faces.

b) There must be presence of chirality in the reaction/asymmetric transformation for the preferential formation of one stereoisomer over the other. Either the substrate, or the reagent, or the solvent, or the catalyst must be enantiomerically pure.

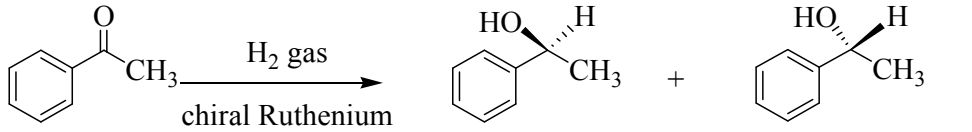
c) The chiral agent must play an important role in the reaction and must involve in the formation of two diastereomeric transition states.

Example 16: Let us consider hydrogenation of Acetphenone by sodiumborohydride ($NaBH_4$). Since, both the reagent and substrate are achiral (optically inactive) and also the reaction takes place in the medium of methanol (achiral), hence, equal amount of (*R*)-1-phenylethanol and (*S*)-1-phenylethanol (racemic mixture) is formed.



Acetophenone (Achiral) | (*S*)-1-phenylethanol 50% | (*R*)-1-phenylethanol 50%

Example 17: However, when the above reaction is allowed to proceed in the presence of a chiral reagent the (*S*)-1-phenylethanol is formed preferentially over (*R*)-1-phenylethanol.



Acetophenone (Achiral) | (*S*)-1-phenylethanol **97.5 *ee*** | (*R*)-1-phenylethanol **2.5 *ee***

Some more example of asymmetric synthesis in presence of chiral reagents is shown in figure 1.

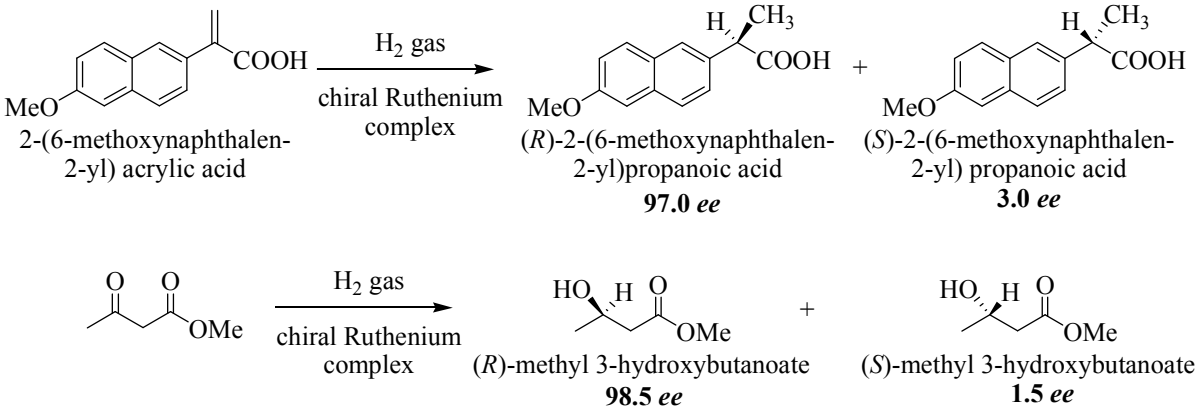
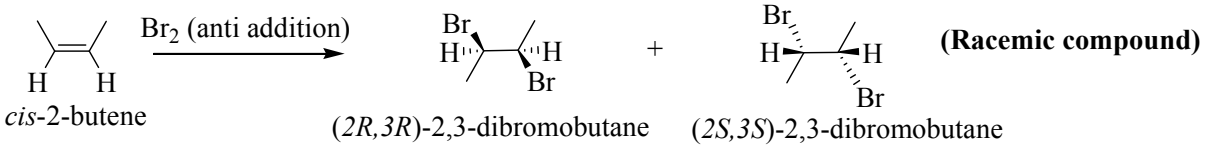


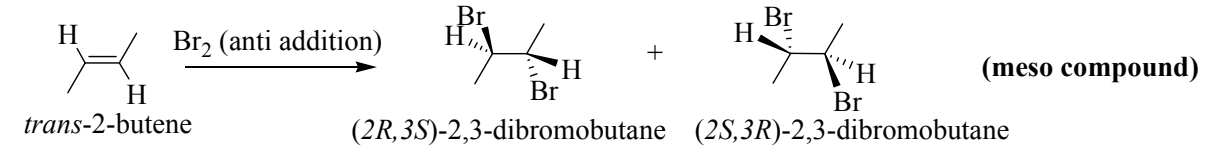
Figure 1: Examples of asymmetric synthesis

5.4.2 STEREOSPECIFIC AND STEREOSELECTIVE REACTIONS:

Stereospecific reactions: Stereospecific reactions or synthesis are those reactions in which a particular stereoisomer reacts with given reagent to give one specific stereoisomer of the product. This property is called stereospecificity. Thus each individual stereoisomeric substrate under stereospecific synthesis gives a different isomer of the product.

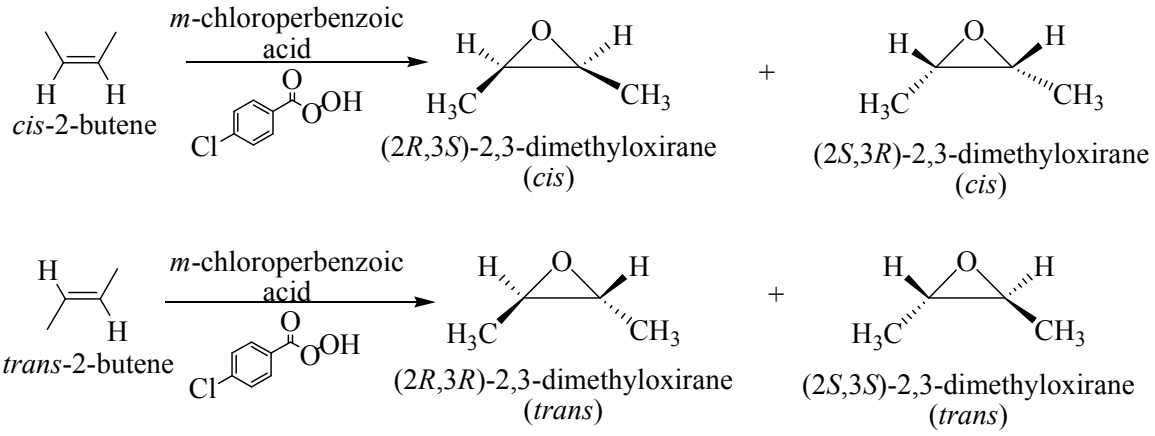
Example 17: For example, *anti* addition of bromine to *cis*-2-butene gives racemic mixture of 2,3-dibromobutane, while the *anti* addition of bromine to *trans*-2-butene gives meso-2,3-dibromobutane. These kinds of reactions are called stereospecific because different stereoisomeric substrate leads different stereoisomeric products.



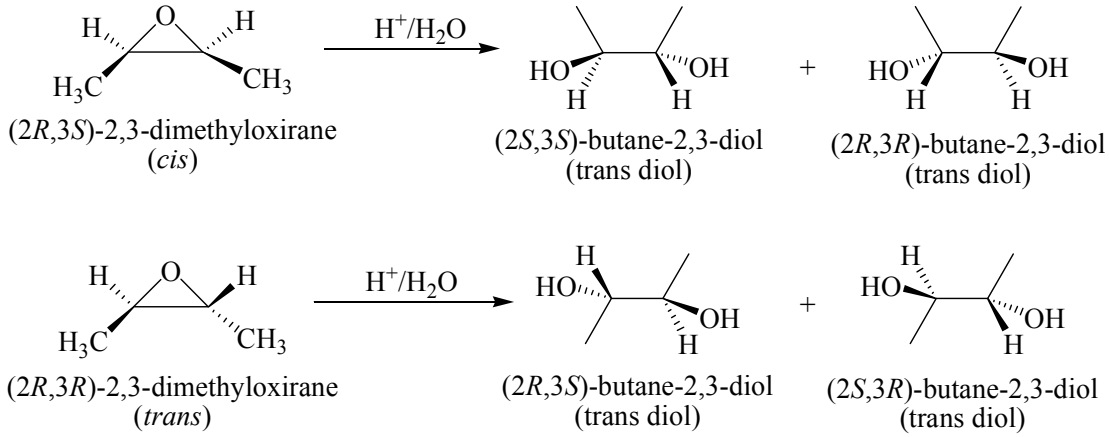


Similarly, *syn* addition of peroxyacid to cis- and trans- alkenes gives stereospecific reaction. **Example 18**: For example, *syn* addition of *meta*-chloroperbenzoic acid (*m*-CPBA) to cis-2-butene gives cis-2-dimethyloxirane [(2*R*,3*S*)-2,3-dimethyloxirane], while *syn* addition of *meta*-

chloroperbenzoic acid (*m*-CPBA) to trans-2-butene gives trans-2,3-dimethyloxirane [(2*R*,3*R*)-2,3-dimethyloxirane]. Thus the reaction is stereospecific.



Example 19: Another example of stereospecific reaction is also considered as the ring opening freactions of oxirans (epoxides). Hydrolysis of epoxides (oxiranes) obtained by the *syn* addition of peroxyacid to *cis*- and *trans*- alkenes leads to the formation *trans*- diols (diols = dihydroxy compounds) in which both the vicinal hydroxy groups are trans to each other.

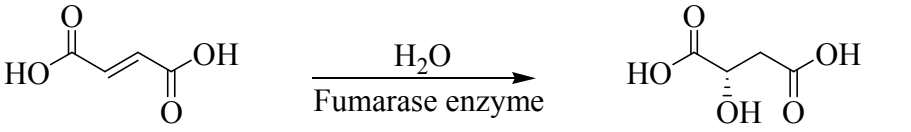


Stereoselective reactions: Stereoselective reactions or synthesis are those reactions in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several possible stereoisomers. This property is called stereoselectivity. In such reactions one stereoisomer is formed more rapidly than other, thus one stereoisomer forms in excess in the resulting mixture of the products. For every stereoselective reaction there is more than one mechanistic path by which reaction may proceed; however, it is observed that the reaction

proceeds either via the most favorable path (for which rate of reaction is fast *i.e.* kinetic control) or via the path that gives the most stable stereoisomer as the major product (*i.e.* thermodynamic control). The stereoselective reactions/synthesis or the stereoselectivity can be further subdivided in to two categories, a) enantioselective reactions/synthesis or enantioselectivity, b) diastereoselective reactions/synthesis or diastereoselectivity.

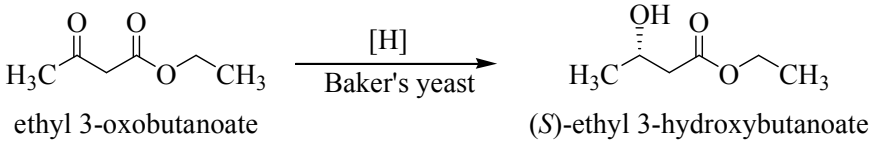
a) **Enantioselective reactions or enantioselectivity:** Enantioselective reactions are defined as the reactions or processes in which one of the enantiomer forms predominantly over the other. This property is known as enantioselectivity. Enantioselectivity is achieved when a stereoselective reaction is performed in the presence of using a chiral environment (*i.e.* either a chiral substrate, or a chiral reagent, or a chiral catalyst, or a chiral solvent).

Example 20: For example, Fumaric acid when hydrolyzed in presence of Fumarase (a chiral enzyme) gives (*S*)-2-hydroxysuccinic acid exclusively.

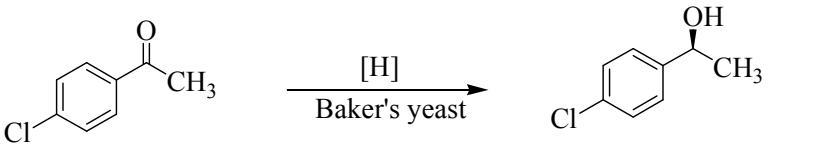


fumaric acid (S)-2-hydroxysuccinic acid

Example 21: Similalry, reduction of carbonyl group by Baker's yeast exclusively leads to the formation of *S*- enantiomer. Examples of reduction of carbonyl groups by baker's yeast are shown below.

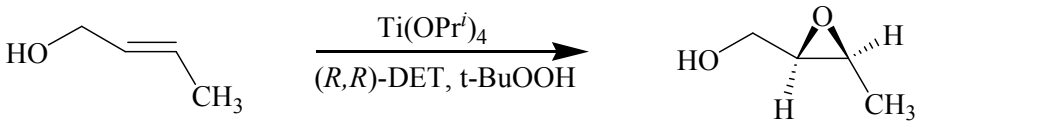


ethyl 3-oxobutanoate (*S*)-ethyl 3-hydroxybutanoate

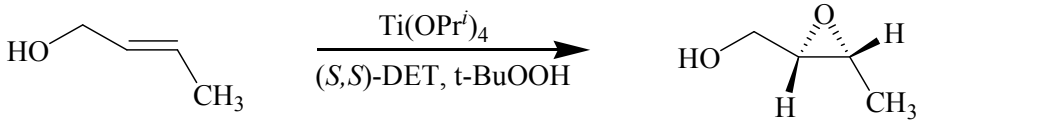


1-(4-chlorophenyl) ethanone (*S*)-1-(4-chlorophenyl)ethanol

The Sharpless epoxidation of allylic alcohol in presence of titanium tetraisopropoxide, *t*-butylhydroperoxide and enantiomerically pure diethyltartrate (DET) gives enantiomerically pure epoxide. The stereochemistry of product depends on the stereochemistry of diethyltartrate. The diethyltartrate is readily available in its enantiomerically pure forms (*i.e. R,R* and *S,S*). (*R,R*)-diethyltartrate (DET) gives (*S,S*)- epoxide, whereas, (*S,S*)-diethyltartrate (DET) gives (*R,R*)-epoxide.



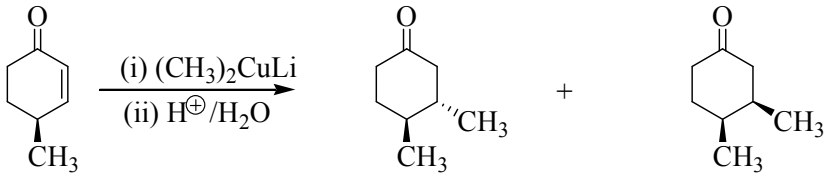
(*E*)-but-2-en-1-ol ((2*S*,3*S*)-3-methyloxiran-2-yl)methanol



(*E*)-but-2-en-1-ol ((2*R*,3*R*)-3-methyloxiran-2-yl)methanol

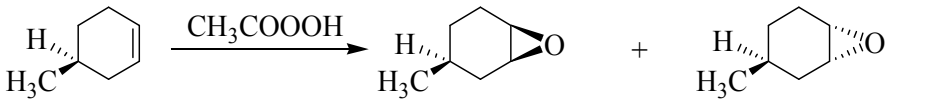
b) **Diastereoselective reactions or diastereoselectivity:** Diastereoselective reactions are defined as the reactions or processes in which one of the diastereomer forms predominantly or exclusively over the other. This property is known as diastereoselectivity. Diastereoselectivity is usually achieved through in the presence of steric hindrance.

Example 22: Let us consider the conjugate addition of lithium dimethylcuprate [$(CH_3)_2CuLi$] to 4-methylcyclohexenone. In this reaction cuprate reagent has equal possibilities to react from the either faces of the 4-methylcyclohexenone; however, the bulky cuprate reagent prefers to approach from the less hindered face (*i.e.* opposite to the methyl group) of the 4-methylcyclohexenone. As a result one diastereoisomer (*i.e. trans*- product: methyl groups are *trans*- to each other) out of two possible diastereoisomers forms in excess. Thus, this reaction is called diastereoselective reaction.



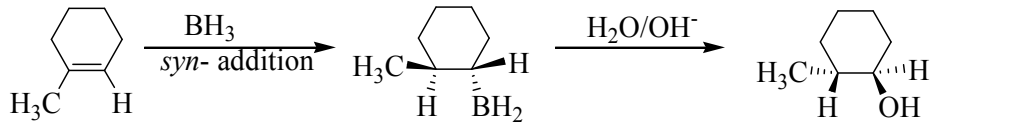
(*S*)-4-methylcyclohex-2-enone (3*S*,4*S*)-3,4-dimethyl cyclohexanone (98%) (3*R*,4*S*)-3,4-dimethyl cyclohexanone (2%)

Example 23: Another example of diastereoselective reaction/synthesis is the epoxidation of cyclic alkenes with peroxyacids. In such reactions the epoxidation also takes place from the less hindered face. Epoxidation of 4-methylcyclohexene by peroxyacetic acid gives 80% addition product from the less hindered face (*i.e.* opposite to the methyl group) and 20% addition product from the more hindered face (*i.e.* from the face of methyl group).



(*S*)-4-methyl cyclohex-1-ene *cis*-epoxide 20% *trans*- epoxide 80%

Example 24: Similarly, synthesis of alcohols from alkenes by the hydroboration-oxidation is another class of example of diastereoselective reactions. Hydroboration-oxidation of 1-methylcyclohexene gives the *trans*- product as the major product.



1-methylcyclohex-1-ene (1*R*,2*R*)-2-methylcyclohexanol (*trans product*)

5.4 ENANTIOMERIC EXCESS (*ee*):

It is a measurement of optical purity of a chiral substances formed in an asymmetric synthesis. It reflects the degree to which a mixture of enantiomer contains one enantiomer in greater amounts than the other. A racemic mixture has an *ee* of 0%, while a single and pure enantiomer has an *ee* of 100%. A sample with 70% of one enantiomer and 30% of the other has an *ee* of 40% (70% − 30%). Enantiomeric excess can be determined by the following mathematical expression.

$$\text{Enantiomeric excess (\% ee)} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

5.5 *DIASTEREOMERIC EXCESS (de)*

It is the measurement of % excess formation of one of the diastereomers over the other in an asymmetric synthesis. It reflects the degree to which a mixture of diastereomer contains one diastereomers in greater amounts than the other. Diastereomeric excess can be determined by the following mathematical expression.

$$\text{Diastereomeric excess (\% } de\text{)} = \frac{[D_1] - [D_2]}{[D_1] + [D_2]} \times 100$$

5.6 *CRAM'S RULE*

Diastereoselectivity of nucleophilic addition on carbon-oxygen double bond of aldehyde and ketones containing an asymmetric α carbon is explained by D. J. Cram and co-workers. According to this the formation of the *major* product was correctly predicted by a model in which the largest group was eclipsed with the other carbonyl substituent. This empirical relationship became known as *Cram's rule*. Since, during nucleophilic addition on symmetrical sp^2 carbonyl carbon, the nucleophile has equal possibilities to give addition on carbonyl carbon from either faces. However, when α-carbon of sp^2 carbonyl carbon is asymmetric, the nucleophile would experience more steric hindrance from one side, leading to unequal synthesis of the two diastereomers. The Cram's rule predicts the formation of major product based on most stable conformation of carbonyl compound. Following points may be considered during the prediction of the most stable conformation of carbonyl compound:

- The existing asymmetric center would have a Small, Medium and Large group, denoted **S, M** and **L** respectively (Fig 2).
- In the reactive conformation, the carbonyl group would orient itself in such a way that it will rest between the Small group and the Medium group.

- The attacking nucleophile would prefer to attack from the side of the small group, resulting in the predominant formation of one diastereomer in the product.

As shown in figure 2 path A is preferred over path B.

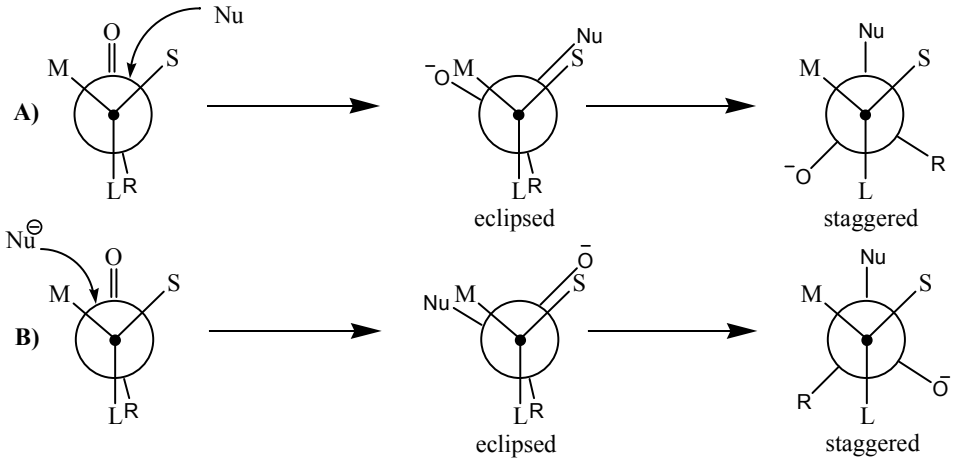


Figure 2: Schematic representation of Cram's rule

For example, the reduction of α-phenylpropionaldehyde ($PhCH(CH_3)CHO$) with Grignard reagent yields the erythro diastereomer as the major product according to Cram's rule, where (*S*=H, *M*=Me, *L*=Ph) [Fig 3(1)]. Similarly, reaction of HCN with 2-methylbutanal to form cyanohydrins with diastereoselectively and the major product will be erythro diastereomer [Fig 3(2)].

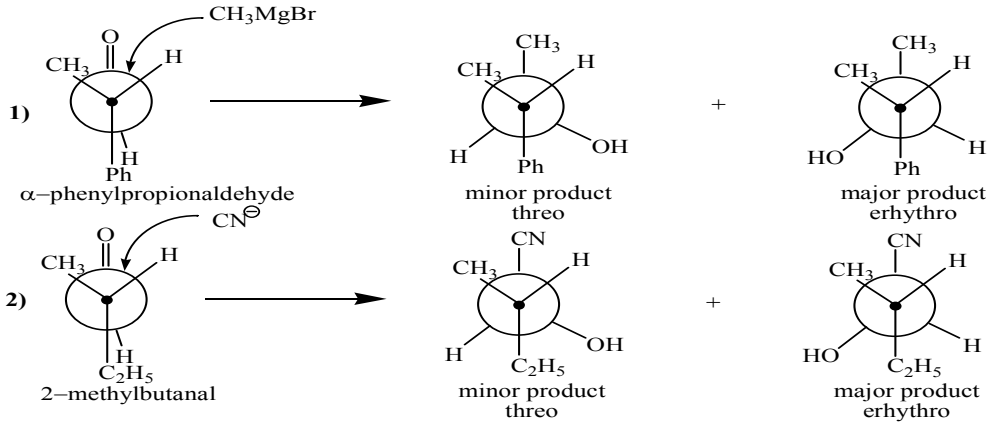
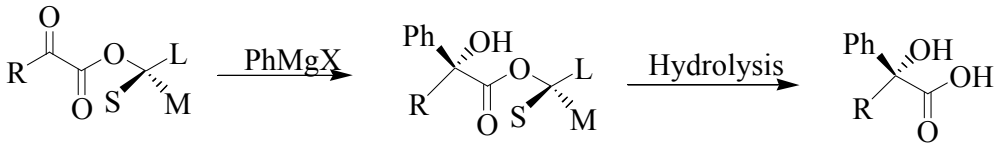


Figure 3: Examples of Cram's rule

5.7 *PRELOG'S RULE*

Prelog's rule is an extension of Cram's hypothesis of reactive conformation to nucleophilic addition on chiral esters of □-ketoesters (pyruvates) and was reported in 1953. It is generally the addition of Grignard reagent to chiral pyruvates to form chiral alcohols. The rule has been applied for asymmetric synthesis of α-hydroxyacids and for assigning the configuration of secondary and tertiary alcohols. The *anti* configurational arrangement of the two α-carbonyl moieties could be rationalized. The negative end of these dipoles would prefer to be as far as possible. The attack from the side of the small (S) group is an extension of Cram's Rules. The asymmetric induction in such reaction is not very effective due to the large distance between the reaction center and the asymmetric center inducing asymmetry at the developing chiral center.

Example 25: Reaction of pyruvates with Grignard reagent (extension of Cram's rule)



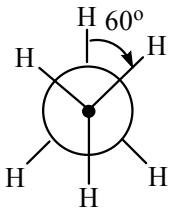
5.8 *CONFORMATIONAL ANALYSIS OF ALKANES*

The different spatial arrangements of atoms in a molecule which is readily interconvertible by rotation about single bonds are called ***conformations***. The study of various preferred conformations of a molecule and the correlation of physical and chemical properties to the most preferred conformer is called conformational analysis. Due to rapid interchange of the spatial positions of groups/atoms these conformers are non-separable under normal conditions. Since, different conformations arises because of the rotation about single bonds, hence, they are also called the rotamers. The conformational and configurational isomerisms are related to energy barrier for interconversions of different spatial arrangements of atoms in a molecule. If the energy barrier for interconversion of different spatial arrangements is between 0.6 kcal/mol-16.0 kcal/mol; it result the conformational isomers or conformers; whereas, if this energy barrier is more than or equal to 16 kcal/mol than the configurational isomers are obtained.

5.8.1 CONFORMATIONAL ANALYSIS OF ETHANE:

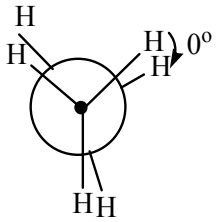
When ethane molecule rotates around carbon-carbon single bond, two extreme conformations (one is highly stable and other is highly unstable) are obtained. The highly stable conformation of ethane is called '*staggered conformation*' and the highly unstable conformation of ethane is called '*eclipsed conformation*'. In between these two extreme conformations (*i.e.* staggered and eclipsed), an infinite number of conformations are also possible.

Staggered conformation: A conformation with a 60° dihedral angle is known as staggered conformation. The angle between the atoms attached to the front and rear carbon atom is called dihedral angle.



Staggered conformation

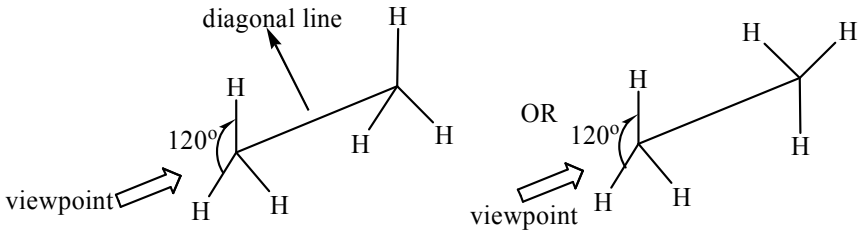
Eclipsed conformation: A conformation with a 0° dihedral angle is known as eclipsed conformation.



Eclipsed conformation

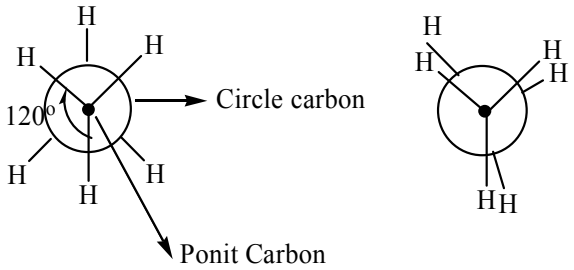
In staggered conformation the atoms are located at maximum possible distance from each other hence they are in their most relaxed spatial arrangement thus the staggered conformation is considered as the most stable conformation; whereas, in eclipsed conformation the atoms are located at minimum distance, hence due to repulsion between the atoms the eclipsed conformation is considered as the least stable (high energy) conformation. There are two methods for the representation of staggered and eclipsed conformations, **a**) the Sawhorse representation formula and, **b**) the Newman representation formula.

a) **The Sawhorse representation formula:** In sawhorse representation formula the spatial arrangement of all the atoms/groups on two adjacent carbon atoms. The bond between adjacent carbon atoms is represented by a diagonal line and rest of the atoms are located on each carbon at +120° or -120° angles to each other. The sawhorse representation is shown as:



Sawhorse representation formula

b) The Newman representation formula is a planar representation of the sawhorse formula. The molecule is viewed along the axis of a carbon-carbon bond. The carbon atom in front of the viewer is represented by a dot (●), whereas the carbon atom away to the viewer is represented by circle. The rest of the atoms/groups are located on each carbon atoms at +120° or -120° angles to each other as shown below:



Newman representation formula

The different conformations of ethane are not equally stable. The staggered form in which the hydrogen atoms are 'perfectly staggered' (dihedral angle is 60°) is the most stable conformation. This is because, in this conformation the all carbon hydrogen (C-H) bonds are located at maximum possible distance to each other, and hence they feel minimum repulsive energy from each other. In eclipsed conformation of ethane, the hydrogen atoms attached to each carbon are directly opposing to each other. This result the minimum separation of the atoms or groups, and

hence they feel maximum repulsive energy from each other. The eclipsed conformation therefore, of highest energy and has the lowest stability. A graph plot for the energy profile for various conformations of ethane is shown on figure 4. The relative stability of various conformations of ethane is

Staggered >> Eclipsed

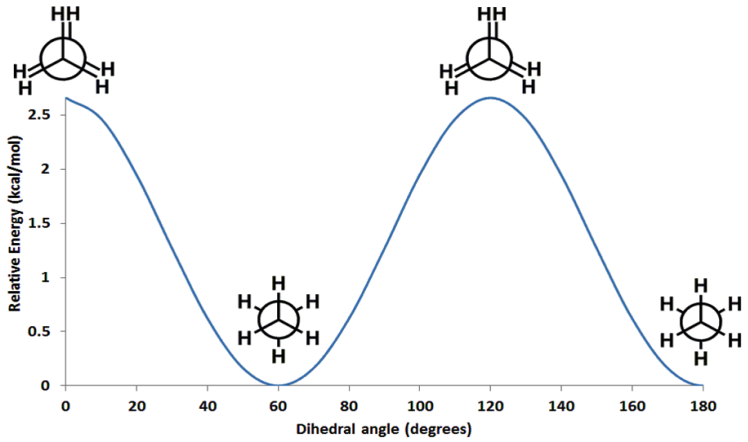


Figure 4: Energy profile diagram of conformational isomer of ethane

5.8.2 CONFORMATIONAL ANALYSIS OF *N*-BUTANE:

n-Butane (C_4H_{10}) has three carbon-carbon single bonds (Figure 5); therefore the molecule can rotate about each of them. The rotation about C2 and C3 bond will provide the symmetrical conformations. To study the conformational analysis of *n*-butane, we must consider it as a derivative of ethane molecule, where one hydrogen at each carbon of ethane is replaced by methyl group ($-CH_3$).

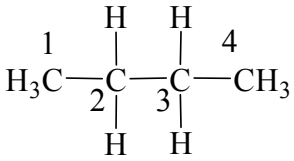


Figure 5: Butane molecule

Various conformation of *n*-butane can be obtained by rotation about C2 and C3 bond are shown in figure 6:

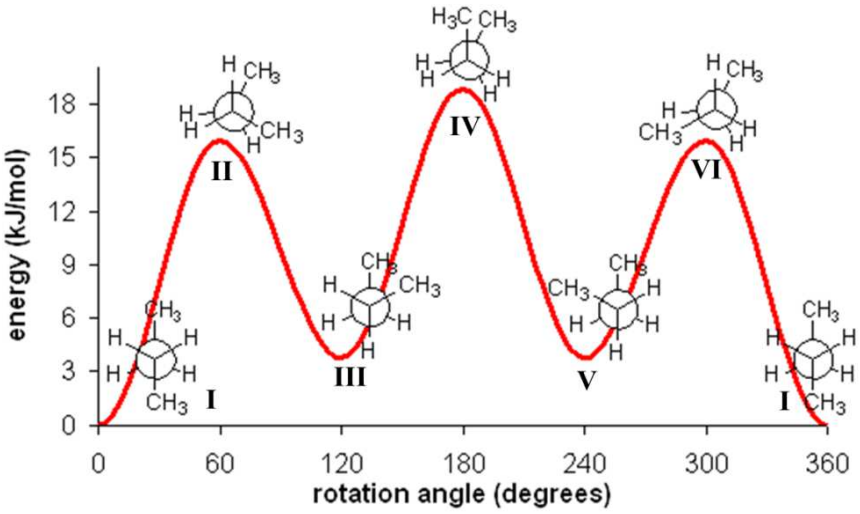


Figure 6: Energy profile diagram of conformational isomer of *n*-butane

From figure 3, we can see that *n*-butane has three staggered conformations (**I, III** and **V**). Conformer **I**, in which two methyl groups are as far as possible, and hence is more stable than other two staggered conformers (*i.e.* **III** and **V**), because conformer **I**, has minimum repulsive energy. As you can see from figure 3; in conformer **I,** both the methyl groups are located opposite to each other. The most stable conformer of *n*-butane, in which both the methyl groups are located opposite to each other is called the *anti-conformer*, whereas other two staggered conformers (*i.e.* **III** and **V**) are called *gauche conformer*. Due to difference in steric strain (repulsion between dihedral atoms/groups) the repulsive energy of *anti* and *gauche* conformers are also different. Three eclipsed conforms (**II**, **IV** and **VI** in figure 6) are also exits for *n*-butane, in which the dihedral atoms/groups are in front of each other (*i.e.* dihedral angle is 0°). The fully eclipsed conformer **IV,** in which the two methyl groups are closest to each other, has maximum steric strain; hence it is of higher energy than the other eclipsed conformers (**II** and **VI)**.Thus the relative stabilities of the six conformers of *n*-butane in their decreasing order is given as follows:

Anti > Gauche > Eclipsed > Fully eclipsed

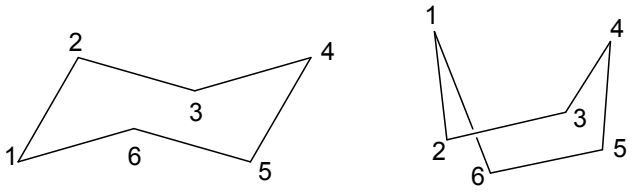
I **III and V** **IV** **II and VI**

5.8.3 CONFORMATION OF CYCLOHEXANE:

It is known to you that in cycloalkane, all the ring carbons are sp^3 hybridized, hence must have tetrahedral geometry with all bond angles of 109.5°. But to sustain its cyclic structure the

cycloalkane could not be able to maintain the bond angle of 109.5°. As a result there is a deviation from the normal tetrahedral bond angle. This deviation leads the development of strain in the molecule. Thus the cycloalkanes exhibit angle strain, due to which cycloalkanes are not as stable as their non-cyclic homolog. To minimize the angle strain the structure of cycloalkane is keep on changing from one cyclic form to another which are readily interconvertible by rotation about single bond. This is the reason why cyclohexane and larger rings are non-planar.

Cyclohexane exists in two readily interconvertible forms which are called the chair and boat conformations of cyclohexane (Figure 7).



Chair Conformation of cyclohexane

Boat Conformation of cyclohexane

Figure 7:

Two readily interconvertible conformations of cyclohexane

Both chair and boat forms are free from angle strain. In chair form carbon C1, C3 and C5 are in one plane and carbon C2, C4 and C6 are in different plane. Similarly, in boat form carbon C1 and C4 are in one plane and carbon C2, C3, C5 and C6 are in other plane. The interconversions of chair to boat and boat to chair *via* various other intermediate conformations are shown in Figure 8.The chair conformation (**I** and **V scheme 1**) is considered as a rigid conformation of cyclohexane in comparison to boat conformation; because during interconversion from chair to boat conformation, some angular deformations are required. These angular deformations usually increase the energy barrier for interconversion from chair to boat conformation. Therefore the chair conformation of cyclohexane is the most stable conformation.

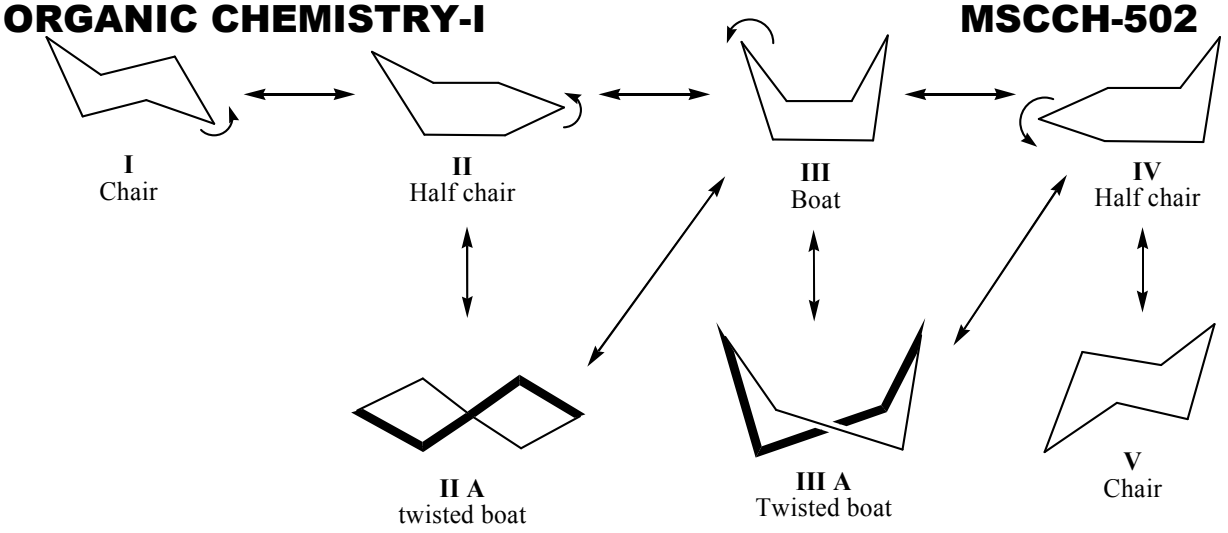


Figure 8: Conformational analysis of cyclohexane

Chair form on distortion gives half chair (**II** and **IV figure 8**) conformations which are of highest energy conformations. In comparison to chair conformation, the boat conformation (**III figure 8**) is flexible and can readily distort into many steps to reduce the C-H bond eclipsing. The boat conformation can be interconvertible in to twisted boat (**IIA** and **IIIA figure 8**) conformations, which has comparatively less angular and steric strains. The twisted boat conformations have lower energy than the boat conformation, hence is more stable than boat conformation. At room temperature 99.9% cyclohexane molecules exist in the most stable chair conformation.

The energy profile diagram along with various possible conformations of cyclohexane is shown in figure 9.

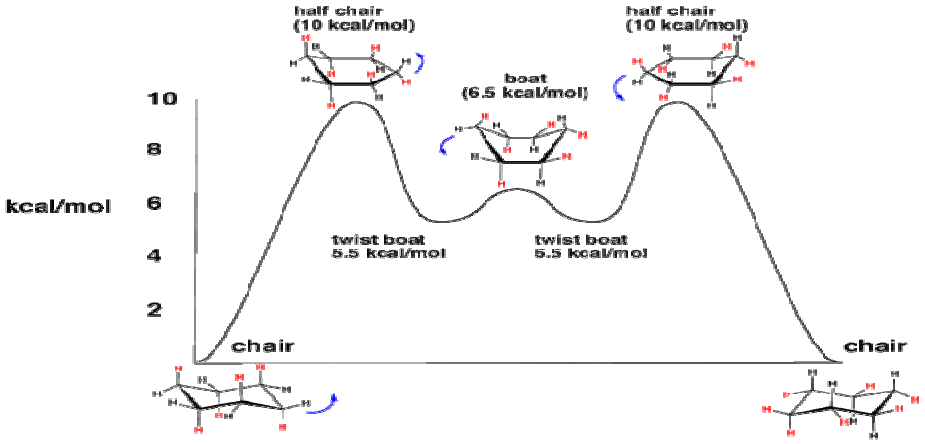
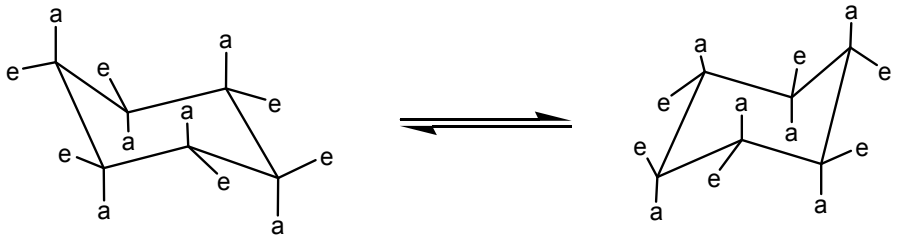


Figure 9: Energy profile diagram of conformation of cyclohexane

5.8.3.1AXIAL AND EQUATORIAL BOND:

In chair conformation of cyclohexane, there are two different positions occupied by the 12 hydrogen atoms of cyclohexane. Out of total 12 Hydrogen atoms of cyclohexane, six hydrogen atoms are located towards perpendicular to average plane of the ring; these perpendicular hydrogen atoms are called axial hydrogens (*a*), and respective bonds are called *axial* bonds. The other six hydrogen atoms are located along with the average plane of the ring; these hydrogens are called *equatorial* hydrogens (*e*), and the respective bonds are called equatorial bond.



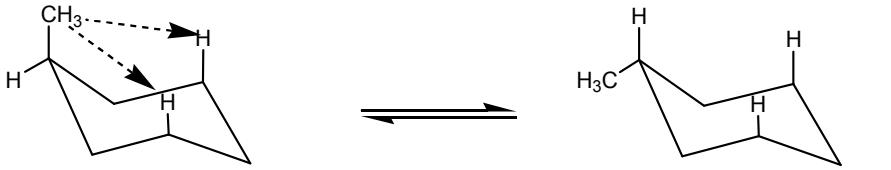
a = axial; e = equatorial

Cyclohexane is rapidly interconvertible (flips) in to its mirror image chair conformations at room temperature. During flipping all the axial hydrogens becomes equatorial and all the equatorial hydrogens becomes axial.The flipping of the cyclohexane is so rapid that it is not possible to differentiate between equatorial and axial hydrogens. These hydrogens can be differentiated at very low temperature (*i.e.* -80°) and analyzed by ^{1}H NMR spectroscopy.

5.8.4 CONFORMATION OF MONO SUBSTITUTED CYCLOHEXANE:

If one hydrogen atom of cyclohexane is replaced by a larger atom or group, the molecule becomes highly hindered. As a result the repulsion between atoms increases. Axial atoms/groups usually face more repulsive interaction in comparison to equatorial atoms/groups. Since three axial atoms/groups are located in one side of the average plane of ring, whereas rest three atoms/groups are located in other side of the average plane of ring. The repulsive interaction experienced by three axial atoms is called *1,3-diaxial interaction.*To minimize the 1,3-diaxial interaction and resulting repulsive energy, the monosubstituted cyclohexane acquires a chair conformation in which the substituents occupies an equatorial position. There are two possible chair conformations for methyl cyclohexane. In one conformation the methyl group located at axial position (**I**), whereas in other conformation the methyl group is located at equatorial

position (**II**). When methyl group is at axial position, it has 1,3-diaxial interaction with hydrogen atoms at C3 and C5 carbons due to which the energy of such conformation is very high in comparison to the conformer in which the methyl group is at equatorial position. The conformer with methyl group at equatorial position does not have any kind of 1,3-diaxial interaction hence is more stable.



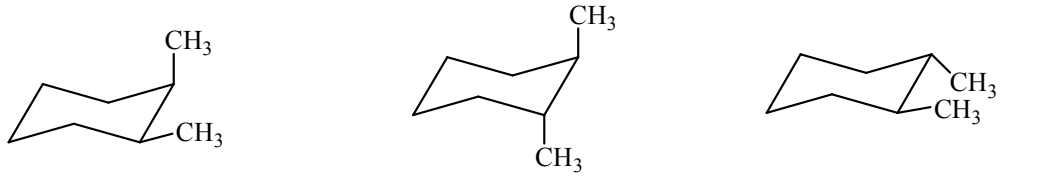
Axial conformer with 1,3-diaxial interaction (I)

Equatorial conformer with no 1,3-diaxial interaction (II)

5.8.5 CONFORMATION OF DISUBSTITUTED CYCLOHEXANES:

Disubstituted cyclohexanes are of three types *viz*. 1,2-; 1,3- and 1,4- with respect to each other. Therefore, the conformational analysis of all three types of disubstituted cyclohexanes is discussed separately in this section. It is also important to note that whether the substituents are either *cis*- or *trans*- to each other. In general, it is observed that in disubstituted cyclohexanes either the chair conformation with both the substituents in equatorial positions will be the preferred conformation, or the conformation with bulkier substituent at equatorial position will be the preferred conformation. Let us consider the disubstituted cyclohexanes containing methyl group as both the substituents.

1,2-Dimethylcyclohexane: For 1,2-dimethylcyclohexane, two isomeric forms (*i.e. cis*- and *trans*-) are possible. The 1,2-dimethylcyclohexane with substituents at one axial and one equatorial positions is known to have a *cis*- configuration, whereas, the 1,2-dimethylcyclohexane with both the substituents at either axial or equatorial positions is known to have a *trans*-configuration. Out of three conformations shown in figure 10, the conformation with diaxial substituent is the least stable conformation of cyclohexane since two axial methyl group causes four 1,3-diaxial interaction (repulsive interaction) between axial methyl group and hydrogen atom.



cis-1,2-dimethylcyclohexane
a,e or *e,a*
(more stable)

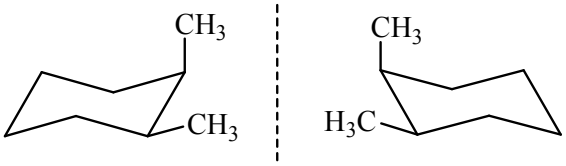
trans-1,2-dimethylcyclohexane
a,a (diaxial)
(least stable)

trans-1,2-dimethylcyclohexane
e,e (diequatorial)
(most stable)

Figure 10: Conformational isomers of 1,2-dimethylcyclohaxane

Whereas, the conformation with diequatorial substituent id the most stable conformation of cyclohexane since there are no 1,3-diaxial interaction between methyl group and hydrogen atom. However, the conformation of 1,2-dimethylcyclohaxane, with one methyl at axial and one methyl at equatorial, causes two 1.3-diaxial interactions hence it is more stable than diaxial conformation and less stable than diequatorial conformation of 1,2-dimethylcyclohaxane. Thus the decreasing order of stability of different conformations of 1,2-dimethylcyclohexane is: *ee*>*ae*~*ea*>*aa*.

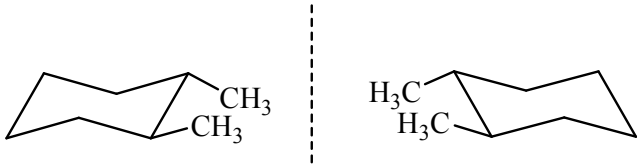
1,2-dimethylcyclohexane shows enantiomerism. It has 2 chiral centers, hence can have four stereoisomers possible, since *cis*-1,2-dimethylcyclohexane is not superimposable on its mirror image but they are readily interconvertible by flipping one chair conformer in to other, hence, only three stereoisomers are exist for 1,2-dimethylcyclohexane (Figure 11). These two readily interconvertible conformers are called conformational enantiomers. It must be noted that the *cis*-1,2-dimethylcyclohexane constitutes a non resolvable racemic mixture, hence it is not a meso compound.



cis-1,2-dimethylcyclohexane
a,e or *e,a*
(readily interconvertible non resolvable racemic mixture)

Figure 11: Interconvertible (racemic mixture) of *cis*-1,2-dimethylcyclohaxane

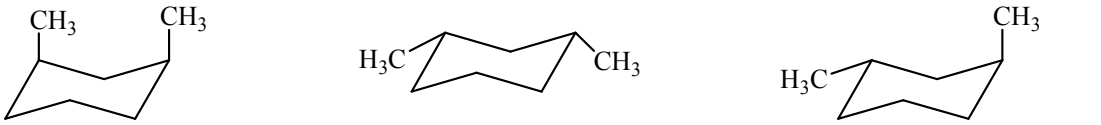
However, *trans*-1,2-dimethylcyclohexane (*ee*) and its mirror image are non superimposable, hence they constitute an enantiomeric pair. They cannot be interconvertible readily by flipping. On flipping *ee* chair conformer leads the formation of *aa* chair conformer. These two stereoisomers are called configurational enantiomers (Figure 12).



trans-1,2-dimethylcyclohexane
ee
(non interconvertible)

Figure 12: Non-interconvertible (enantiomeric mixture) of *trans*-1,2-dimethylcyclohaxane

1,3-Dimethylcyclohexane: In case of 1,3-Dimethylcyclohexane (molecule with two identical substituents) two *cis*- and one *trans*- chair conformations are possible as shown in figure 13.



cis-1,3-dimethylcyclohexane
a,a (diaxial)
(least stable)

cis-1,3-dimethylcyclohexane
e,e (diequatorial)
(most stable)

trans-1,2-dimethylcyclohexane
a,e or *e,a*

Figure 13: Conformational isomers of 1,3-dimethylcyclohaxane

In the case of 1,3-dimethylcyclohexane the *cis*- stereoisomer (*ee*) is more stable than the trans-stereoisomer (*ae*). Since, *cis*- stereoisomer (*ee*) has no 1,3-diaxial interactions, while, *trans*-stereoisomer (*ae*) has two 1,3-diaxial interactions between hydrogen of cyclohexane and methyl group. However, another *cis*- stereoisomer (*aa*) of 1,3-dimethylcyclohexane is the least stable stereoisomer due to maximum 1,3-diaxial interactions. The decreasing order of stability of these stereoisomers is: *ee*>*ae*~*ea*>*aa*.

Likewise 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane has also two chiral centers, hence, it must have four stereoisomers. However, both the conformational isomers of *cis*-1,3-dimethylcyclohexane has plane of symmetry, hence, it is achiral and called meso compound

Figure 14. The *trans*-1,3-dimethylcyclohexane does not have plane of symmetry hence it exist in two configurational enantiomeric forms. These two configurational enantiomers are not interconvertible by flipping of the chair forms Figure 14.

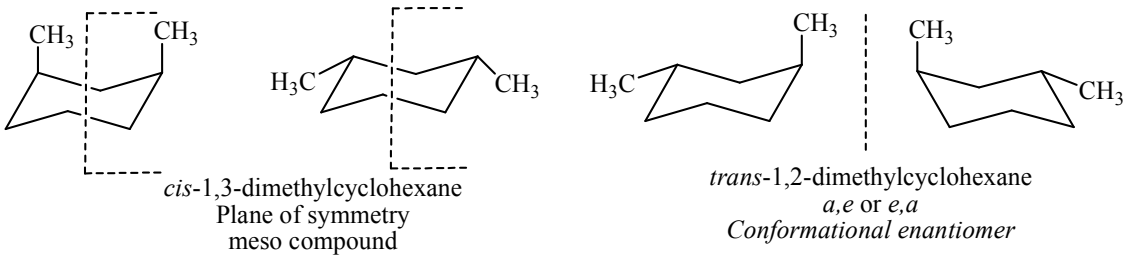


Figure 14: Stereochemistry of 1,3-dimethylcyclohaxane conformations

1,4-Dimethylcyclohexane: Similar to 1,2-Dimethylcyclohexane, 1,4-dimethylcyclohexane have also one *cis*- and two *trans*- conformational isomers are possible, as shown in figure 15.

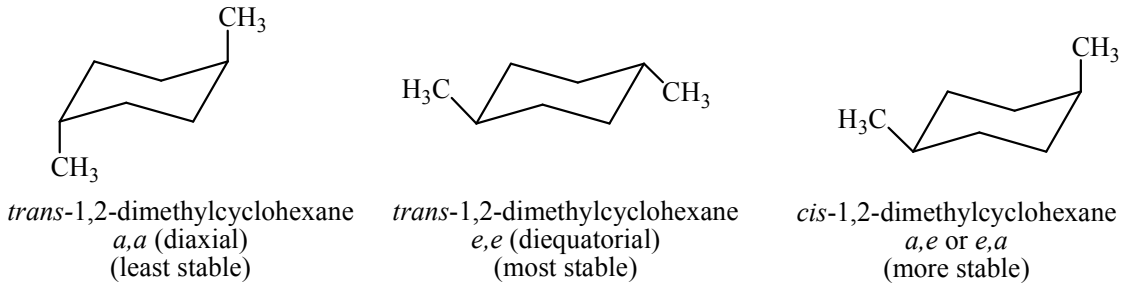
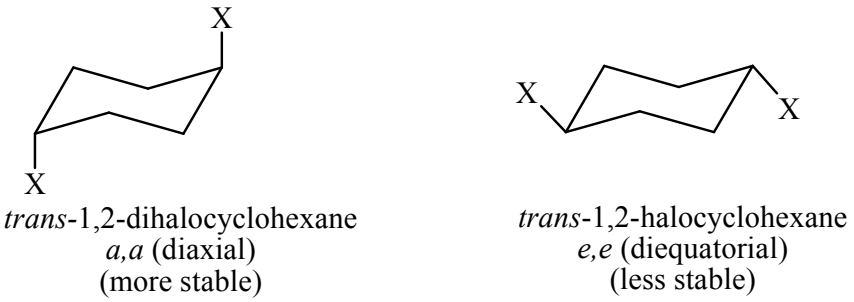


Figure 15: Conformational isomers of 1,4-dimethylcyclohaxane

Due to plane of symmetry in all the isomeric forms of 1,4-dimethylcyclohexane does not have any chiral center. It exists only in *cis*- and *trans*- diastereomers. Neither its *cis*- nor *trans*-diastereomeric forms is chiral.

As we have observed that, if cyclohexane is substituted with alkyl groups diequatorial conformation is the most stable conformation in all types of disubstituted cyclohexanes. However, if the substituents are different than methyl group then the above observation may not be applicable. For example, when methyl groups are replaced with halogens (*i.e.* Cl or Br), the *trans*- conformations (*i.e. ee* and *aa*) of 1,4-dihalocyclohexane are equally populated, and most of the *trans*-1,4-dihalocyclohexane exists predominantly in *aa* conformation due to dipole and gauche interactions Figure 16. Similarly, for 1,2-dihalocyclohexane the *aa* conformation is more

stable than *ee* conformation Figure 16. In the case of 1,3-cyclohexnediol, it is observed that the *aa* conformation is found to be more stable than the *ee* conformation due to the stabilization of diaxial conformation by formation of hydrogen bonding between the oxygen atom of one hydroxyl group and hydrogen atom of other hydroxyl group (intramolecular H bonding).

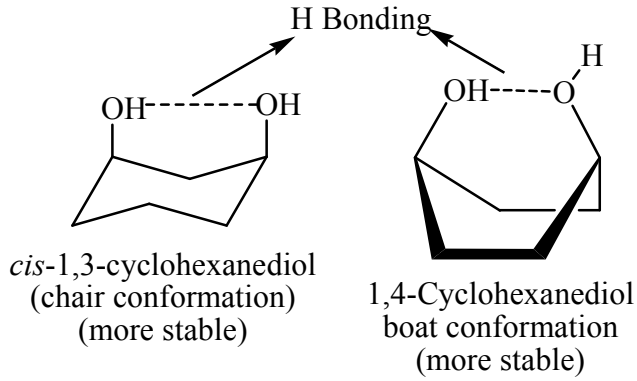


trans-1,2-dihalocyclohexane
a,a (diaxial)
(more stable)

trans-1,2-halocyclohexane
e,e (diequatorial)
(less stable)

Figure 16: Stability of *trans*-1,4-dimethylcyclohexane

In the case of 1,3-cyclohexnediol the preferred conformation is the chair form; while, when the hydroxyl substituent are at 1, 4- position (1,4-cyclohexnediol) then the boat conformation is preferred to stabilize the 1,4-cyclohexnediol via formation of intramolecular hydrogen bonding (Figure 17).



cis-1,3-cyclohexanediol
(chair conformation)
(more stable)

1,4-Cyclohexanediol
boat conformation
(more stable)

Figure 17: Hydrogen bonding in *trans*-1,4-dihydroxycyclohexane

5.8.6 CONFORMATION OF DECALINS:

Decalin is a bicyclic compound. Generally, bicyclo [4,4,0] decane is known as decalin. Two cyclohexane rings are fused together in chair conformation to generate decalin. It exists in two diastereomeric forms (*i.e. cis*- and *trans*-decalins). Decalin is structural analogous to 1,2-

disubstituted cyclohexane. When both the cyclohexane rings are fused together in *ea* form the decalin thus formed is called *cis*-decalin. However, when two cyclohexane rings are fused together in *ee* form the decalin thus formed is called *trans*-decalin. The *cis*- and *trans*-decalins are shown in figure 19.

Figure 19: Conformations of decalin

The *trans*-decalin is more stable than *cis*-decalin by 2.7 kcal/mol of energy. Thus *cis*-decalin can be easily converted in to *trans*-decalin but the reverse process is not possible. Due to flexibility in structure of cis-decalin, its ring flipping is possible. Thus cis-decalin exists in two interconvertible conformational isomers Figure 20. In comparison to *cis*-decalin, the *trans*-decalin is a rigid molecule. Due to the presence of two equatorial bonds the ring flipping of *trans*-decalin is not possible.

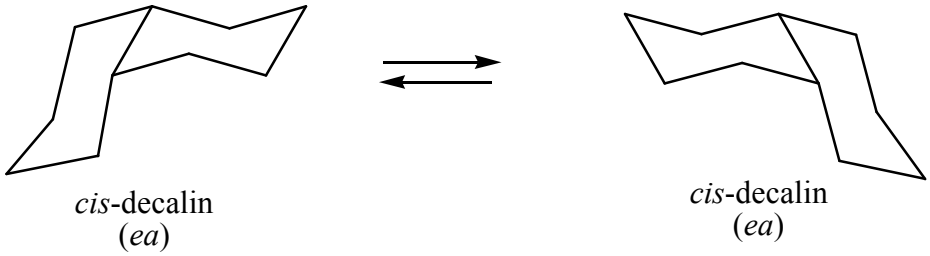
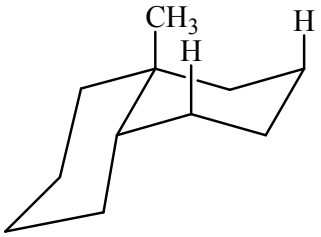


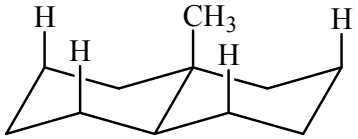
Figure 20: Flipping of *cis*-decalin

The *cis*-decalin is chiral in both the conformation, since, these conformations are non-superimposable mirror image of each other. Hence, *cis*-decalin exists in a conformational enantiomeric pair. On the other hand, the *trans*-decalin due to center of symmetry is achiral. In case of substituted decalins, the substituent located at the fusion point of both the rings. In the case of *cis*-decalin the substituent at fusion point is axial with respect to one ring and equatorial with respect to other ring. On the other hand, in *trans*-decalin the substituent is located at axial

position with respect to both the rings (Figure 21). It must be noted that the substituent to the *cis*-decalin is free to adopt the equatorial position.



Methyl substituted *cis*-decalin
There are twor sets of 1,3-diaxial interaction
with axial methyl substituent
(more stable)



Methyl substituted *trans*-decalin
There are four sets of 1,3-diaxial interaction
with axial methyl substituent
(less stable)

Figure 21: Position of substituents on *cis*- and *trans*-decalin

5.9 *STEREOCHEMISTRY OF COMPOUNDS CONTAINING N, P AND S.*

Like tetravalent carbon compounds, the nitrogen, phosphorous and sulphur containing compounds also exhibit stereochemical behaviour. Compounds of N, P and S show both enantiomerism and/or geometrical isomerism. This section deals with the brief discussion on the stereochemistry of compounds of N, P and S.

5.9.1 STEREOCHEMISTRY OF NITROGEN COMPOUNDS:

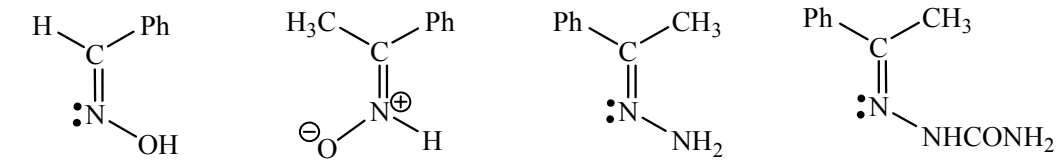
Geometrical isomerism of nitrogen compounds: Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are (Figure 22):

(e) Oximes

(f) Nitrones

(g) Semicarbazones

(h) Hydrazones

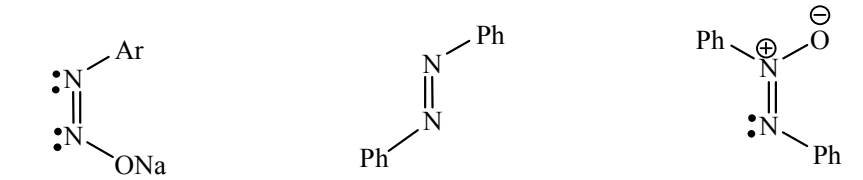


(*Z*)-benzaldehyde oxime (*E*)-nitrone (*E*)-1-(1-phenylethylidene) hydrazine (*E*)-1-(1-phenylethylidene) semicarbazide

Figure 22: Geometrical isomers of compounds having >C=N

Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism.

Some examples of compounds exhibiting geometrical isomerism containing –N=N- are shown in figure 23.

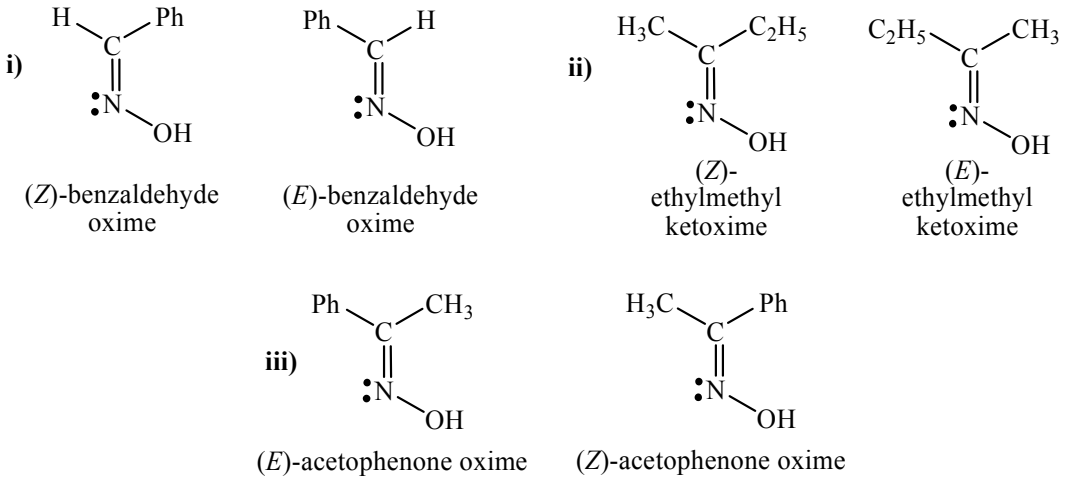


(*Z*)-Diazoate (*E*)-Azobenzene (*E*)-Azoxybenzene

Figure 23: Geometrical isomers of compounds having -N=N

The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*-isomer.

Example 26: E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime



Enantiomerism of nitrogen compounds: The tetrahedral concept of carbon has also been successfully extended to nitrogen containing compounds. The only difference in nitrogen compounds is that one of the sp^3 hybridized orbital of nitrogen usually contains a lone pair of electrons which is not involved in bonding. Thus nitrogen containing compound have three ligands and one lone pair in sp^3 orbital. Thus in terms of a chiral center, nitrogen is analogous to carbon. The tertiary amines of with all three different atoms or groups attached with center nitrogen atom have chiral nitrogen, but do not have optical activity. Thus is due to the rapid interconversion of lone pair from one face of the other resulting in rapid racemization Figure 24. The amine interconversion is described as an inversion, such enantiomers are called invertomers.

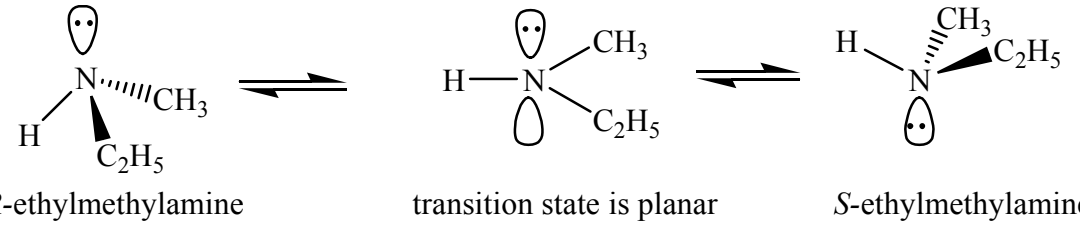


Figure 24: Inversion of lone pair in nitrogen containing compounds

5.9.2 STEREOCHEMISTRY OF COMPOUNDS CONTAINING P:

Phosphorous can also exhibit covalencies of 3, 4 and 5, hence they give rise to more possible configuration than nitrogen. In tetravalent phosphorous compounds the valence deposition is tetrahedral (sp^3 hybridized) in which one sp^3 orbital being occupied by lone pair, whereas, in

quinquevalent (pentavalent) phosphorous compounds the valence deposition is trigonal bipyramidal (sp^3d). The following are examples of the various resolvable compounds of phosphorous in its different hybrid states (Figure 26).

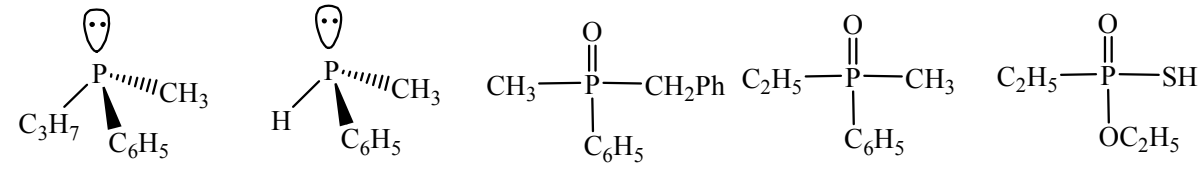


Figure 27: Examples of the various resolvable compounds of phosphorous

5.9.3 STEREOCHEMISTRY OF COMPOUNDS CONTAINING S:

Similar to nitrogen and phosphorous containing compounds, various sulphur containing compounds have also been identified to exhibit enantiomerism. Some common examples are Sulphonium salts, Sulphuris esters, Sulphoxides and Sulphines, Figure 28.

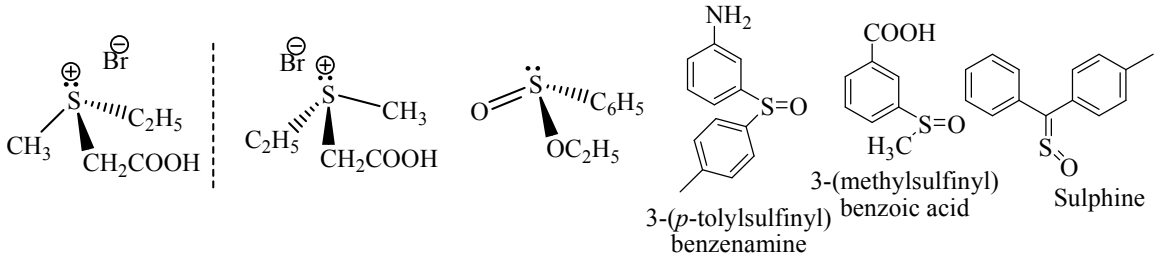


Figure 28: Examples are Sulphonium salts, Sulphuris esters, Sulphoxides and Sulphines

5.10 SUMMARY

The present unit may be summarized as:

- Topicity is the stereo-chemical relationships between individual atoms or groups within a single molecule.
- The property by which the replacement of two similar atoms or groups of a carbon center generates the chirality is called prochirality.

- Two apparently identical atoms/groups of a prochiral centre are called homomorphic atoms/groups.
- If the replacement of two homomorphic ligands generates enantiomers the ligands are called enantiotopic ligands.
- If the replacement of two homomorphic ligands generates diastereomers the ligands are called diastereotopic ligands.
- Stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment is called asymmetric induction.
- Those reactions in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several possible stereoisomers are called stereoselective reactions.
- The reactions or processes in which one of the enantiomer forms predominantly over the other is called enantioselective reaction.
- The reactions or processes in which one of the diastereomer forms predominantly or exclusively over the other are called diastereoselective reaction.
- Rotation around bonds in alkane structures, exemplified in ethane and butane, gives rise to conformational isomers.
- In the staggered form, the torsional angle between attached groups is at 60^{o}. In the eclipsed form, it is at 0^{o}.
- A staggered conformation of ethane or butane has a lower rotational energy than the eclipsed conformation.
- Anti-conformations are usually the more stable with gauche and eclipsed structures of higher energy.
- Analysis of cyclohexane derivatives pays attention to substituents in axial and equatorial positions, with equatorial substituents being more stable.
- The most stable form of cyclohexane is the chair conformation. In this form, the molecule has both axial and equatorial substituents.
- Cyclohexane undergoes a chair-boat-chair ring flip in which the axial substituents become equatorial, and vice versa.

- Interconversions between chair forms involve higher energy structures known as boat, twist and half-chair structures that are unstable.
- Cyclohexanes with axial substituents are less stable than those with the same substituents equatorial, because of unfavorable interactions among axial substituents.

5.11 TERMINAL QUESTION

Q.1 Define Topicity.

Q.2 What is prochirality?

Q.3 What are enantiotopic ligands and faces?

Q. 4 What do you understand with asymmetric synthesis?

Q. 5 Define configurational and conformational isomers.

Q. 6 Why the geometrical isomers are called diastereomers?

Q. 7 What is cyclization method for determination of configuration of geometrical isomers?

Q. 8 How do you determine the configuration of geometrical isomerism using physical method?

Q. 9 What are staggered and eclipsed conformations of alkanes?

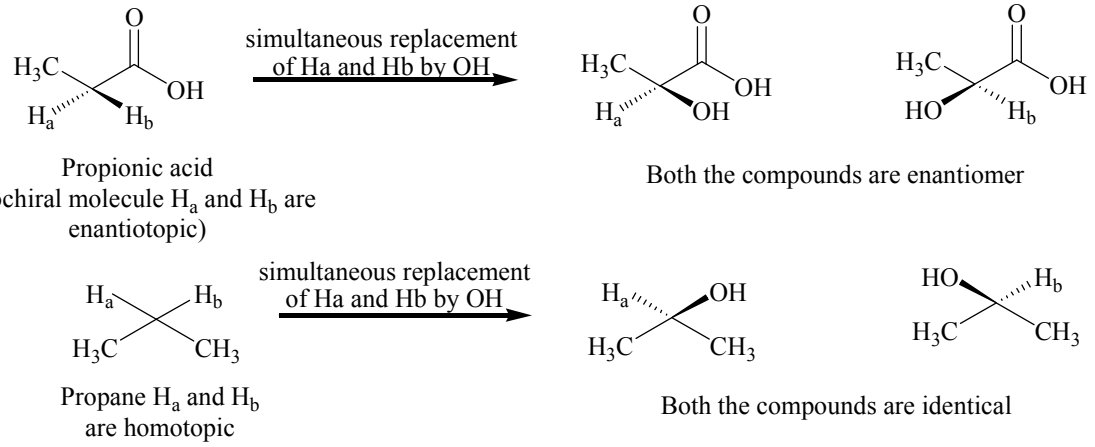
Q. 10 Which conformation of cyclohexane is the most stable and why?

Q. 11 What will be the preferred position for methyl group in the conformation of methyl cyclohexane?

5.12 ANSWERS

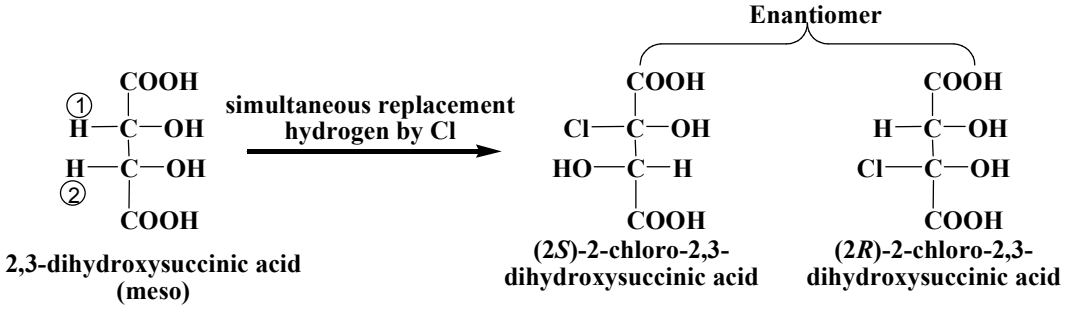
1. Stereo-chemical relationships between individual atoms or groups within a single molecule can be defined in terms of topicity. Thus, two atoms equated by a mirror reflection of the molecule are enantiotopic and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are homotopic. Two protons placed in diastereomeric positions by a mirror reflection are in diastereotopic environments.

   Examples: Propane has homotopic ligands; however, propionic acid has enantiotopic ligands



2. It is the property of some molecules due to which these molecules can be converted in to stereoisomers (enantiomers or diastereomers) by replacing one of the identical atoms or groups by a different atom or group. It is also known as '*prostereoisomerism'* more specifically. If the replacement of such atoms or groups leads the formation of enantiomer the atoms or groups are called enantiotopic; whereas, if such replacement lead the formation of diastereomers the atoms or groups are termed as diastereotopic.
3. When the replacement of each equivalent atom or groups by a different atom given enantiomeric products, such equivalent atoms or groups are called enantiotopic atoms or enantiotopic ligands.

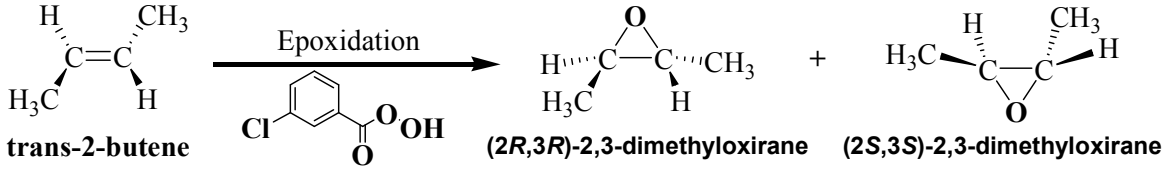
   Example: For example, two hydrogen atoms of meso-tartaric acid are enantiotopic since the replacement of each one of them by a different atom or group gives the enantiomeric pair of (*2S*)-2-chloro-2,3-dihydroxysuccinic acid and (*2R*)-2-chloro-2,3-dihydroxysuccinic acid.



Similarly, when two faces of a double bond gives enantiomers on addition of suitable reagents, such faces are called enantiotopic faces. For example, trans-2-butene and

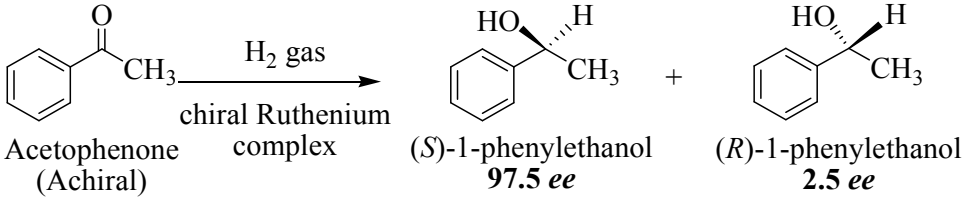
unsymmetrical ketones have enantiotopic faces since they also give enantiomers on addition of suitable reagents.

Example: Epoxidation of trans-2-butene on either face of double bonds gives the enantiomeric pair of (*2R,3R*)-2,3-dimethyloxirane and (*2S,3S*)-2,3-dimethyloxirane.



4. Asymmetric induction is a stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment. This is also known as asymmetric synthesis.

   Example: Let us consider hydrogenation of Acetphenone by sodiumborohydride ($NaBH_4$). Since, both the reagent and substrate are achiral (optically inactive) and also the reaction takes place in the medium of methanol (achiral), hence, equal amount of (*R*)-1-phenylethanol and (*S*)-1-phenylethanol (racemic mixture) is formed.



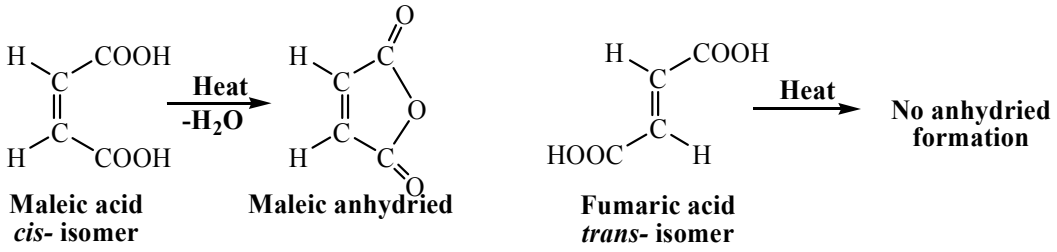
5. The stereoisomerism which is due to the rotation about a single bond is referred to as conformation. Conformers are easily interconvertible and it is difficult to isolate the isomer. On the other hand, when two compounds are different in their configuration, e.g., a pair of enantiomers of bromofluoromethane, or a pair of geometrical isomers, maleic acid and fumaric acid, these are distinguishable compounds, and their isolation is possible

6. Geometrical isomers are non-mirror image of each other hence they are called diastereomers. Therefore their physical and chemical properties are different.

7. Cyclization method**:** Cyclization within a molecule (intramolecular) is usually depends upon the distance of two associating groups of a molecule. In other words if the reacting groups are closer to each other than the intramolecular cyclization takes place more effectively. This principal is also helps to identify the configuration of geometrical isomers.

   Let us take an example of two geometrical isomer of Butenedioic acid (*i.e. Maleic acid and Fumaric acid*) can be differentiated by possibility of formation of anhydride. Maleic acid which is c*is*- form of Butenedioic acid can only give the respective anhydride on heating; whereas, the trans- form of Butenedioic acid (*i.e.* Fumaric acid) does not give its anhydride on heating. If the Fumaric acid is strongly heated it get converted into Maleic acid.

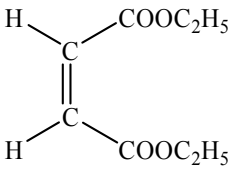
   Example : Cyclization of Maleic acid to Maleic anhydride. Fumaric acid does not give the anhydride on heating.



8. The geometrical isomers are non-mirror image of each other hence are called diastereomers. We have discussed in Unit 4 that diastereomers have different physical and chemical properties. Based on this fact, we can determine the configuration of geometrical isomers by comparing their physical properties. For example the melting point and absorption intensity of the *cis*-isomer are lower than the *trans*-isomer. Similarly the boiling point, solubility, heat of hydrogenation, density, refractive index, dipole moment and dissociation constant of *cis*-isomer is greater than the *trans*-isomer.

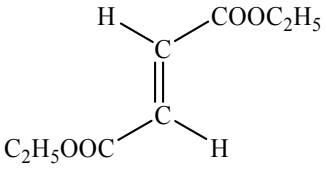
   Thus if you have a set of geometrical isomers, then by comparing their above mentioned physical properties you can assign their configuration (means you can identify the *cis*- and *trans*-isomers).

Example : Diethyl maleate and diethyl fumarate are the *cis*- and *trans*- form to each other. The configuration of these can be determined by comparing their dipole moment. The dipole moment of diethyl maleate is 2.54D whereas the dipole moment of diethyl fumarate is 2.38D. Based on the fact that the dipole moment of *trans*- form of an isomer is lower than that of *cis*- form, you can easily predict the *cis*- and *trans*- form for diethyl maleate and diethyl fumarate.



diethyl maleate

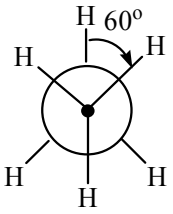
dipole moment = 2.54D



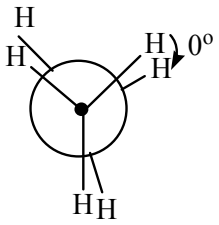
diethyl fumarate

dipole moment = 2.38D

9. Conformation with a 60° dihedral angle is known as staggered conformation. The angle between the atoms attached to the front and rear carbon atom is called dihedral angle.A conformation with a 0° dihedral angle is known as eclipsed conformation.



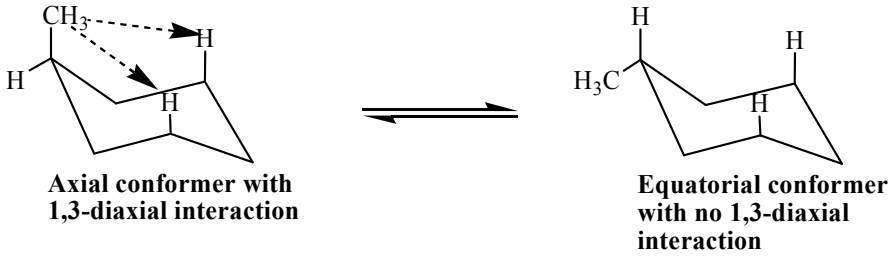
Staggered conformation



Eclipsed conformation

10. The chair conformation is considered as a rigid conformation of cyclohexane in comparison to boat conformation; because during interconversion from chair to boat conformation, some angular deformations are required. These angular deformations usually increase the energy barrier for interconversion from chair to boat conformation. Therefore the chair conformation of cyclohexane is the most stable conformation.
11. There are two possible chair conformations for methyl cyclohexane. In one conformation the methyl group located at axial position, whereas in other conformation the methyl group is located at equatorial position. When methyl group is at axial position, it has 1,3-diaxial interaction with hydrogen atoms at C3 and C5 carbons due to which the

energy of such conformation is very high in comparison to the conformer in which the methyl group is at equatorial position. The conformer with methyl group at equatorial position does not have any kind of 1,3-diaxial interaction hence is more stable.



Axial conformer with 1,3-diaxial interaction

Equatorial conformer with no 1,3-diaxial interaction

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9. Stereochemistry of Organic Compounds by Ernest L. Eliel; Published by John Wiley; ISBN- 0-471-01670-5
10. Organic Chemistry by Leroy G. Wade. Published by Pearson Education; ISBN-9780321768414
11. Stereochemistry: Conformation and Mechanism by P. S. Kalsi. Published by New Age International Publication. ISBN-10: 8122435645; ISBN-13: 978-8122435641
12. Stereochemistry of Organic Compounds: Principles and Applications by D Nasipuri, Published by New Academic Science ISBN-10: 190657491X; ISBN-13: 978-1906574918

UNIT 6: ALIPHATIC NUCLEOPHILIC SUBSTITUTION

CONTENTS:

6.1 OBJECTIVES

After studying this chapter, you shall be able to:

- Know what is Nucleophilic Reaction

- Learn mechanism of Nucleophilic Reactions like SN2, SN1, Mixed SN1 and SN2, SNi and SET mechanisms.
- Learn neighbouring group mechanism
- Learn mechanism of anchimeric assistance
- Identify functional groups taking part in anchimeric assistance
- Evaluate outcomes of anchimeric assistance for various reactions
- To know about Classical and nonclassical carbocations
- To know about various Common carbocation rearrangements reaction

6.2 INTRODUCTION

In organic chemistry, nucleophilic substitution is a fundamental class of reactions in which an electron rich nucleophile selectively bonds with or attacks the positive or partially positive charge of an atom or a group of atoms to replace a leaving group; the positive or partially positive atom is referred to as an electrophile. The whole molecular entity of which the electrophile and the leaving group are part is usually called the substrate.

The most common aliphatic nucleophilic reaction may be given as the following:

Nuc: + R-LG → R-Nuc + LG:

The electron pair (:) from the nucleophile (Nuc) attacks the substrate (R-LG) forming a new bond, while the leaving group (LG) departs with an electron pair. The principal product in this case is R-Nuc. The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged.

6.3 NUCLEOPHILIC REACTION

6.3.1 The SN_2, SN_1 Reaction:

SN1 reaction:

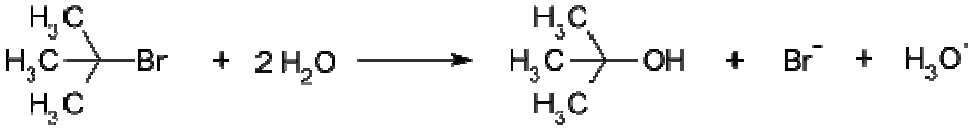
The SN1 reaction is a substitution reaction in organic chemistry. "SN" stands for nucleophilic substitution and the "1" represents the fact that the rate-determining step is unimolecular. Thus,

the rate equation is often shown as having first-order dependence on electrophile and zero-order dependence on nucleophile. This relationship holds for situations where the amount of nucleophile is much greater than that of the carbocation intermediate.

This type of mechanism involves two steps. The first step is the reversible ionization of Alkyl halide in the presence of aqueous acetone or an aqueous ethyl alcohol. This step provides a carbocation as an intermediate. In the second step this carbocation is attacked by the nucleophile to form the product.

Mechanism:

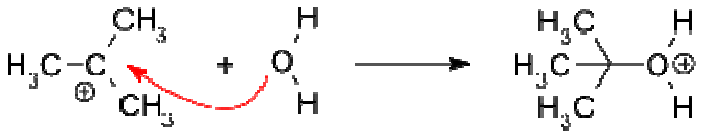
An example of a reaction taking place with an SN1 reaction mechanism is the hydrolysis of tert-butyl bromide with water forming tert-butanol.:



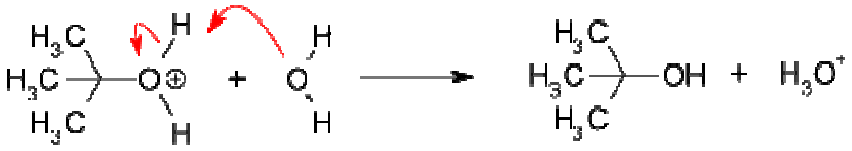
This SN1 reaction takes place in three steps:

Step 1: Formation of carbocation: Formation of a tert-butyl carbocation by separation of a leaving group (a bromide anion) from the carbon atom: this step is slow and reversible.

Step 2: Nucleophilic attack: the carbocation reacts with the nucleophile. If the nucleophile is a neutral molecule (i.e. a solvent) a third step is required to complete the reaction. When the solvent is water, the intermediate is an oxonium ion. This reaction step is fast.



Step 3: Deprotonation: Removal of a proton on the protonated nucleophile by water acting as a base forming the alcohol and a hydronium ion. This reaction step is fast.



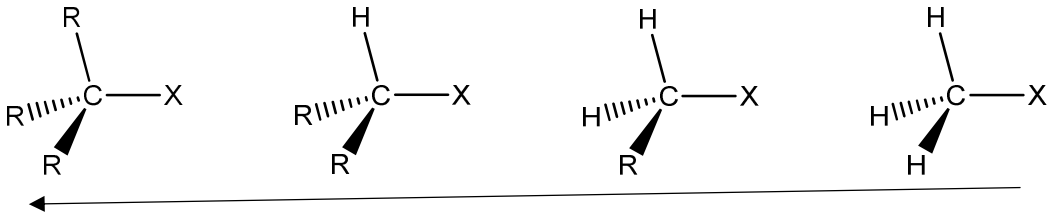
Factor Affecting the SN^1 reaction:

Some of the factor which can affect the SN^1 reaction are given below:

(a) **Nature of substrate:**

For SN^1 reaction reactant should be of the such type that can generate stable carbocation intermediate.

According to the concept reactivity order of the alkyl halide for SN^1reaction can be given as:



-Increase stability of corresponding carbocation.

-Increase reactivity of alkyl halide toward the SN^1 reaction.

(b) Nature of Nucleophile:

Nature of Nu does not affect the SN^1 reaction because Nu does not involve in the slow step of SN^1 reaction.

(b) Nature of leaving group:

For the SN^1 reaction always leaving group less basic in nature.

Stereochemistry of SN^1 reaction:

Reaction is the two step reaction during which there can occur the inversion as well as retention of configuration i.e. there can occur racemization during the SN^1 reaction

Effect of the solvent on the rate of SN^1 reaction: During the slow step or rate determining step of the SN^1 reaction there occurs the formation of polar nature of transition state before generating the carbocation. The polar solvent with high dielectric constant value stabilize the transition state by which energy of activation for the slow step or rate determining step is decrease in the dielectric constant value of polar solvent. While on the other hand nonpolar solvent does not interact with T.S. of substrate due to which they does not decrease the activation energy of rate determining step i.e. they does not affect the rate of SN^1 reaction.

SN^1

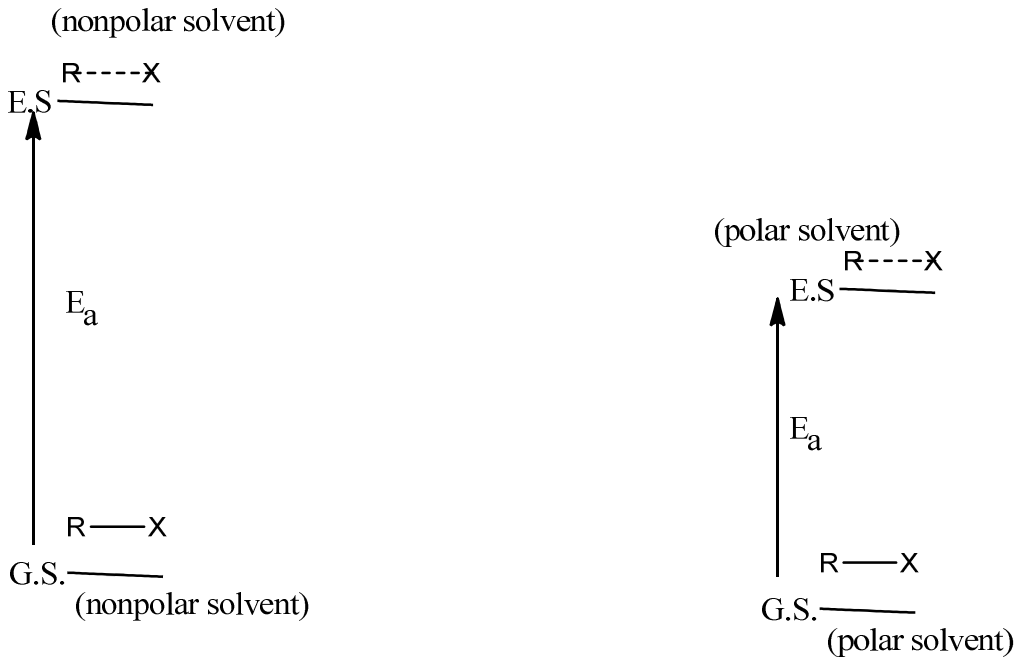


Figure: 1

Polar solvent stabilizes the T.S. of SN^1 reaction and increase the rate of reaction.

Relative rate of SN^1 in t-butyl chloride according to the dielectric constant of same polar solvent can be given as:

Solvent	Dielectric constant	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	1,50,000

Potential energy diagram for SN^1 reaction:

SN^1 reaction is the two step reaction for with P.E diagram can be represented as:

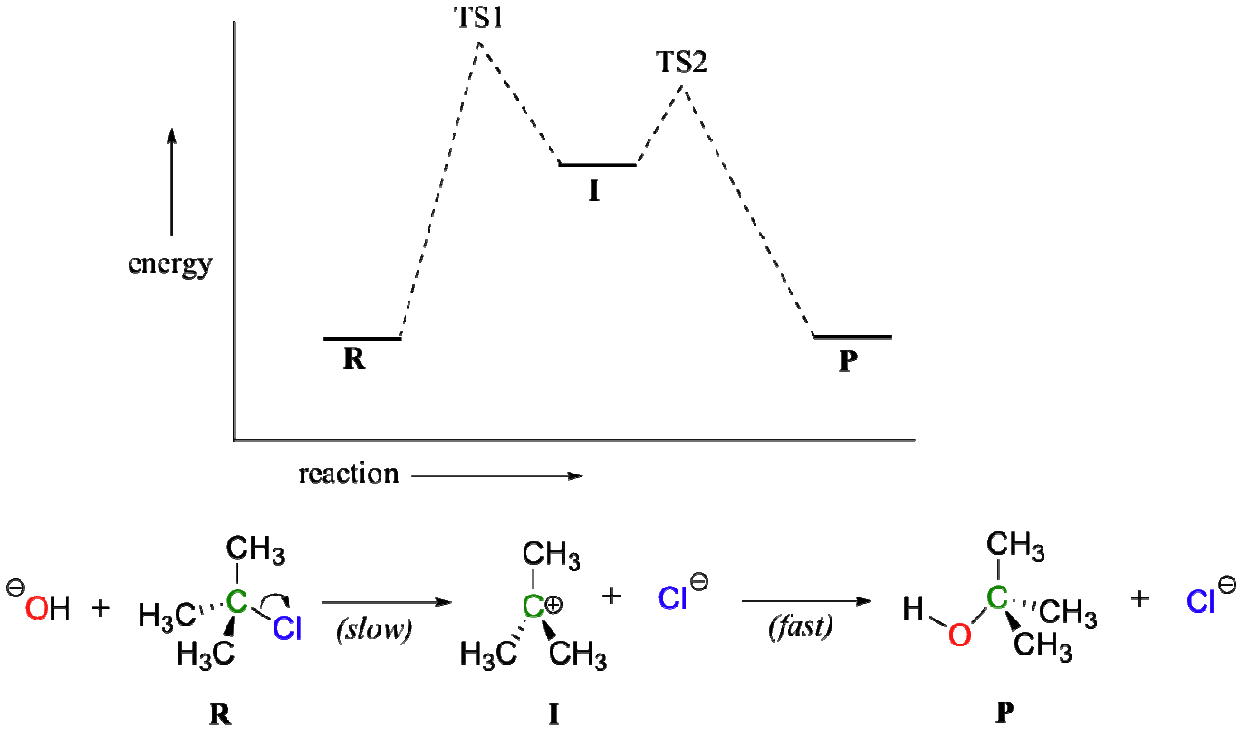


Figure.2

SN2 Reaction:

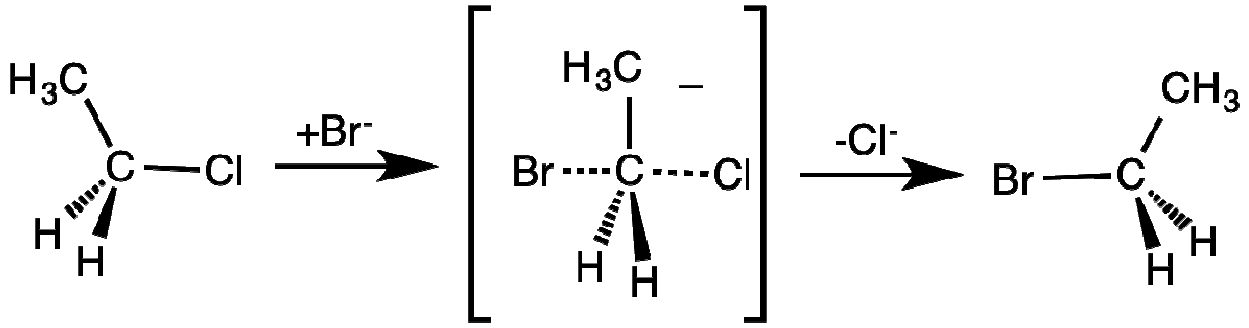
The SN2 reaction is a type of reaction mechanism that is common in organic chemistry. In this mechanism, one bond is broken and one bond is formed synchronously, i.e., in one step. SN2 is a kind of nucleophilic substitution reaction mechanism. Since two reacting species are involved in the slow (rate-determining) step, this leads to the term substitution nucleophilic (bi-molecular) or SN2, the other major kind is SN1. Many other more specialized mechanisms describe substitution reactions.

Mechanism of SN2 reaction:

The reaction most often occurs at an aliphatic sp^3 carbon center with an electronegative, stable leaving group attached to it (often denoted X), which is frequently a halide atom. The breaking of the C–X bond and the formation of the new bond (often denoted C–Y or C–Nu) occur simultaneously through a transition state in which a carbon under nucleophilic attack is pentacoordinate, and approximately sp^2 hybridised.

The nucleophile attacks the carbon at 180° to the leaving group, since this provides the best overlap between the nucleophile's lone pair and the C–X σ* antibonding orbital. The leaving group is then pushed off the opposite side and the product is formed with inversion of the tetrahedral geometry at the central atom.

In an example of the SN_2 reaction, the attack of Br^- (nucleophile) on an ethyl chloride (electrophile) results in ethyl bromide, with chloride ejected as the leaving group.:

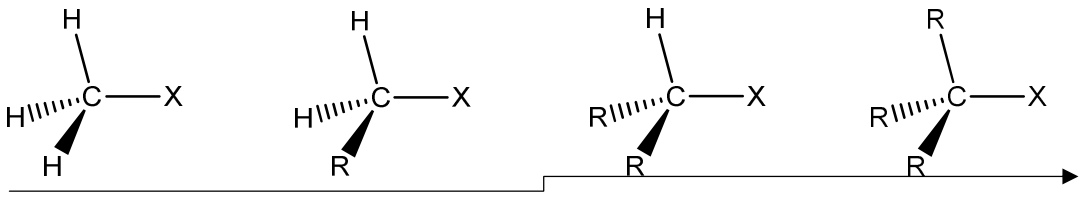


Factor affecting SN^2 Reaction:

Some of the factors which can affect the SN^2 reaction are given below:

(a) Nature of Substrate:

For the SN^2 reaction substrate should contain less bulky atoms or group otherwise backside attack of nucleophile will not be possible. On the basis of the above given concept the order of reactivity for 1^o, 2^o and 3^o alkyl halide toward the SN^2 reaction will becomes as:



-Increase number of bulky substituent.

-Decrease possibility of back attack of Nu.

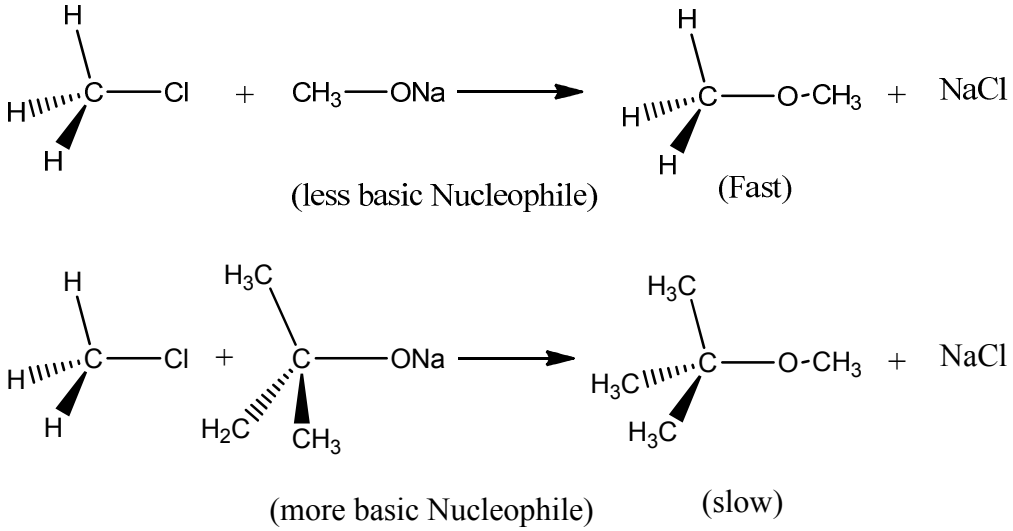
-Decease reactivity of alkyl halide toward the SN^2 reaction.

(b) Nature of nucleophile:

(i) For the SN^2 reaction nucleophile should be less bulky otherwise back side attack of Nu will not possible due to steric reason.

(ii) For the SN^2 reaction Nu should more basic in nature. Sometime bulkiness factor of Nu can be dominated over the basicity factor.

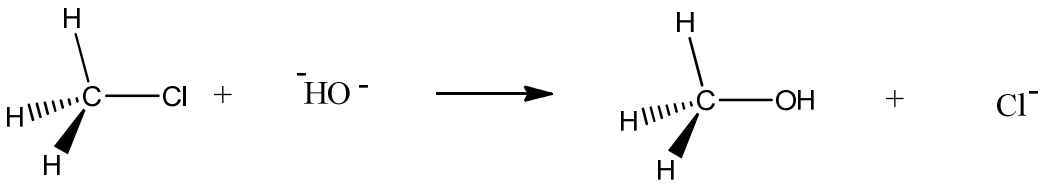
Example: CH_3Cl exhibit 1000 times faster reaction with CH_3O^- in compare to the reaction with more basic $(CH_3)_3CO^-$.



(c) Nature of leaving group: For the SN^2 reaction leaving group should be less basic in nature.

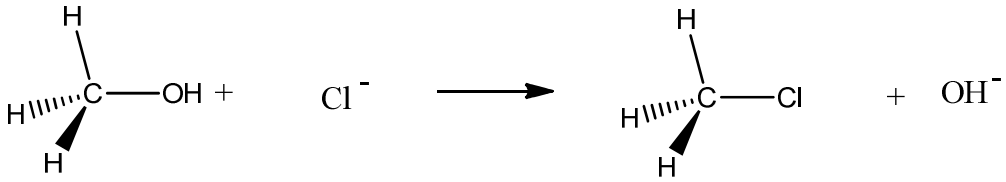
(d) Always basicity of Nu should be more in compare to the basicity of leaving group otherwise reaction will not be possible.

EXAMPLE:



This reaction is possible due to more basic strength of OH^- ion (nucleophile) than the Cl^- ion (leaving group)

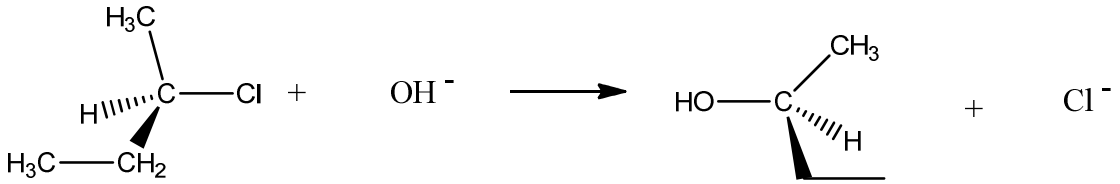
Example:



This reaction is not possible due to less basic strength of Cl^- ion (Nucleophile) than the OH^- ion (leaving group)

Stereochemistry of SN^2 reaction:

During the SN^2 reaction attack from the back side in the substrate due to which always there will occur the inversion in configuration.



R **(Inversion of configuration)** S

Walden Inversion:

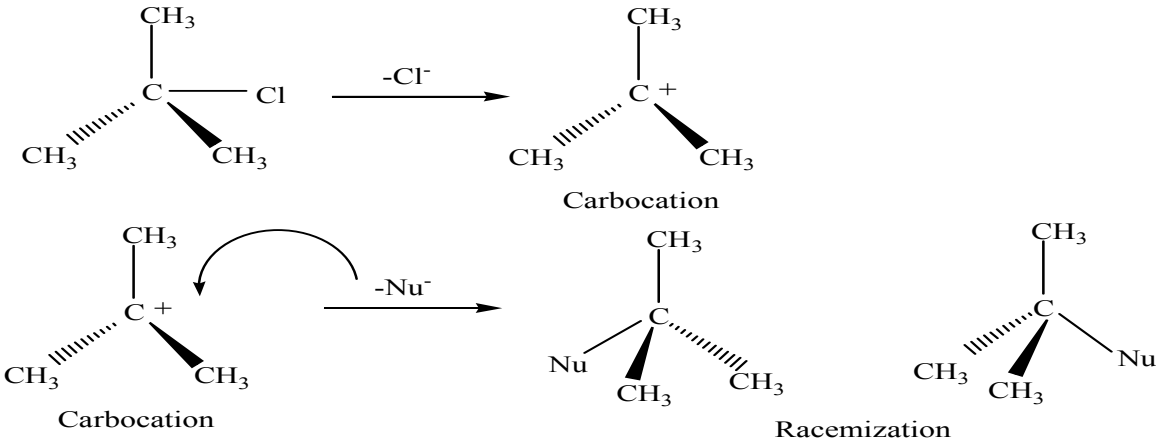
If the inversion in configuration occur at chiral center by the SN^2 reaction than such type of inversion in configuration is called as Walden inversion.

6.3.2 Mixed SN1 and SN2 Nucleophilic Substitution:

Mixed SN1 and SN2 reaction consists of a nucleophile and a substrate. When a nucleophile reacts with a substrate, substitution takes place. This substitution is known as nucleophilic substitution reaction. A substitution reaction occurs and the leaving group from the substrate departs. The nucleophile is an electron pair donor. The substrate acts an electrophile (electron pair acceptor). The electrophile has sp_3 hybridization. There must be a leaving group in the electrophile.

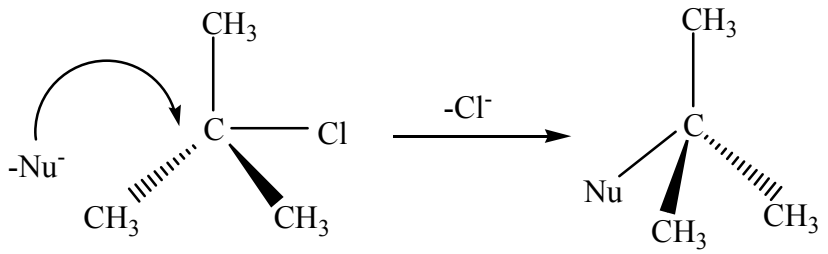
Substitution Nucleophilic Unimolecular (SN1) Reaction:

In SN1 reaction, there is one molecule reacting in the reaction intermediate state or the transition state. A carbocation which is planar in nature is first formed. Then a nucleophile attacks on the carbocation to form the intermediate or the transition state. Here the nucleophile is free to attack from either side of the substrate. Therefore, there occurs racemization.



Substitution Nucleophilic Bimolecular (SN2) Reaction:

In SN2 reaction, there are two molecules react in the reaction intermediate state or the transition state. The leaving group departs simultaneously as soon as the nucleophile attacks the molecule or the substrate from the backside. Hence in the product side, there occurs inversion of the configuration.

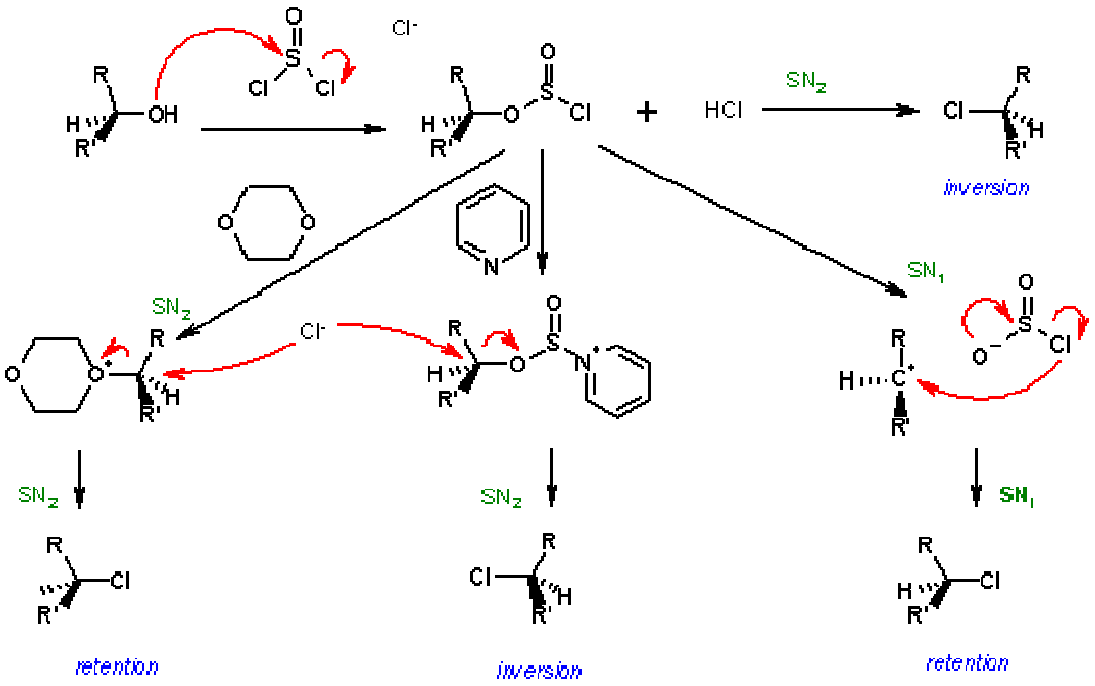


Inversion of configuration

In the above, both nucleophilic substitution reactions (mixed SN1 and SN2), there is a competition between the leaving group and the nucleophile.

SNi Mechanism: SNi or Substitution Nucleophilic internal stands for a specific but not often encountered nucleophilic aliphatic substitution reaction mechanism. This reaction type is linked to many forms of neighbouring group participation, for instance the reaction of the sulfur or nitrogen lone pair in sulfur mustard or nitrogen mustard to form the cationic intermediate.

This reaction mechanism is supported by the observation that addition of pyridine to the reaction leads to inversion. The reasoning behind this finding is that pyridine reacts with the intermediate sulfite replacing chlorine. The dislodged chlorine has to resort to nucleophilic attack from the rear as in a regular nucleophilic substitution.

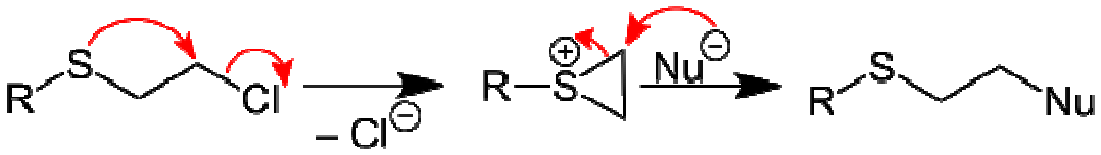


6.4 THE NEIGHBOURING GROUP MECHANISM

During the SN2 reaction if hydrocarbons of heteroatom like N, S etc. being present at β position or π bond being present at the γ- position with respect to the leaving group than there occur the enhancement (increase) in the rate of the SN2 reaction. The mechanism operating in such neighboring group participation.

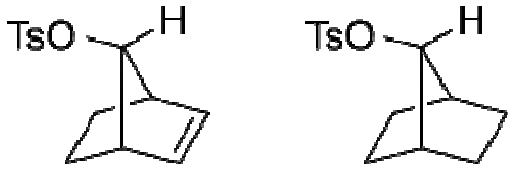
During the neighbouring group mechanism there occurs the formation of highly reactive three membered cyclic intermediate by the intramolecular reaction but the final substitution product formation occur with the retention of configuration because there occur the two consecutive SN2 reactions.

Due to the formation of highly reactive three membered cuclic intermediate these reaction being thousand times faster than the normal SN2 reaction.

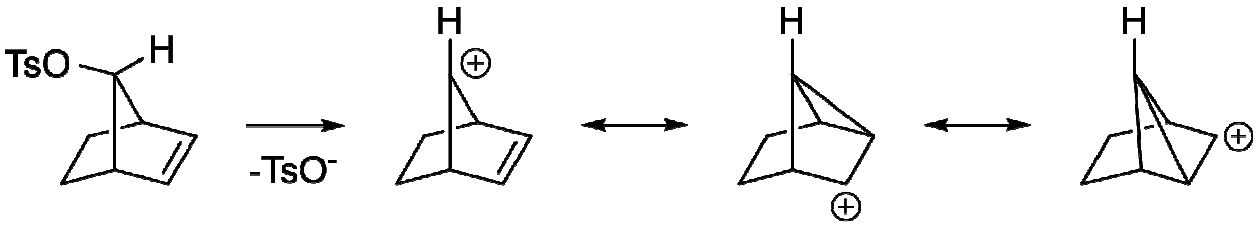


NGP by an alkene:

The π orbitals of an alkene can stabilize a transition state by helping to delocalize the positive charge of the carbocation. For instance the unsaturated tosylate will react more quickly (10^{11} times faster for aqueous solvolysis) with a nucleophile than the saturated tosylate.

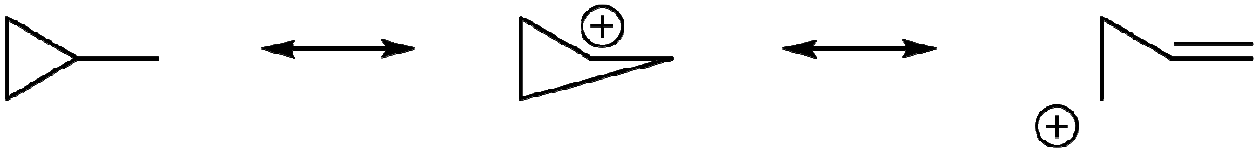


The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms; in the diagram below this is shown.



NGP by a cyclopropane, cyclobutane or a homoallyl group:

If Cyclopropylmethyl chloride is reacted with ethanol and water then a mixture of 48% cyclopropylmethyl alcohol, 47% cyclobutanol and 5% homoallyl alcohol (but-3-enol) is obtained. This is because the carbocationic intermediate is delocalised onto many different carbons through a reversible ring opening.



6.5 ANCHIMERIC ASSISTANCE

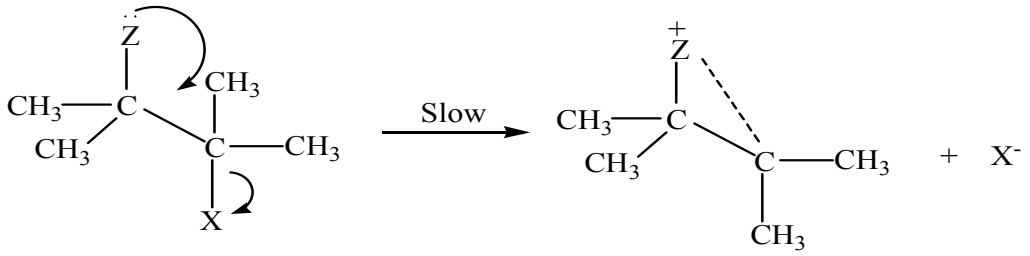
When a catalytic functional group or atom is part of the reacting molecule, the catalysis is called intra-molecular catalysis. Anchimeric assistance (anchimeric in Greek means "adjacent parts") is a case of intra-molecular catalysis where a suitably placed intra-molecular nucleophile assists in a substitution reaction by enhancing rate of reaction.

Mechanism of anchimeric assistance:

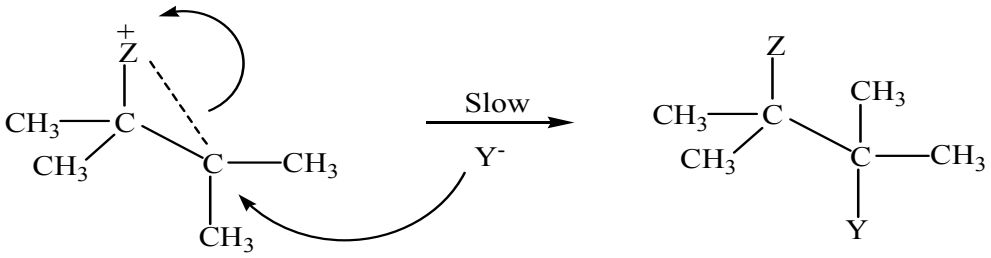
The bimolecular mechanisms for nucleophilic substitution are termed SN2 reactions. SN2 reactions follow second order rate kinetics. The geometric alignment of transition state for SN2 mechanism is such that the nucleophile attacks from the rear of the leaving group, leading to inversion of configuration.

However, there are some examples of retention of configuration in SN2 reactions, where an atom or group (Z) close to the carbon undergoing subsitution assist in the reaction with its available pair of electrons. Such a group is called a neighbouring group (NG) and the assistance provided is termed neighbouring group participation (NGP). If such participation leads to an enhanced reaction rate, the group is said to provide anchimeric assistance.

Step-I



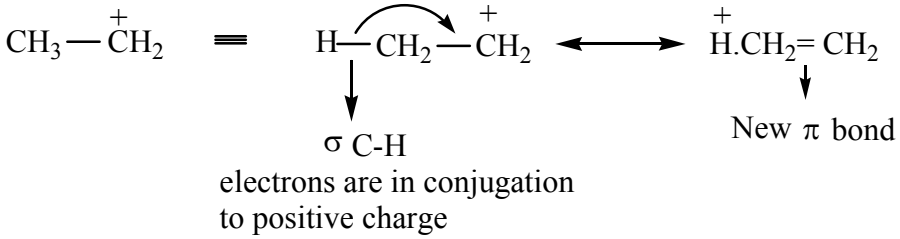
Step-2



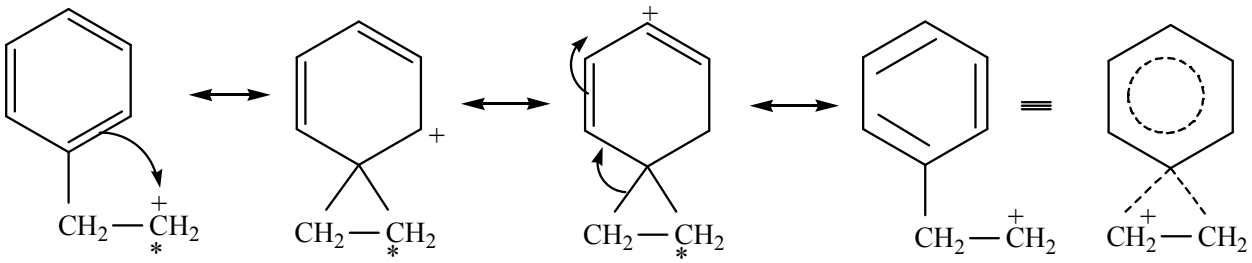
The mechanism for anchimeric assistance is a two step mechanism where two consecutive SN2 reaction leads to retention of configuration. In the first step, the neighbouring group (Z) acts as a nucleophile, attacking the substitution centre and expelling out the leaving group. In the next step, the external nucleophile (Y) attack from backside displacing the neighbouring group and retaining the overall configuration. Since the first step is slow and is rate determining, the reaction follows first order kinetics and there is no effect of concentration of Y- on rate of reaction.

6.6 CLASSICAL AND NON-CLASSICAL CARBOCATIONS

Carbocations discussed so far are called classical carbocations. Classical carbocations are those which get stabilised by the movement of either the loan pair of electrons or C-H sigma –electrons or pi- electrons, in conjugation to the positive charged carbon atom to form a new pi- bond.



On the other hand, if in a carbocation the positive charge does not get conjugated with the pi-bond, and then the resonance structure cannot be written in a normal way. However, in some cases the resonance structures can ce written by the participation of the neighbouring groups. The resultant in the formation of bridged cation which are called non-classical carbocation.



Nonconjugation I

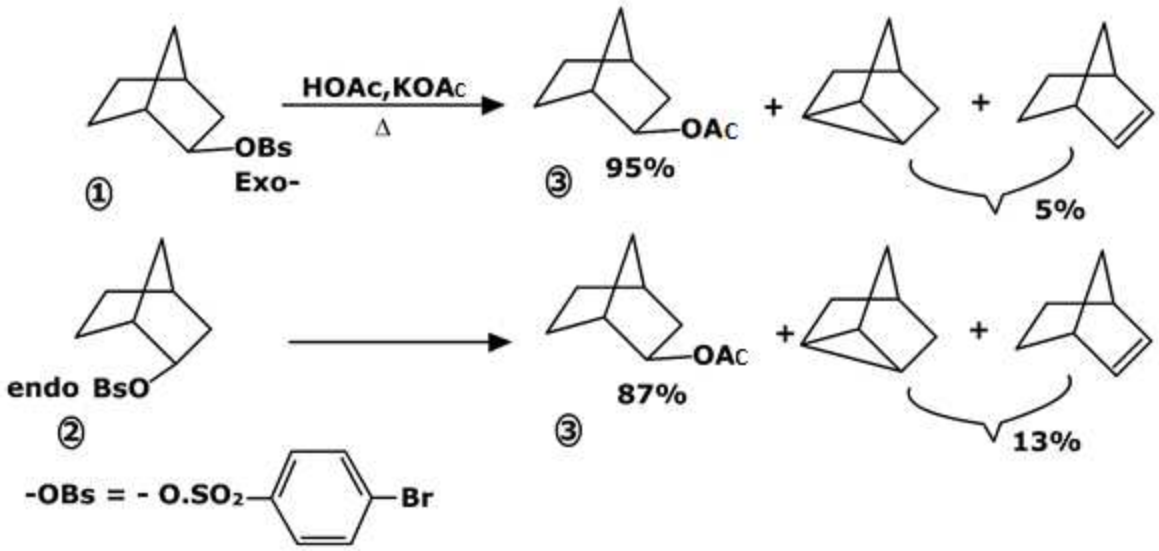
In structure (I) two carbons, carbon -1 and carbon- 2 are bonded together by sigma bon. The third carbon is bonded with other two carbons by two electrons three centered bon. The thired atom however, can also be a hydron atom. The leades the formation of bridiged structure. These bridiged structures which involve delocalised of sigma electrons and formation of three centered, two electron bonds are called non- classical ion. In classical carbocation positive charge is either located on one carbon or is delocalised due to conjugation of pi- electrons or loan pair of electrons in allylic position. In non- classical carbocation positive charge is delocalised either by sigma electrons of C-C or C-H bond of carbob carbon double bond which is not in allylic position.

6.7 NORBORNYL CATION

Vaious naturally occurring terpenes are derivatives of Norbornane. Molecular rearrangements are common among these bicyclic terpenes. Winstein and roberts (1950) actively pursued the mechanism of the rearrangemts and the associated stereochemical problems using the basic norbornyl system.

Acetolysis of 2-norbornyl brosylates:

Each of the isomeric brosylates (1 and 2) is prepared and subjected to acetolysis. (solvolysis using acetic acid as solvent and nucleophile)



In the above reactions following observations takes place:

(i) Rate of solvolysis of 1 to 2 is about 400

(ii) Both 1 and 2 give 3, the exo-acetate

(iii) Optically active exo-brosylate (1) gives 3 which is racemic (±)

(iv) The recovered brosylate (1) is also racemic

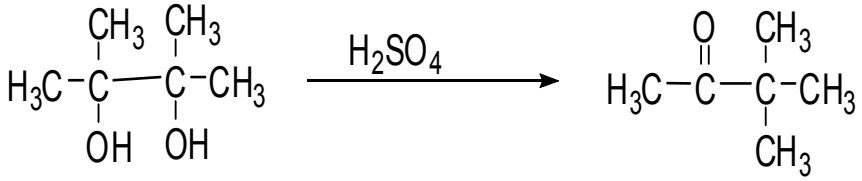
(v) The rate of racemisation (measured from specific Rotation) is greater than solvolysis in the case of the exo-isomer

(vi) The rate of racemization is equal to the rate of solvolysis in the case of endoisomer.

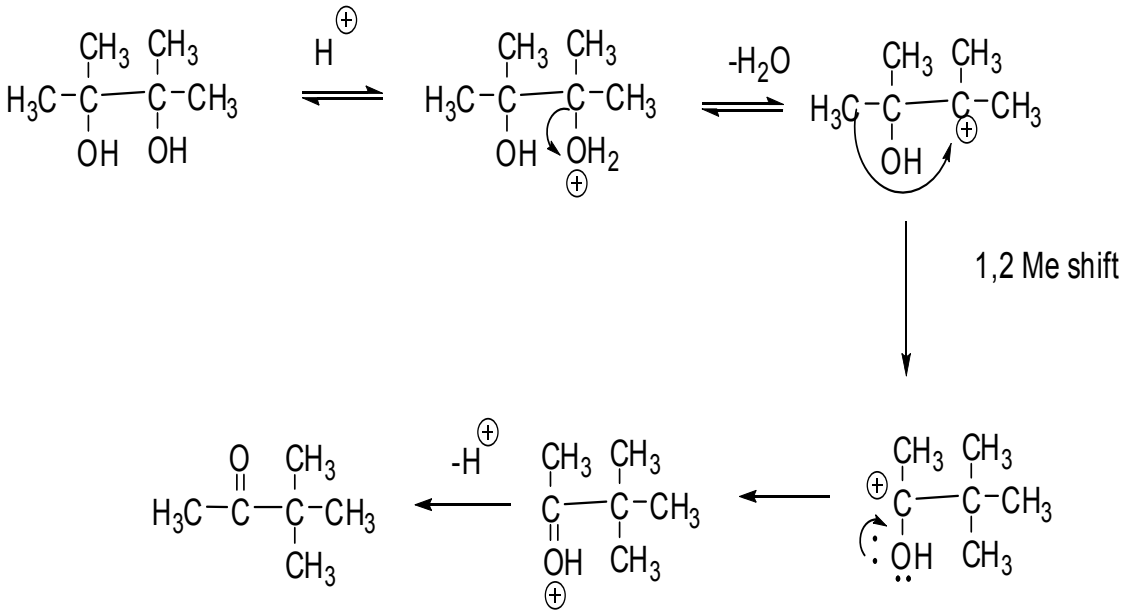
6.8 COMMON CARBOCATION REARRANGEMENTS

6.8.1 Pinacol-Pinacolone rearrangement:

Acid catalysed rearrangement of vicinal diol (Pinacol) into ketone or aldehyde (Pinacolone) is known as Pinacol-Pinacolone Rearrangement.



Mechanism:



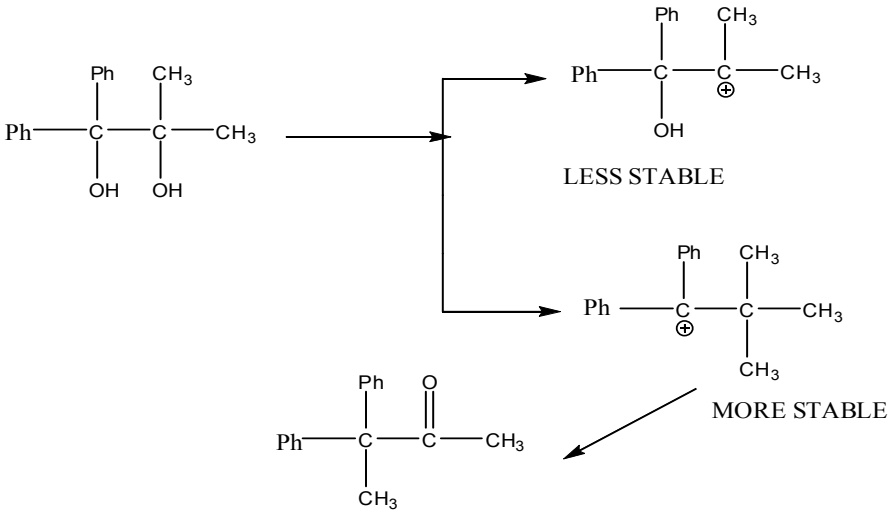
This reaction can be catalysed by the protic acids like H2SO4, H3PO4, HClO4 etc.

During the Pinacol-Pinacolone Rearrangement the migrating aptitude of various atoms or groups having following order:

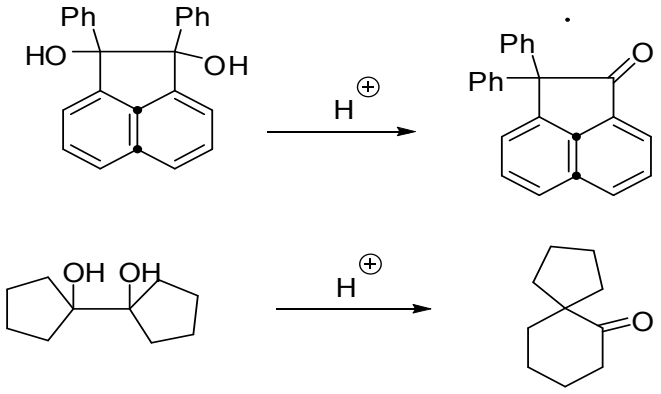
H>Aryl>Alkyl

Some of the examples related to these reactions can be given as:

This order of the migrating aptitude being applicable during reactions.

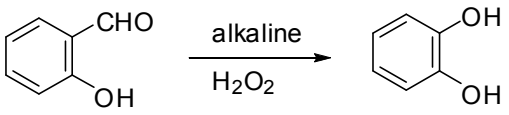


In the case of aryl subsistent if there will be. EDG in the aryl–substitutent than migrating aptitude will further be higher while there will be EWG in the aryl substituent then migrating aptitude will be lower than un substituted aryl group.

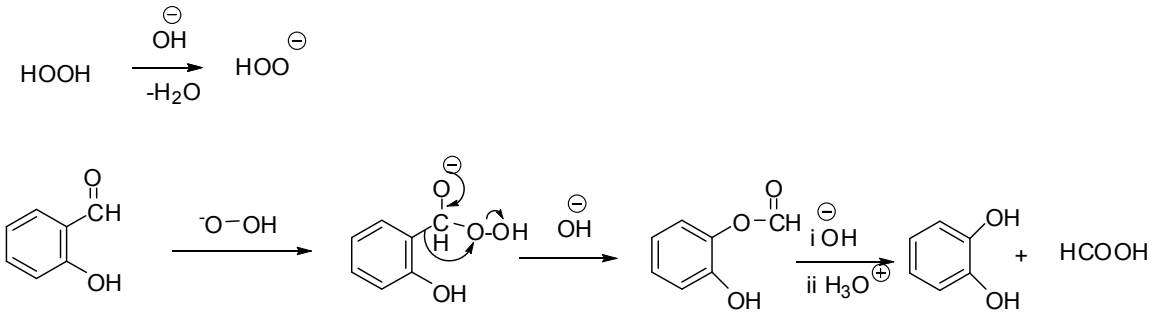


6.8.2 Dakin Reaction:

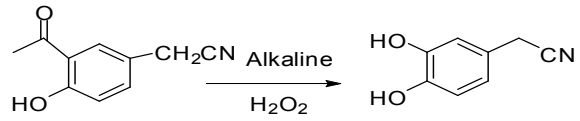
Replacement of an aldehyde or keto group by the hydroxyl group when it is present ortho or para with respect to the hydroxyl or amino group, on treating with alkaline H2O2 is called as Dakin Reactions.

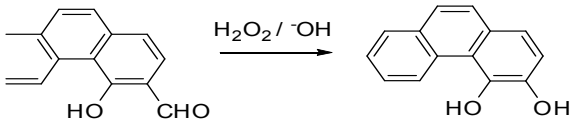


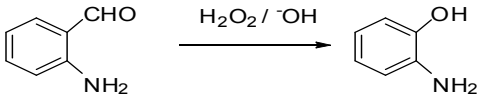
Mechanism:

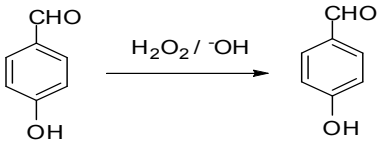


Some other examples of these reactions can be given as:





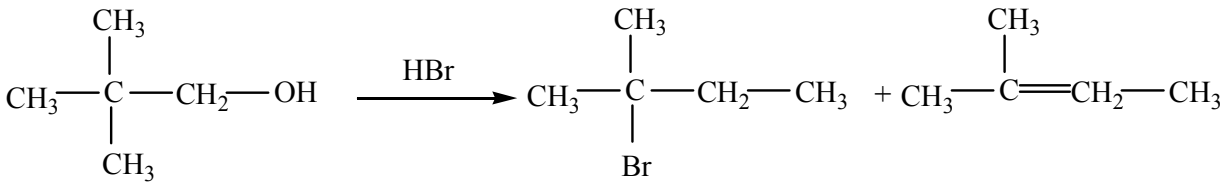




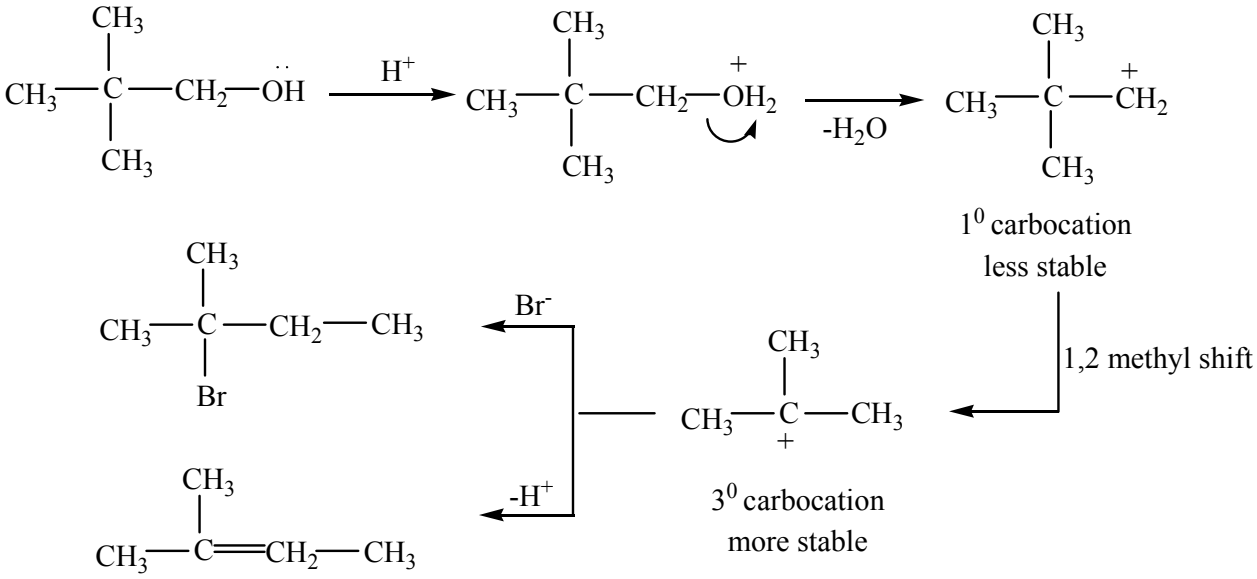
6.8.3Wagner-Meerwein rearrangement:

All those chemical reactions (Generally substitution or elimination reactions) which give the product through the carbocation intermediate with the rearranged carbon skeleton are called as Wagner- Meerwein Rearrangement reactions.

During these reaction carbocation intermediate having the tendency to increase their stability.

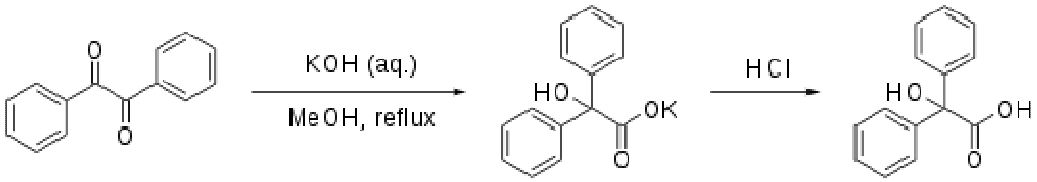


Mechanism:

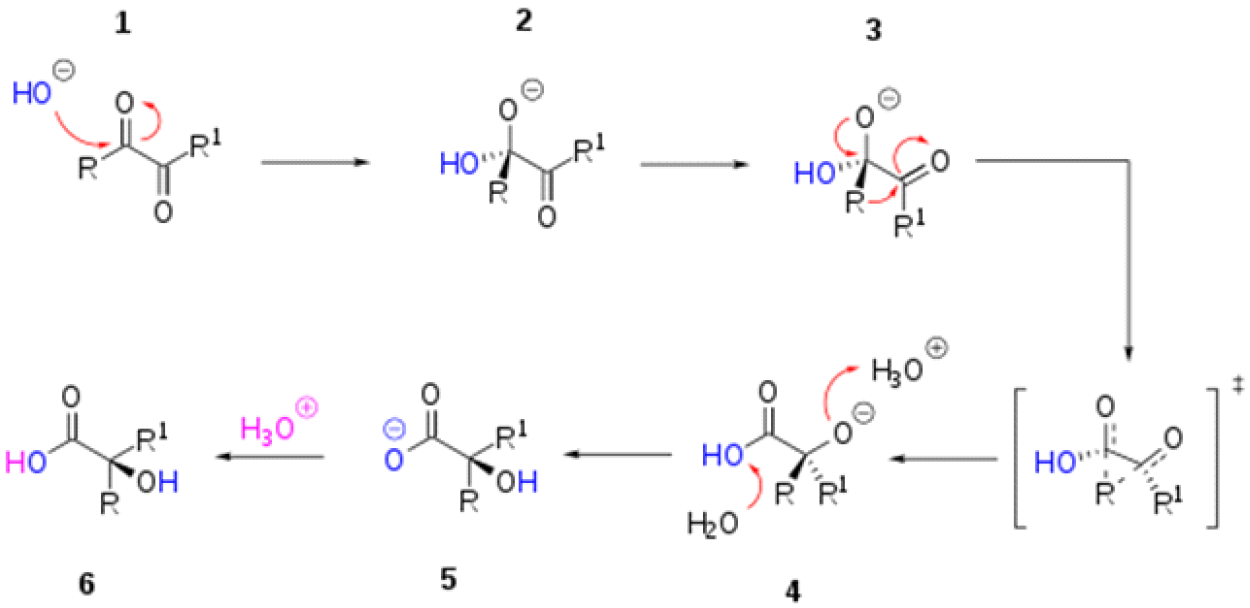


6.8.4 Benzilic acid rearrangement:

Rearrangement of α-diketone into α-hydroxyl acid in the presence of any strong base is known as benzilic Acid rearrangement.

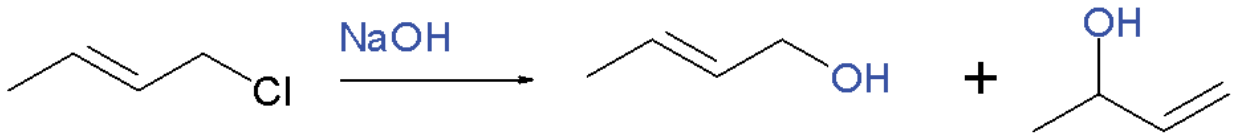


Mechanism:

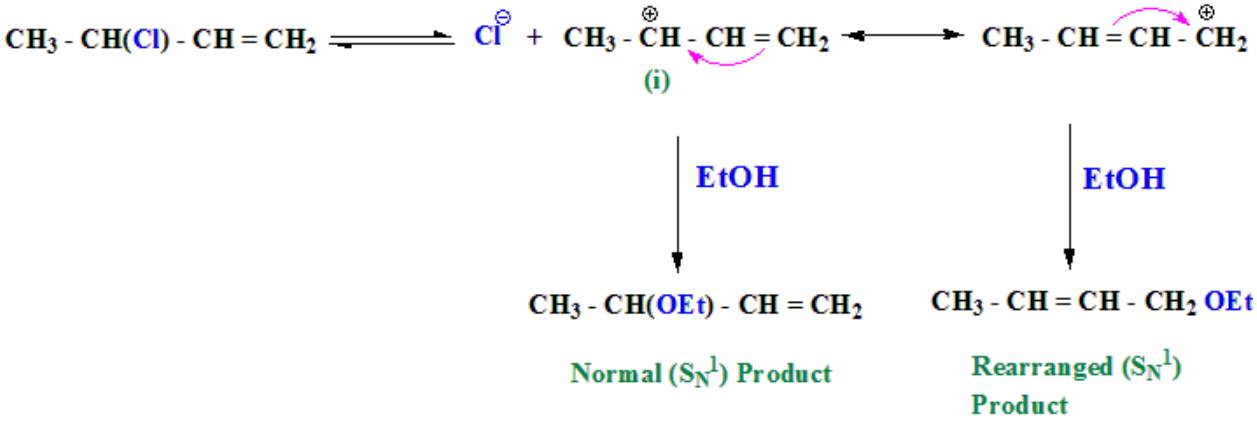


6.8.5 Allylic rearrangement:

An allylic rearrangement or allylic shift is an organic reaction in which the double bond in an allyl chemical compound shifts to the next carbon atom. It is encountered in nucleophilic substitution.



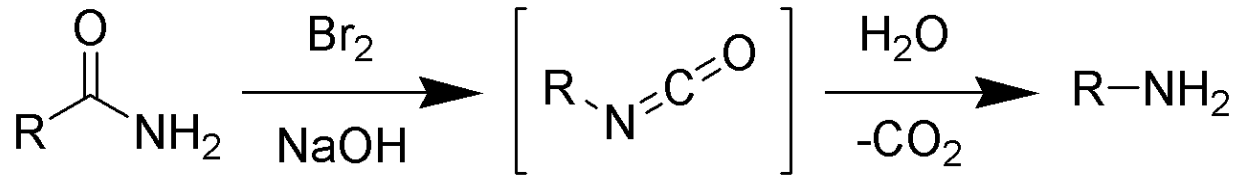
Mechanism:



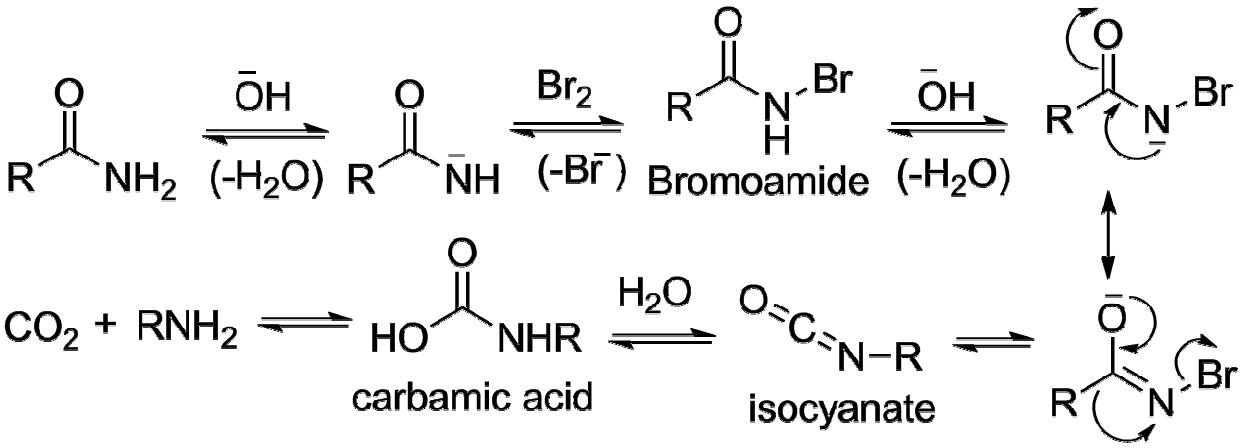
6.8.6 Hofman reaction, Schmidt reaction:

Hofman reaction:

In this reaction amide is converted in to primary amine.

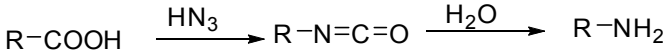


Mechanism:

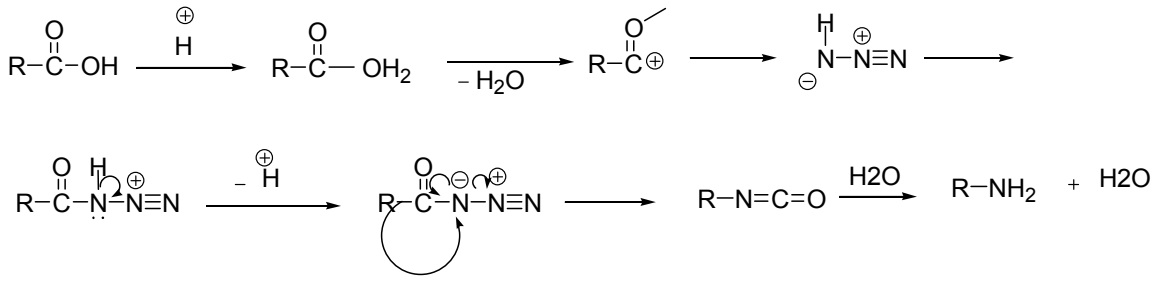


Schmidt reaction:

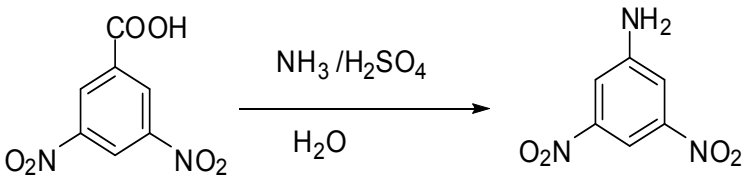
When the carboxylic acid react with the hydrazoic acid in the presence of conc. H2SO4 than their occur the formation of isocyanate which on reaction with H2O gives amine. This reactions is known as Schmidt reaction.

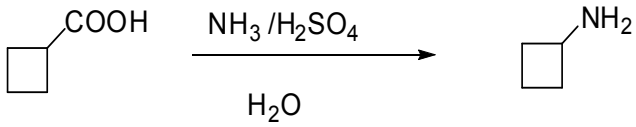


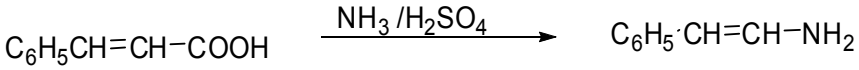
Mechanism:

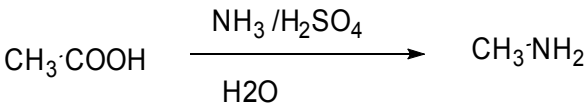


Some other example of these reactions can be given as:



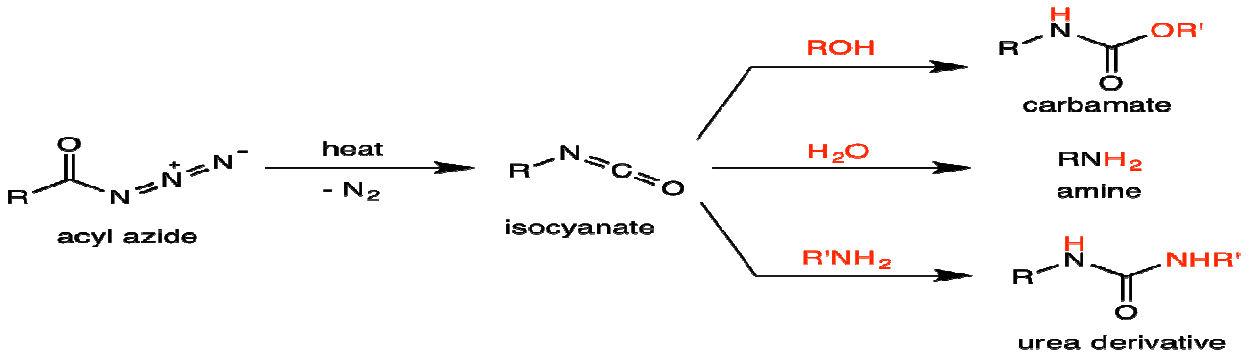






6.8.7 Curtius Rearrangement:

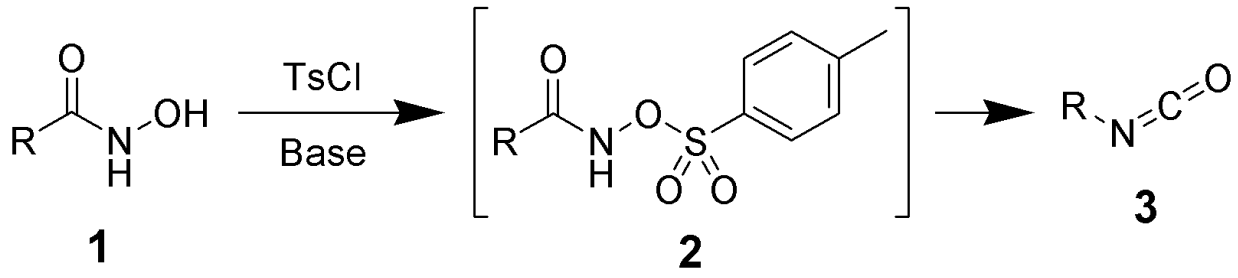
Thermal decomposition of the acyl azide into corresponding isocyanates is known as curtius rearrangement.



6.8.7 Lossen rearrangement and Dakin reaction:

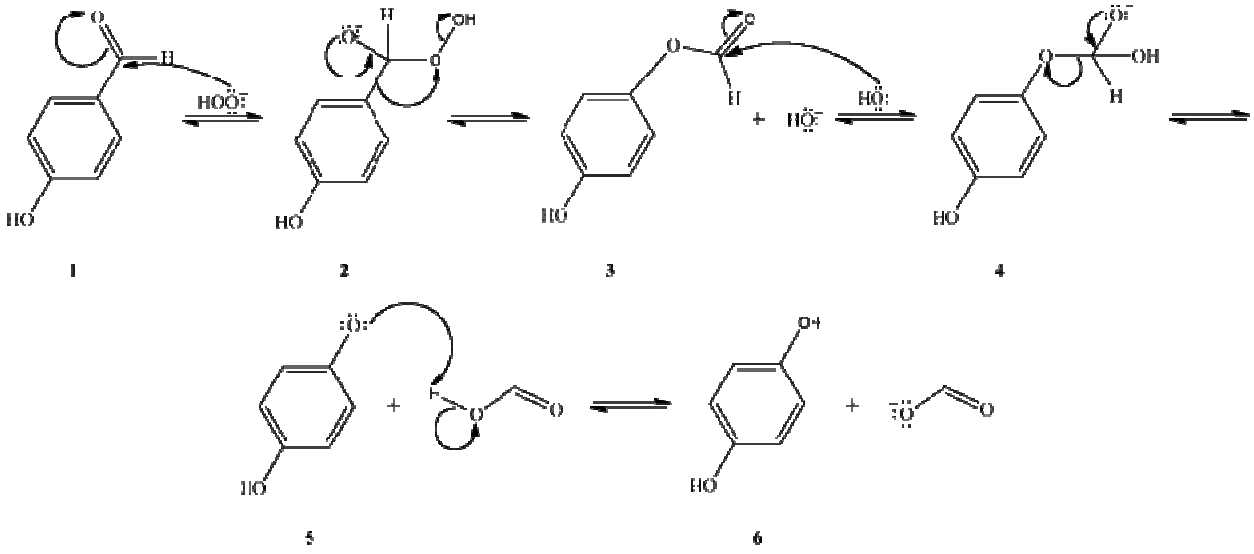
Lossen rearrangement:

Consversio of o-acyl derivative of hydroxamic acid into isocyanate on reaction with base is known as Lossen rearrangement reaction.



Dakin reaction:

The Dakin reaction is an organic redox reaction in which an ortho- or para-hydroxylated phenyl aldehyde (2-hydroxybenzaldehyde or 4-hydroxybenzaldehyde) or ketone reacts with hydrogen peroxide in base to form a benzenediol and a carboxylate.



6.9 SUMMARY

Replacement or displacement of an atom or group by any other atom or group is known as substitution reaction. If displacement takes place by nucleophile then it is known as nucleophilic substitution while on the other hand if substitution tahes place by electrophile then it is known as electrophilic substitution reaction. All nucleophiles are Lewis base and contain atleast one loan

pair of electrons. In nucleolhilic substitutions a nucleophile attacks the substrate carbon with its unshared electrons to form a covalent bond, and the leaving groupn (nucleophile) departs with electron pair of the breaking bond.

6.10 TERMINAL QUESTIONS

1. Write a mechanism of SN2 reaction.
2. Write a mechanism of SN1 reaction.
3. What is the difference between SN1 and SN2 reaction?
4. Write a short note on Anchimeric assistance.
5. What is neighbouring group participation.
6. Explain brief on Classical and nonclassical carbocations.
7. Write the mechanism of the followings:
    a) Pinacol-Pinacolone rearrangement
    b) Dakin Reaction
    c) Wagner-Meerwein rearrangement
    d) Hofman reaction and Schmidt reaction
    e) Curtius rearrangements

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2. March, J. (1992). Advanced Organic Chemistry (4th ed.). New York: Wiley. ISBN 0-471-60180-2.
3. Advanced Organic Chemistry By Jagdamba Singh and L.D.S. Yada, Volume- I, Pragati Prakashan.

UNIT-7 AROMATIC NUCLEOPHILIC SUBSTITUTION

CONTENTS:

7.1 *OBJECTIVES*

- After studying this unit you will be able to know what are aromatic nucleophilic substitution (ANS) reactions.
- Learn about the different possible mechanism of ANS reactions.
- Identify the benzyne mechanism.
- Evaluate the product formation of ANS reactions.
- Identify the mechanistic differentness between addition-elimination and elimination-addition mechanisms.
- Learn about the factors which affect the rates of aromatic nucleophilic substitution reaction.
- Identify suitable substrates, leaving groups and incoming nucleophiles for $S_{RN}1$ reactions, benzyne reactions and S_N1 and S_N2 type reactions.

7.2 *INTRODUCTION*

Why do aromatic compounds give nuclophilic substitution reactions when aromatic ring itself act as nucleophile! If it is giving aromatic nucleophilic substitution reactions what will be the condisions? are their mechanism like an aliphatic reaction?

Nucleophilic substitutions on aromatic ring are relatively less common reactions that involved bond formation between aromatic carbon atom and nucleophile along with bond breaking to the leaving group. Because of the following reasons:

1. The presence of π-electrons of aromatic ring. These π-electrons make the aromatic system an electron rich system that is more liked by electrophile rather than nucleophile.
2. Secondly aromatic ring loses its stabilization if a nucleophile attack because it looses aromaticity which subsequently gained by the removal of leaving group (six π-electrons in conjugation).
3. The back side attack (as in S_N2) and inversion are prohibited by the geometry of the aromatic ring.

4. The formation of phenyl cation in nucleophilic substitution of aromatic ring render less stable than a primary carbocation (as in S_N1).

Therefore overall under special reaction conditions such as high pressure, high temperature and the presence of different electron withdrawing groups (NO_2, CN, -CO etc.), aromatic substitution reactions are facilitated that we shall learned in this unit.

Example; The early industrial synthesis of phenols and anilines in fact were based on the nucleophilic aromatic substitution reaction (operated under high temperature and pressure).

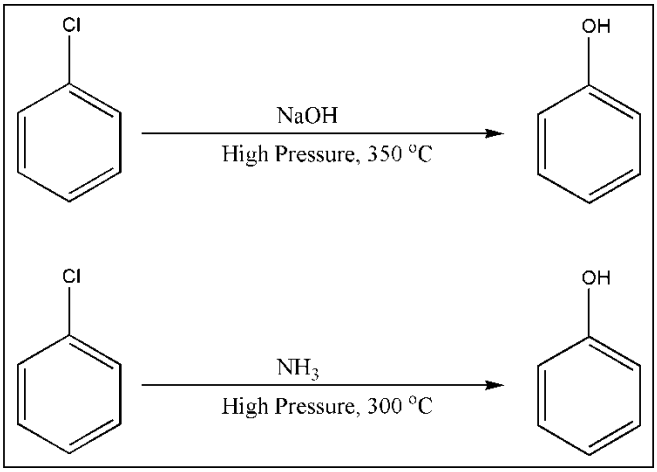


Fig 7.1: Early industrial synthesis of phenol at high temperature and pressure

Note: Both true S_N1 and S_N2 reactions are not energetically feasible in aromatic systems.

7.3 *TYPES OF MECHANISMS*

There are four principal mechanisms for aromatic nucleophilic substitution which are similar to that of aliphatic nucleophilic substitution but required special conditions to proceed.

S_N Ar

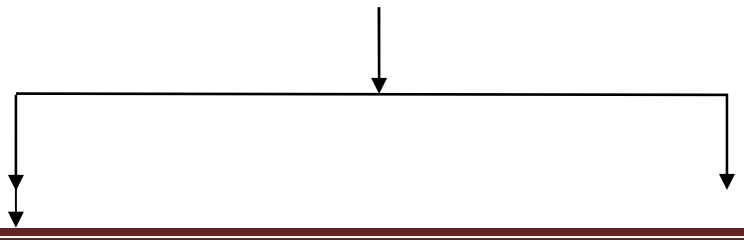


Fig 7.2: Different mechanisms of aromatic nucleophilic substitution reactions

7.3.1 Nucleophilic Aromatic Substitution (S_NAr2) by Addition–Elimination

Mechanism of S_NAr2 by Addition–Elimination is depicted in figure 7.3 with leaving group (X), nucleophile ($Nu:^-$) and a general electron-withdrawing group W.

The mechanism of S_NAr2 proceeds in two steps, in first step [1] nucleophile attacks to the aromatic substrate and forms a resonance-stabilized intermediate carbanion structure called Meisenheimer complex with a new C-Nu bond as shown in Figure 7.3. This step is a slow step and rate determining. In second step [2], loss of leaving group re-forms the aromatic ring. This step is fast compared to the first step.

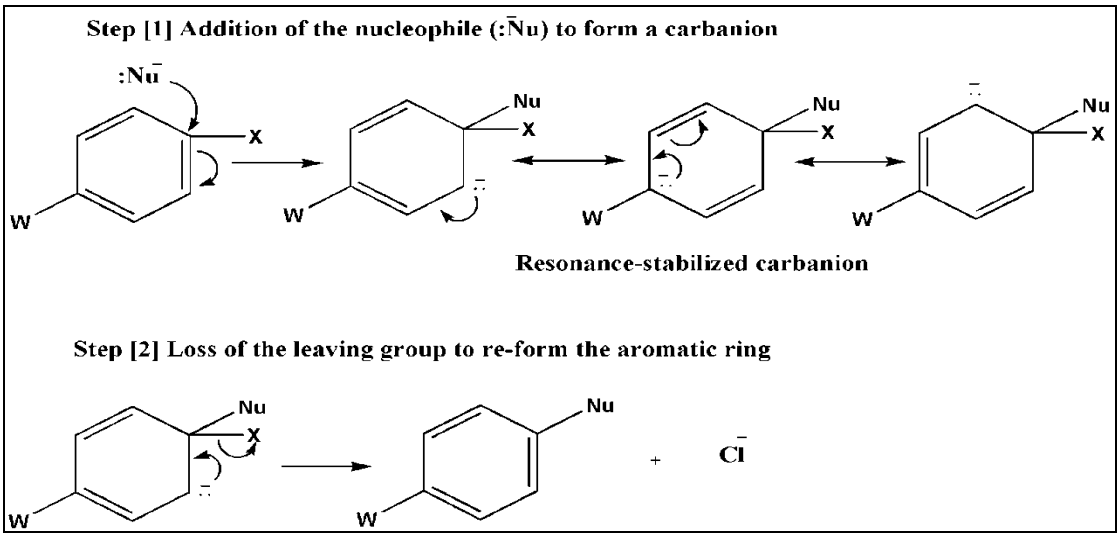


Fig 7.3: Mechanism of S_NAr2 addition-elimination

The presence of electron withdrawing group (W) on the aromatic ring facilitatates the attack of nucleophile while the presence of electron donating group (D) on aromatic ring slow-down the rate of reaction. However this effect is more pronounced when W present at *ortho* or *para* position compared to *meta* position on aromatic ring with respect to the leaving group (X) as shown in figure 7.4 (A) and (B).

Therefore, electron withdrawing group (W) is activating at *ortho, para*-positions compared to *meta* position in nucleophilic attack. These principles are opposite of those that apply to electrophilic substitution.

Note:

i. Generally leaving groups(X) in aromatic nucleophilic substitution are Halogens, Alkoxy, NO_2, Sulfonyl.
ii. and Nucleophiles are Alkoxides, Phenoxides, Sulfides, fluoride ion or amines.

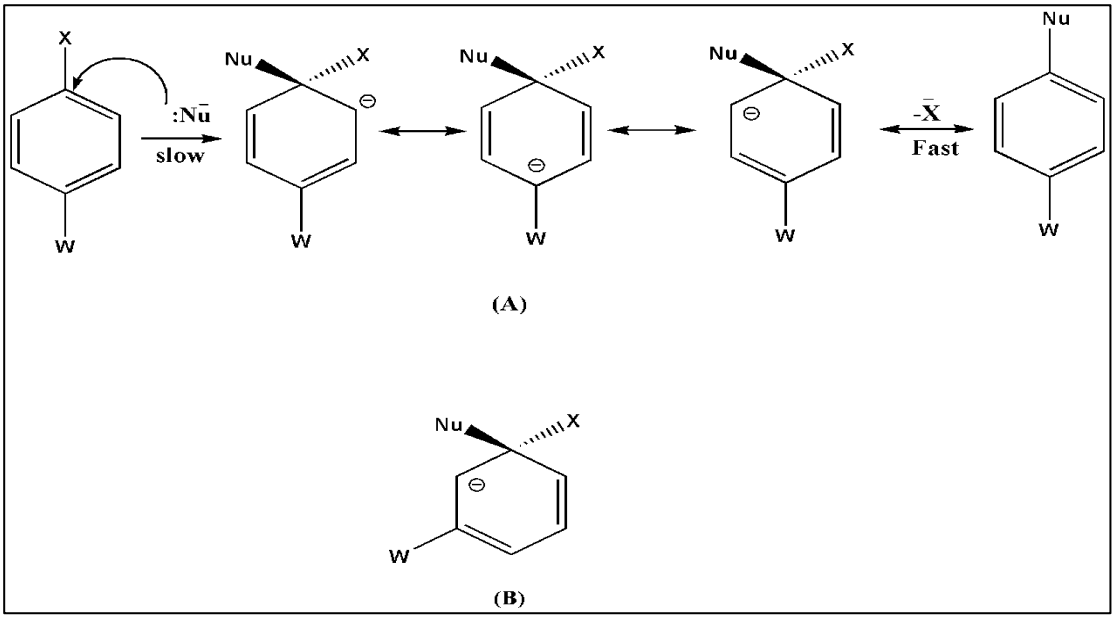


Fig 7.4: Attack of nucleophile on aromatic ring with respect to electron withdrawing group (W) present at *para*-position(A) and at *meta* position(B).

7.3.2 Nucleophilic Aromatic Substitution (S_NAr2) by Elimination-Addition (benzyne mechanism)

Nucleophilic aromatic substitution reactions proceeding through elimination-addition mechanism lead the formation of intermediate benzyne, therefore elimination-addition reaction mechanism also called benzyne mechanism of aromatic nucleophilic substitution.

In such reactions products with substitution on the carbon directly bonded to the leaving group or to the carbon adjacent to it are formed in equal proportion. As an example, treatment of *p*-chlorotoluene with $NaNH_2$ forms *para*- and *meta*-substitution products,

shown in fig.7.5

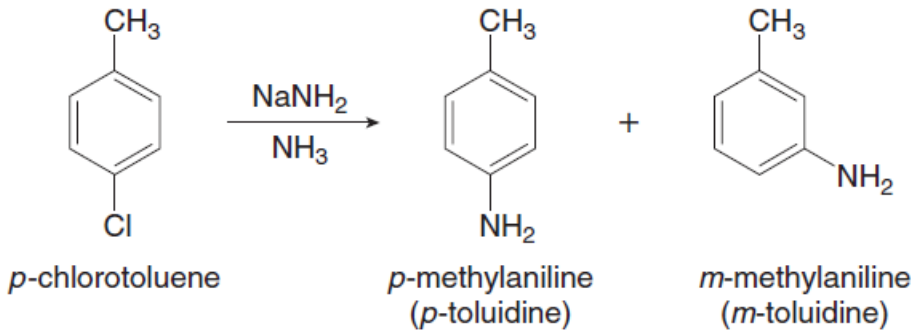


Fig 7.5: Ellimination-addition reaction results in two products in almost equal proportions.

The mechanism of elimination-addition reaction proceeds in two steps fig 7.6, in first step, attacking of strong base or nucleophile (^-OH) removes the proton from adjacent carbon relative to the leaving group attached carbon followed by the removal of leaving group and the formation of benzyne takes place. In second step, further addition of nucleophile to generate carboanion and protonation of carboanion takes place.

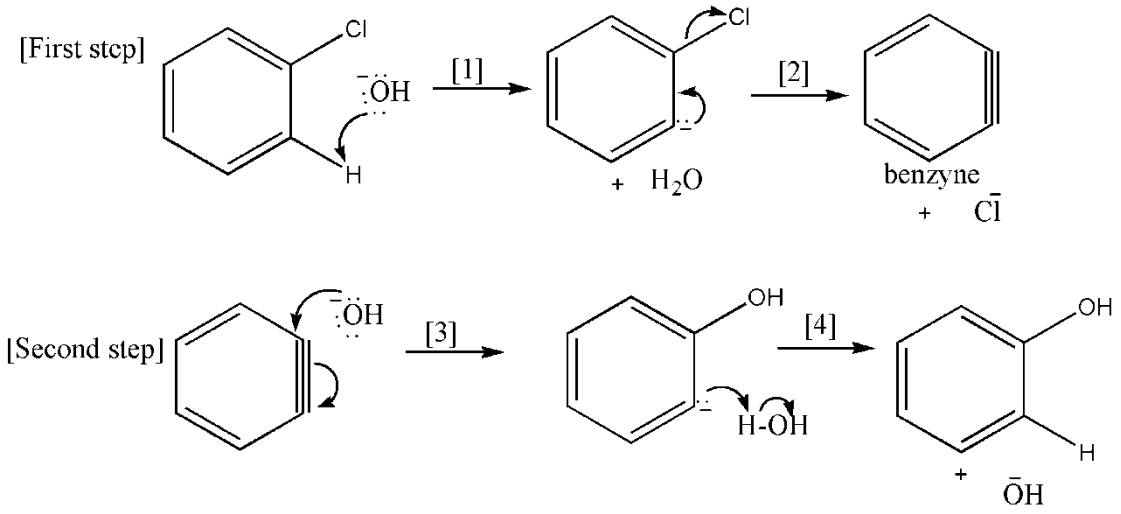
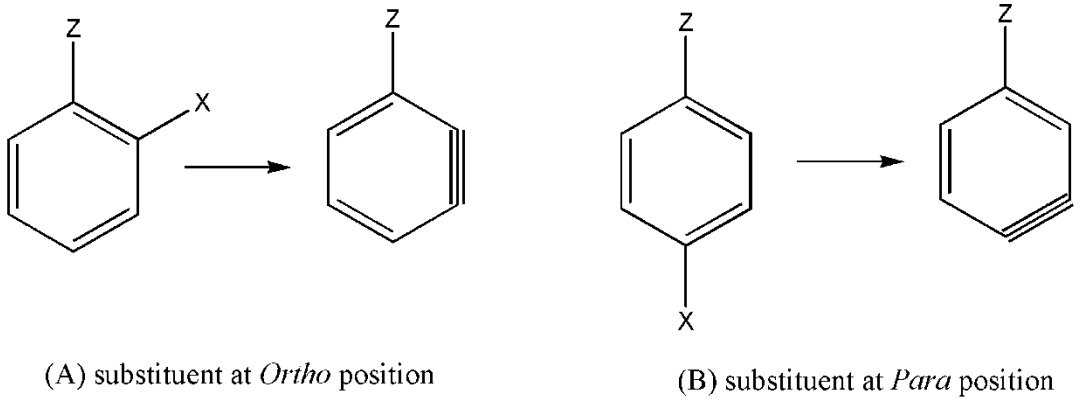


Fig 7.6: Mechanism of elimination-addition reaction (benzyne mechanism)

The benzyne intermediate has a triple bond in benzene ring which makes it a highly reactive species (very unstable). When *ortho* and *para*-substituent are present on the substrate, only one benzyne intermediate can formed as shown below:



(A) substituent at *Ortho* position

(B) substituent at *Para* position

Fig. 7.7: Benzyne mechanism of aromatic nucleophilic substitution at *ortho* and *para* positions

However, if *meta* substituent are present then two benzynes may be formed (as shown in fig 7.8) based on which protons are more acidic. More acidic protons will be removed for benzyne formation.

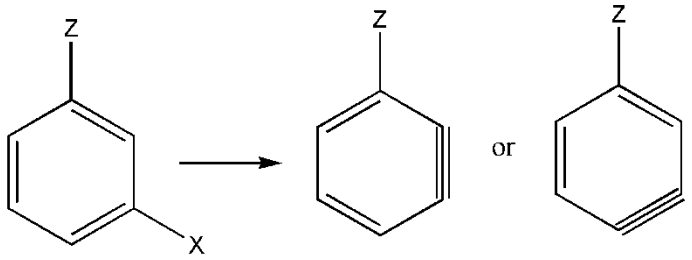


Fig. 7.8: Benzyne mechanism of aromatic nucleophilic substitution at *meta*-position

The nature of substituent Z is decisive towards benzyne intermediate formation. An electron withdrawing Z group favors removal of the *ortho*-hydrogen, whereas, an electron-releasing Z group favors removal of the *para*-hydrogen. Also, once the aryne intermediate is formed, there are two possible sites where the nucleophile may attack, again the field effect of substituent Z plays an important role and an intermediate carbanion which gets better stabilization by Z will be favoured. For substituent with -I effect, the more stable carbanion is the one in which the negative charge is closer to the substituent. Unlike addition-elimination, the order of halogen reactivity in these reactions is I > Br > Cl > F.

7.3.4 Radical-nucleophilic aromatic substitution or $S_{RN}1$

The $S_{RN}1$ (Unimolecular Radical Nucleophilic Substitution) is a process through which nucleophilic substitution is achieved on aromatic and aliphatic compounds that do not react or react slowly through polar nucleophilic mechanisms. This reaction type was discovered in 1970 by Bunnett and Kim. A number of useful reactions proceed via this mechanism including photo stimulation reactions, electrochemical reactions.

Due to involvement of radical anions, the $S_{RN}1$ reactions may occur via a chain or non-chain mechanism. Fig 7.9 shows the generalized reaction with an aryl halide. This transformation takes place through electron transfer steps with radicals and radical anions as intermediates.

$$ArX + Nu^- \longrightarrow ArNu + X^-$$

Fig 7.9: Generalized nucleophilic substitution reaction

The key steps of the $S_{RN}1$ reaction mechanism proceeding through chain process are presented in Scheme I.

As depicted below in fig 8, in the $S_{RN}1$ mechanism, the initial attack takes place via an electron donor, rather than a nucleophile. The radical anion thus formed leads to removal of leaving group and left behind a radical available for attack by the incoming nucleophile.

As shown in fig 10, the aryl halide substrate first accept an electron from a donor and becomes an anion radical (Eq 1) , which losses the halide anion giving rise to an aryl radical (Eq 2), which can be easily attacked by the nucleophile to form a new radical anion (Eq 3), electron transfer from this radical anion to the substrate reforms the substrate radical anion (Eq 4), and the propagation cycle continues. Summation of Eqs. 1–4 leads to the net nucleophilic substitution.

Because the $S_{RN}1$ reaction is a chain process, its overall rate depends on the efficiency of the initiation, propagation and termination steps. Any of the intermediates (radicals and radical anions) can initiate the chain, but by far the most commonly used is the radical anion of the substrate. Destruction of any of the intermediates can terminate the process. One important practical consequence of the chain mechanism is that $S_{RN}1$ reactions should be carried out under an inert atmosphere to avoid inhibition by oxygen. Some terminations depend on the method of initiation, while others depend on the intermediates involved and the solvent used.
For instance, electron transfer from any radical anion to an aryl radical (Eq. 5) is one of the proposed termination steps in solvents such as liquid ammonia that are poor hydrogen donors. Hydrogen atom abstraction by the aryl radical (Eq. 6) is a possible termination step in organic solvents. The net effect of these termination reactions is formation of the reduced dehalogenated product.

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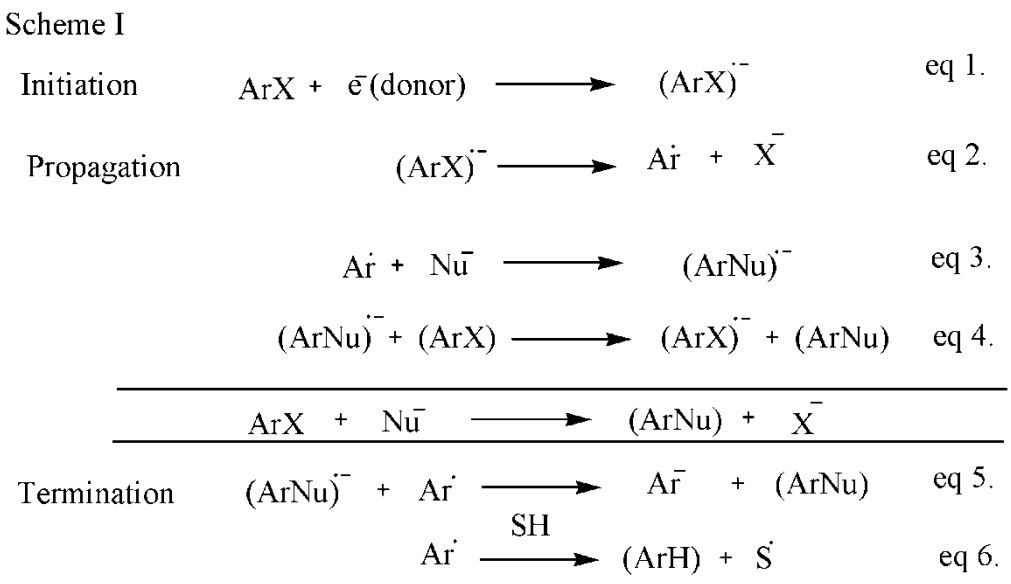


Fig 7.10: $S_{RN}1$ reaction mechanism proceeding through chain process

For example the reaction of 5-iodo-1,2,4-trimethylbenzene with a strong base such as KNH_2 in presence of NH_3 (fig 7.11), two products were formed in the ratio of 0.63:1 different from benzyne mechanism where products formed in equal ratio.

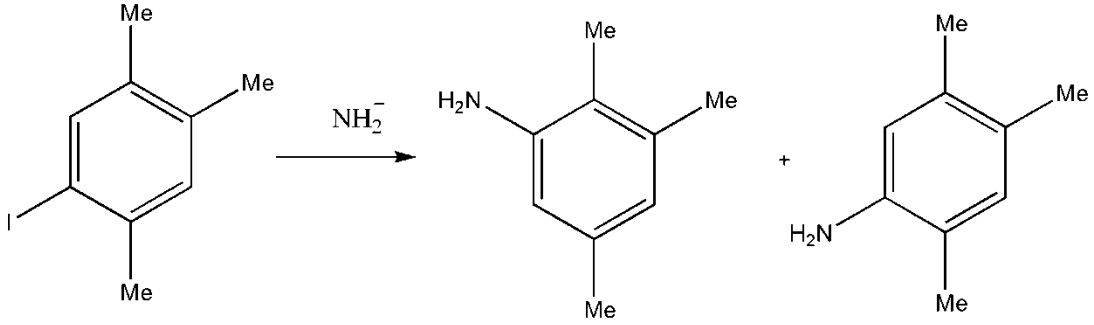


Fig. 7.11: $S_{RN}1$ reaction in 5-iodo-1,2,4-trimethylbenzene

Additionally, it was discovered that the $S_{RN}1$ reaction can occur via a non-chain mechanism as well. Non-chain $S_{RN}1$ reactions are less known. Non-chain $S_{RN}1$ reactions occur in solvent cages, which are defined as a region of space which includes the reacting species surrounded by solvent molecules. The solvent cage restricts the movement of reactive intermediates thereby not

allowing a propagation, while, stepwise substitution occur giving rise to product formation only. Following is an example of non chain $S_{RN}1$ reaction (fig 7.12).

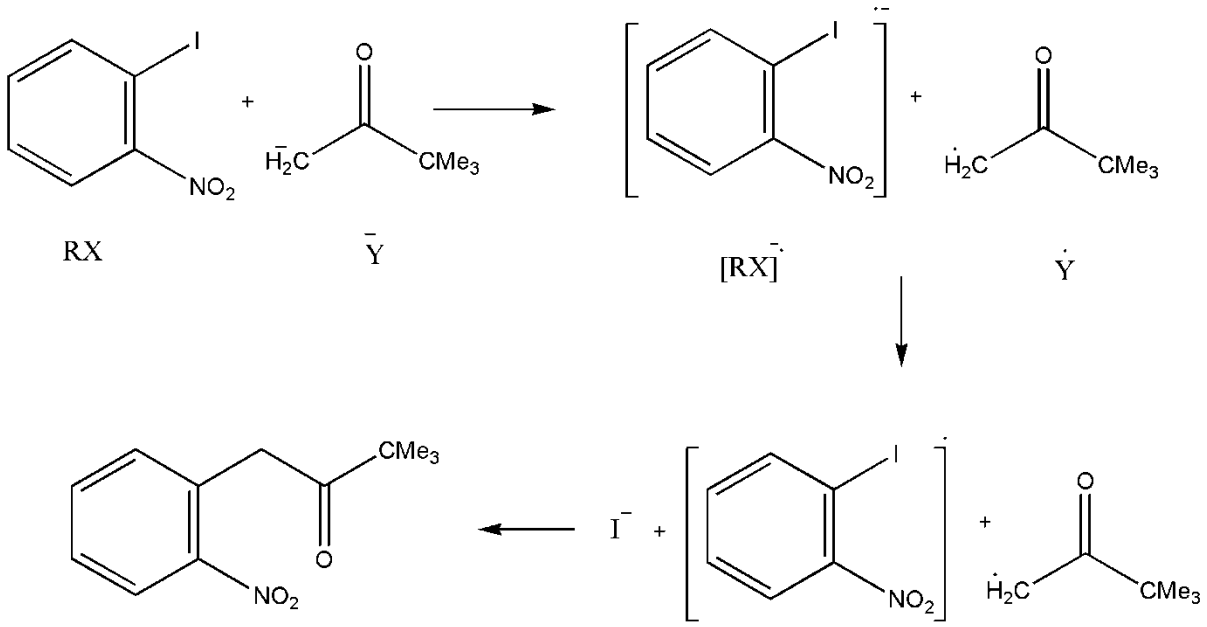


Fig. 7.12: An example of non-chain $S_{RN}1$ reaction

7.3.5 Nucleophilic Aromatic Substitution by ionic mechanism (S_N1)

The S_N1 mechanism operates in the reaction of diazonium salts with nucleophiles (fig 7.13). This is because in diazonium salts the leaving group is di-nitrogen, which is an excellent leaving group, and on leaving it affords a positive charge on benzene ring, making it available for attack by incoming nucleophiles. The rate of reaction depends only upon the nature of substrate and there is no effect of concentration of incoming nucleophile.

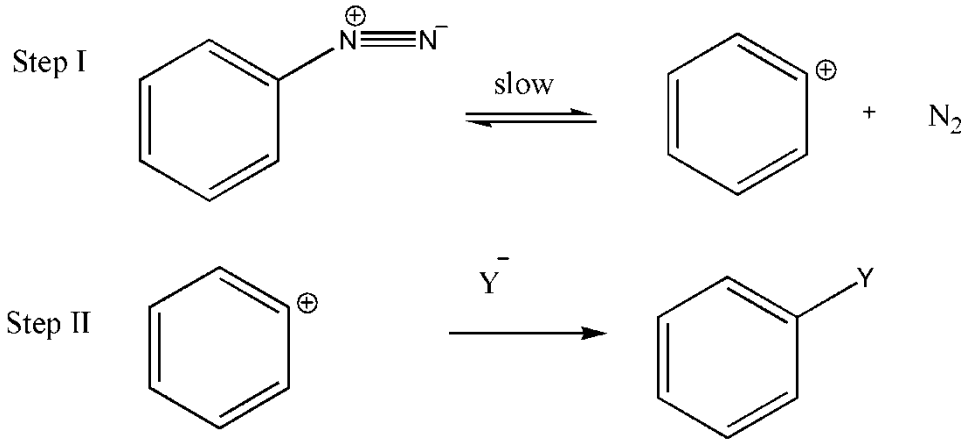


Fig 7.13: General mechanism of S_N1 proceeds in two steps, Step (I) removal of N_2 and formation of aryl cation, Step (II) attack of nucleophile and formation of corresponding product.

For example synthesis of phenol from aromatic diazonium salt explained below in fig 7.14

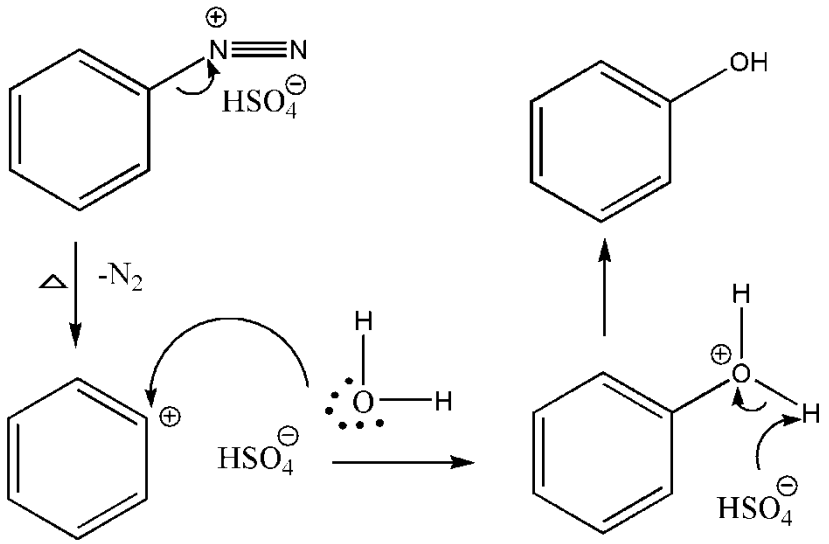


Fig 7.14: Synthesis of Phenol by heating a benzenediazonium salt.

7.4 REACTIVITY-EFFECT OF SUBSTRATE STRUCTURE, LEAVING GROUP AND ATTACKING NUCLEOPHILE IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

The common factors influencing rate of all these three mechanisms are substrate structure, leaving group and solvent. We shall discuss each of them separately.

7.4.1 Effect of Substrate Structure

As explained above in normal conditions, it is difficult for a nucleophile to attack an electron rich ring that is more liked by electrophile rather than nucleophile. When the aromatic ring contains electron withdrawing groups (W), the reactions go faster. However, contrary, the reactions proceed slowly if the ring contains electron donating group (D).

W at *ortho* or *para* position considerably facilitates to aromatic ring to delocalize negative charge and to form additionally more resonating anionic structures compared to W at *meta* position (Fig 7.15). This additional contribution makes the system more susceptible to nucleophilic attack ($Nu:^-$) and elimination of leaving group (X) in *ortho, para* positions compared to *meta* position. Meta position is inductively stabilized not by mesomeric effect.

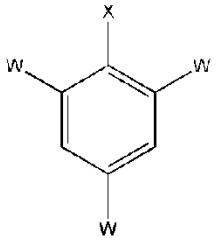
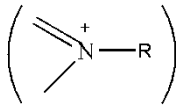
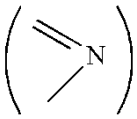


Fig 7.15: Presence of electron withdrawing group (W) at *ortho* and *para*-position compared to leaving group (X)

Following is the order of electron donating groups in increasing ability to activate aromatic rings for SNAr substitutions

$N_2^+ > NO > NO_2 > SO_2Me > NMe_3^+ > CF_3 > CN > CHO > COR > COOH > SO^-_3 > Br > Cl > I > COO^- > H$

Table 1: Descending order of activating ability of different groups in SNAr mechanism.

Diazonium salt group	($-N_2^+$)	Activate halogen exchange at room temperature or below
Cationic carbon	($-CR_2^+$)	
Alkylated hetero nitrogen		Activate replacement by strong nucleophilic reagents at room temperature
Nitroso group(NO) Nitro group (NO_2)		Activate reaction with strong nucleophilic reagents at 80-100 ^oC temperature
Hetero nitrogen atom		
Methylsulfonyl	(CH_2SO_2)	With nitro also present, activate reaction with strong nucleophilic reagents at room temperature
Trimethylammonia	($(CH2)_2N^+$)	
Trifluoromethyl	(CF_3)	
Acyl group	(RCO)	
Cyano groups	(CN)	
Carboxyl	(COOH)	With nitro also present, activate reaction with strong nucleophilic reagents at 40-60 ^oC temperature
Ionized sulfo	(SO_3^-)	
Halogens	(Cl, Br, I)	
Carboxylate	(COO^-)	
Phenyl		

7.4.2 Effect of Leaving Group

However most of the leaving groups such as sulfate, halide, NR_3^+, sulfonate etc. are common in both aliphatic nucleophilic substitution and aromatic nucleophilic substitution reactions. But the groups, NO_2, OR, OAr, SO_2R, and SR, which are not generally lost in aliphatic systems, are also act as leaving groups when attached to aromatic rings.

As greater the electronegativity of leaving-group or polarity of bond between aromatic carbon and leaving group (X) faster will be the release of leaving group by lowering the activation energy while increasing the rate of reaction.

An approximate order of leaving-group ability is

$F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAr, OR, SR, NH_2$

Amongst the halogens, fluoro is generally a much better leaving group than the other halogens, because of its highest electronegativity,

The order is usually F>Cl>Br>I, but not always.

The leaving-group order is quite different from that for the S_NAr1. The most likely explanation is that the first step of the SNAr mechanism is usually rate determining, and this step is promoted by groups with strong -I effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the benzyne mechanism is operating. The only important leaving group in the S_NAr1 mechanism is N_2^+.

7.4.3 Effect of Attacking Nucleophile

Generally the strength of nucleophile or substituting capability of nculeophile depends on the basicity. Greater the basicity of attacking atom more will be the nucleophilicity. However as in aromatic nucleophilic substitution reactions, the strength of nucleophile or substituting capability of nculeophile depends not only on the basicity but also on the types of substrates and reaction conditions. Therefore, it is not possible to construct a constant nucleophilicity order, however, an overall approximate order is as given below:

$^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism)$>ArS^->RO^->R_2NH>ArO^->^-OH>ArNH_2>NH_3>I^- Br^- >Cl^->H_2O>ROH$

Nucleophilicity increases as the attacking atom moves down a column in the periodic table except some exceptions e.g., ^-OH a stronger base than ArO^-, is a poorer nucleophile.

7.5 VON-RICHTER REACTION

The Von-Richter reaction, also named Von-Richter rearrangement, is a name reaction in the organic chemistry. It is named after Victor von Richter, who discovered this reaction in year 1871. It is the chemical reaction of aromatic nitro compounds with potassium cyanide giving carboxylation *ortho* to the position of the former nitro group.

When cyanide ion treated to aromatic nitro compounds it displaces nitro group and a carboxyl group enters with cine substitution, always ortho to the displaced group, never *meta* or *para* as shown in fig. 7.16. The von Richter reaction can be inhibited in the presence of potassium ferricyanide ($K_3Fe(CN)_6$) and sodium sulfite.

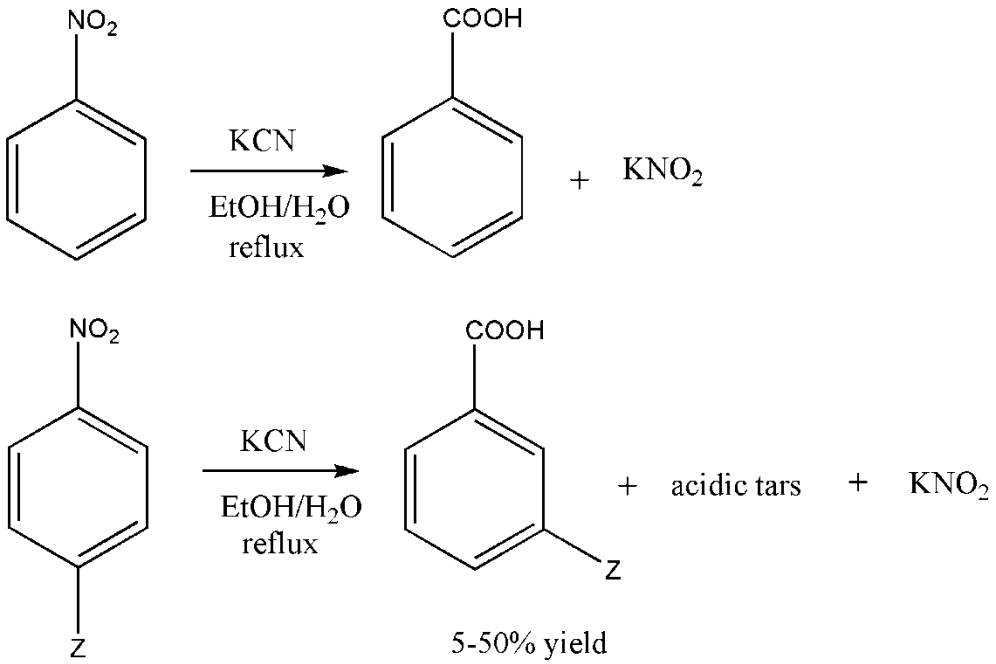


Fig 7.16 Von-Richter reaction

As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in *ortho* and *para* positions, but yields are low, usually 50%. This reaction has a limited application in organic synthesis.

Mechanism of Victor Von Richter Reaction

The reaction proceeds through a nucleophilic attack of cyanide ion *ortho* to nitro group followed by intramolecular rearrangement, as shown in fig 7.17

First, the cyanide attacks the carbon-atom in *ortho*-position to the nitro-group. After this the compound regains its aromaticity once again. In the latter step, the negative charged oxygen-atom attack the neighbouring carbon-atom and a five-membered ring is build. It opens under building a carboxylic acid group. Next, another five-membered ring is formed. After a condensation reaction, (resembling Michael reaction) a double bond is built between the two nitrogen-atoms. Elemental nitrogen then leaves the system for opening the ring. In the last step, the compound is protonated and the 3-halogenbenzoic acid is built.

7.6 SOMMELET-HAUSER REARRANGEMENT

The rearrangement involves the reaction of benzyl quaternary ammonium salts in presence of sodium amide or another alkali metal amide to form N-dialkyl benzyl amine having a new alkyl group in the aromatic *ortho* position is known as Sommelet–Hauser rearrangement as shown in fig 7.18.

As the α-hydrogen is too weak acidic to induce hydroxide ion based rearrangement, a strong base such as amide ion in liquid ammonia is to be used. The Sommelet-Hauser reaction is highly favored in polar solvents like, NH_3, DMSO, HMPA. Low temperature conditions also favour the reaction.

The reaction proceeds with deprotonation of the benzylic methylene proton which is acidic to yield benzylic ylide. The ylide formed is in equilibrium with the second ylide which is formed by deprotonation of one of the ammonium methyl groups. The second ylide which is present in much smaller amounts undergoes a [2,3] sigmatropic rearrangement and subsequent aromatization in order to form the final product as shown in fig 7.19.

Sommelet-Hauser rearrangement is in competition with Stevens rearrangement as shown in fig 7.20.

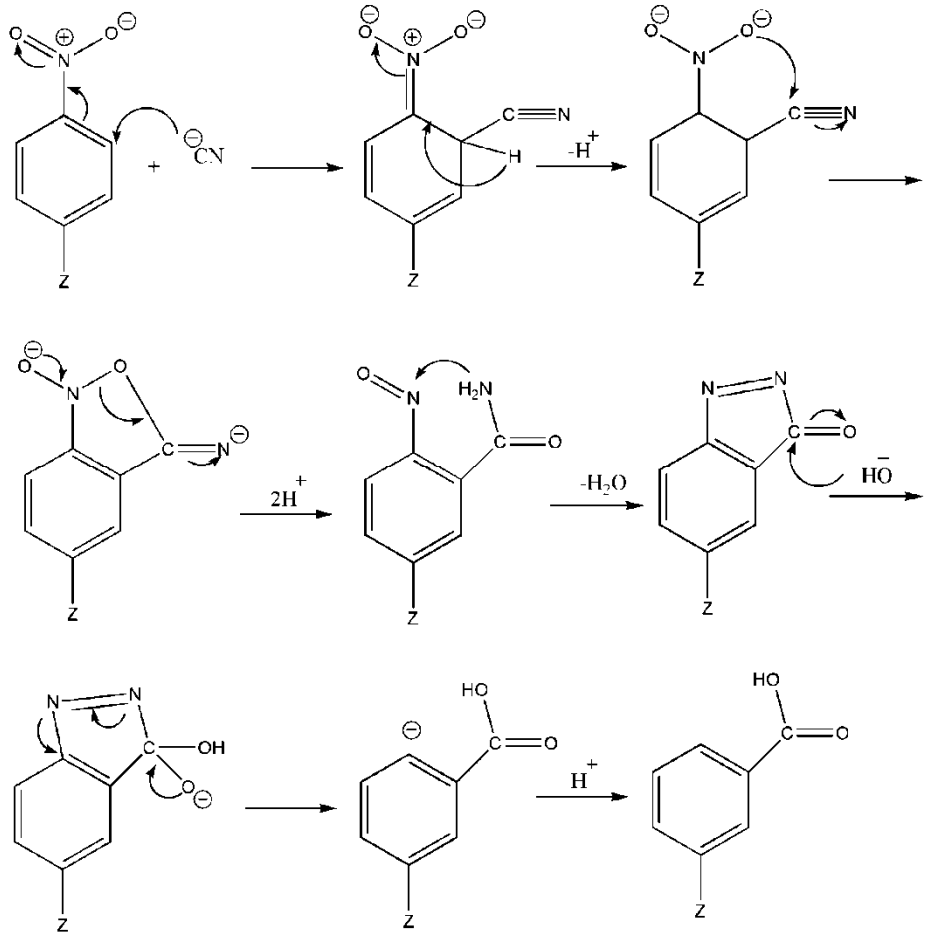


Fig 7.17: Mechanism of Victor Von Richter Reaction

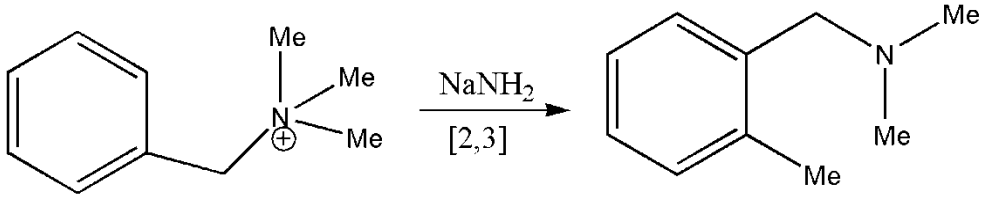


Fig 7.18: Sommelet-Hauser Rearrangement

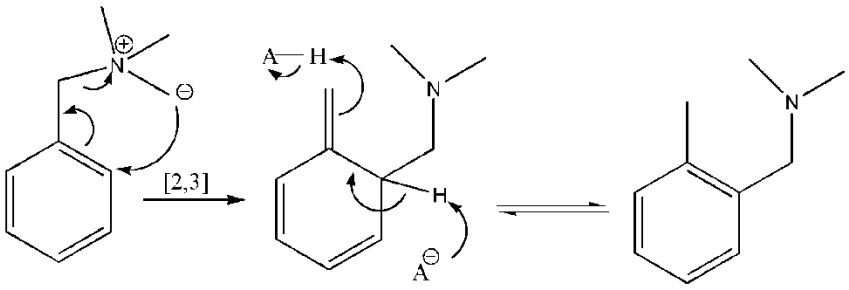


Fig 7.19 Mechanism of Sommelet-Hauser Rearrangement

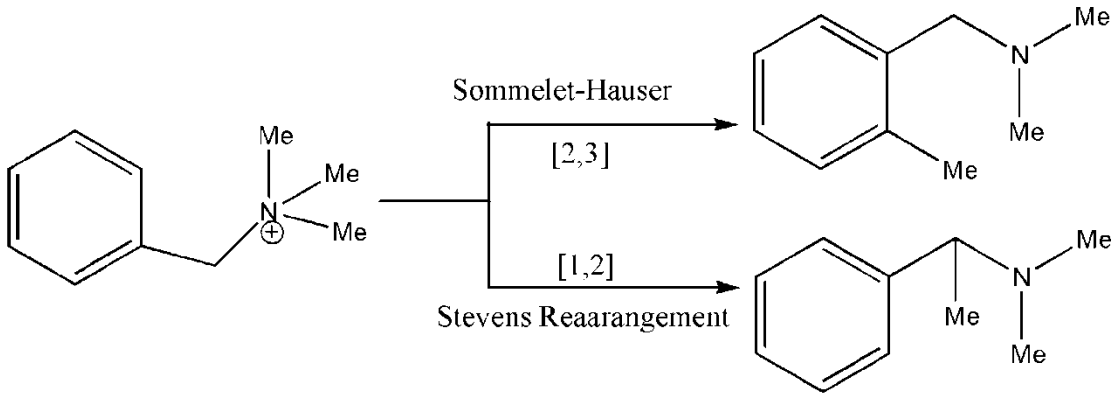


Fig 7.20: Stevens vs. Sommelet-Hauser Rearrangement

7.7 *SMILE REARRANGEMENT*

The Smiles rearrangement is an example of intramolecular nucleophilic substitution (fig 7.21). It involves attacking on an aromatic system possessing an activating electron-withdrawing group at *ortho*- or *para*-position to the reaction centre connected to a heteroatom. Smiles rearrangement is further involves the migration of an aromatic ring from the heteroatom binding to the reaction centre to a more nucleophilic heteroatom.

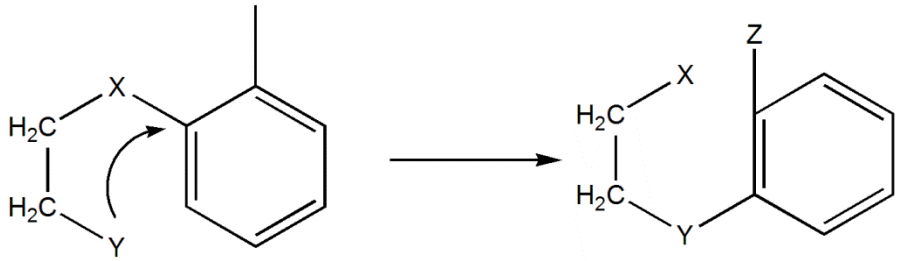


Fig 7.21: Smiles intramolecular rearrangement

Where, **X** can be a sulfone, a sulfide, ether or any other substituent which can dislodge from the arene with a negative charge.

The terminal functional group in the chain end *i.e,* **Y** acts as a strong nucleophile for example an alcohol, amine or thiol. In the Smiles rearrangement, the nucleophile Y is generally the conjugate

base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, OR.Molecular mechanism of smiles interamolecular rearrangement shown in fig 7.22.

It has been observed that a moderate electron-withdrawing group, preferably in the aromatic *ortho* position, such as chloro and alkoxide can accelerate this rearrangement. On the contrary, the steric hindrance that arises from a substituent at a particular position in the aromatic ring may help in making the rearrangement more facile. The solvent, such as THF has been found to give positive effect and increase the rate of the Smiles rearrangement. This reaction has been thoroughly modified by the use of different ethers as well as various reaction conditions

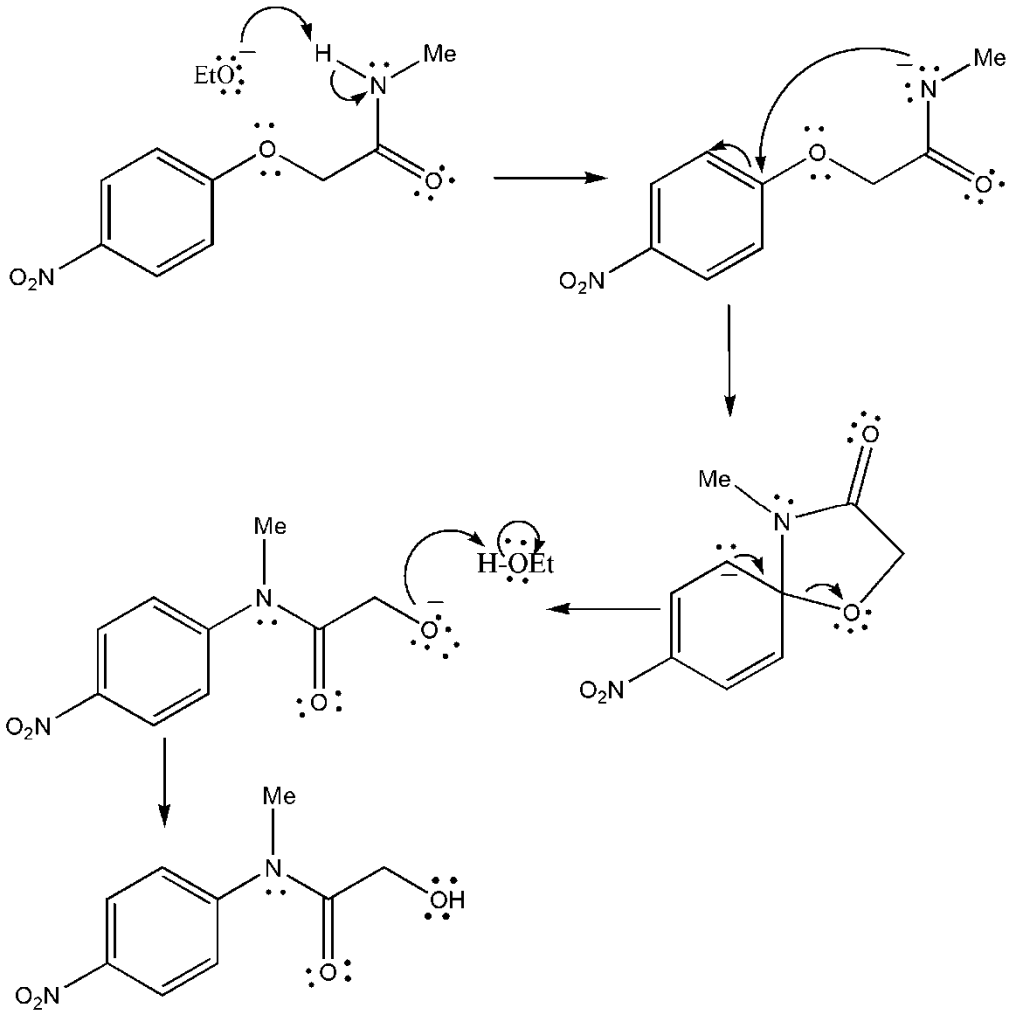


Fig 7.22: Molecular mechanism of Smiles Rearrangement

7.8 SUMMARY

- Aromatic nucleophilic substitution reactions are rare where nucleophile attack on substituted aromatic rings
- These are classified as unimolecular or bimolecular reactions.
- Bimolecular S_NAr reactions operate via two mechanisms; addition/elimination or elimination/addition.
- Meisenheimer complexes are 1:1 reaction adducts intermediates in bimolecular nucleophilic aromatic substitution that are stable and isolated as early as in 1902.
- Aromatic nucleophilic substitutions are favored by electron withdrawing substituents on benzene ring and good leaving groups.
- Bimolecular S_NAr reactions proceeding through the formation of "benzyne" intermediate called elimination-addition.
- In elimination-addition reactions products with substitution on the carbon directly bonded to the leaving group or to the carbon adjacent to it are formed in equal proportion.
- For substituents with -I effect, the more stable carbanion is the one in which the negative charge is closer to the substituent in case of benzyne mechanism.
- If the electron withdrawing groups are present on the *ortho* or *para* positions to the leaving group, great accelerations in rate of reactions in case of S_NAr reactions has been observed, however, the reverse is observed for electron donating groups.
- The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R, and SR, which are not generally lost in aliphatic systems, are leaving groups when attached to aromatic rings.
- Fluoro and nitro are good leaving groups in S_NAr reactions, but poor leaving groups in case of the benzyne mechanism depending upon the intermediates formed in the rate determining step.

- Aromatic nucleophilic substitution reactions of diazonium salts with nucleophiles operate unimolecularly and called S_N1 reactions.
- In S_N1 reactions, diazonium is a good substrate as di-nitrogen is a good leaving group affording a positive charge on benzene ring making it available for attack by incoming nucleophiles.
- Nucleophilic aromatic substitution reactions on an aromatic compound mediated through intermediary free radical species called Unimolecular Radical-Nucleophilic aromatic Substitution or $S_{RN}1$ reactions.
- $S_{RN}1$ reactions are usually performed in either liquid ammonia or dipolar aprotic solvents such as dimethyl sulphoxide or hexa methyl phosphoric acid.
- Unlike S_NAr mechanism that require suitably substituted substrates and benzyne mechanism which require strong basic conditions, the $S_{RN}1$ mechanisms proceed under relatively milder conditions and give convenient yields.
- Initiation of $S_{RN}1$ reactions can be achieved by a number of methods, the most commonly used being photo stimulation, introduction of solvated electrons or thermal reactions.
- The reaction of aromatic nitro compounds with potassium cyanide to generate a carboxylic acid *ortho* to the nitro group is known as Victor von Richter reaction.
- The rearrangement reaction of certain benzyl quaternary ammonium salts in presence of sodium amide or another alkali metal amide to form N-dialkyl benzyl amine with a new alkyl group in the aromatic ortho position is known as Sommelet–Hauser rearrangement. The Sommelet-Hauser reaction is highly favored in polar solvents.
- The Smiles rearrangement is an example of intramolecular nucleophilic substitution. It involves attacking on an aromatic system bearing an activating electron-withdrawing group at *ortho*- or *para*-position to the reaction center connected to a heteroatom.

7.9 GLOSSARY

Aromatic compounds: A cyclic (ring-shaped), planar (flat) molecule having each atom in conjugation (resonance) and must having [4n+2] pi electrons.

Acidic protons: Protons attached to some function group directly or electronegative atom (O, S, N).

Aromatic carbon: A carbon of aromatic ring.

Aprotic solvents: An aprotic solvent is a solvent that has no O-H or N-H bonds or do not have any free -H (protons) to participate in reaction or interaction.

Benzyne: Described as having a strained triple bond formed by removal of two ortho substituents from an aromatic ring .

Benzylic ylide: The structure formed after the removal of acidic proton from benzylic methylene called benzylic ylide.

Benzyl quaternary ammonium salts :A quaternary ammonium salt attached to benzyl group

Bimolecular reaction: A reaction whose order depends upon two reacting molecules.

Carbanion: A carbanion is an anion in which carbon has an unshared pair of electrons and bears a negative charge.

Electrophile: An electrophile is a species that accepts a pair of electrons to form a new covalent bond.

Electron-withdrawing group: An atom or group that draws electron density from neighboring atoms towards itself, usually by resonance or inductive effects.

Electron donating group: An atom or group that releases electron density from neighboring atoms towards itself, usually by resonance or inductive effects.

Electronegativity: Electronegativity is a measure of the tendency of an atom to attract a bonding pair of electrons.

α-Hydrogen: A hydrogen atom directly bonded to an α-carbon.

Leaving group: A leaving group is a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage.

***Meta* -position:** Two benzene ring substituents on two benzene ring carbons separated by one benzene ring carbon.

Meisenheimer complex: Meisenheimer complex in organic chemistry is a 1:1 reaction adduct between an arene carrying electron withdrawing groups and nucleophile. These complexes are found as reactive intermediates in nucleophilic aromatic substitution.

Nucleophile: A nucleophile is a reactant that provides a pair of electrons to form a new covalent bond.

***Ortho-position*:** The relationship between two benzene ring substituents on adjacent benzene ring carbons.

***Para-position*:** Para describes a molecule with substituents at the 1 and 4 positions on an aromatic compound. In other words, the substituent is directly opposite the primary carbon of the ring.

Polarity: It's a power of electronegativity difference between atoms in a bond. Partial negative charges are found on the most electronegative atoms, the others are partially positively charged.

Polar solvents: A solvent with high dielectric constant.

Radical species: A radical that carries an electric charge. A positively charged radical is called a 'radical cation' (e.g. the benzene radical cation $C_6H_6^{\cdot+}$); a negatively charged radical is called a 'radical anion' (e.g. the benzene radical anion $C_6H_6^{\cdot-}$).

Strong base: A strong base is a base that is completely dissociated in an aqueous solution. These compounds ionize in water to yield one or more hydroxide ion (OH^-) per molecule of base.

Solvent cages: Defined as a region of space which includes the reacting species surrounded by solvent molecules.

Sigmatropic rearrangement: Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called sigmatropic reactions.

Steric hindrance: Steric hindrance at a given atom in a molecule is the congestion caused by the physical presence of the surrounding ligands, which may slow down or prevent reactions at the atom.

Unimolecular reaction: A reaction whose order depends upon one reacting molecule.

7.10 SELF ASSESSMENT QUESTIONS

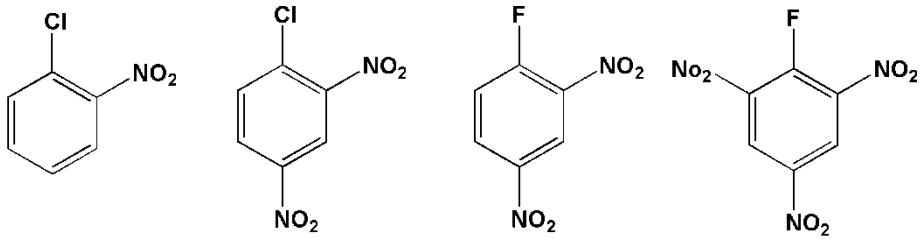
7.10.1 Multiple choice questions:

1. Which one of them is strongest nucleophile in aromatic nucleophilic substitution reactions?

(a) $-NH_2$ (b)$-OH$

(c) $-Cl$ (d) ArO^-

2. Which one of the substituted benzenes undergoes easily in addition-elimination of nucleophilic substitution reaction?

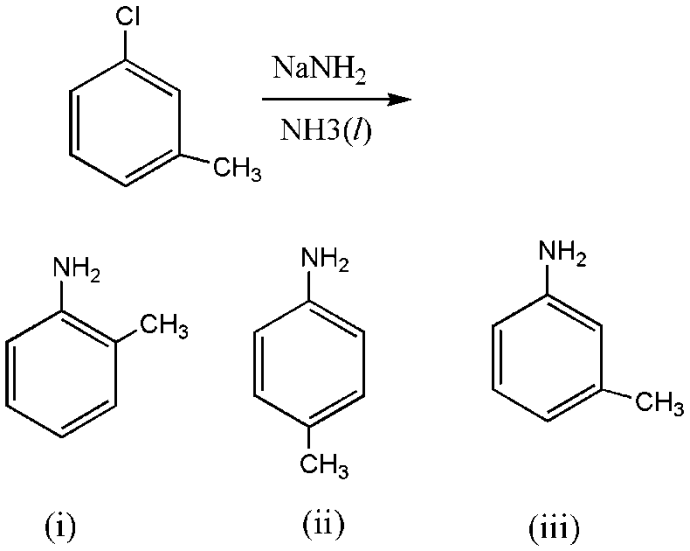


(i) (ii) (iii) (iv)

(a) (i) (b) (ii)

(c) (iv) (d) (iii)

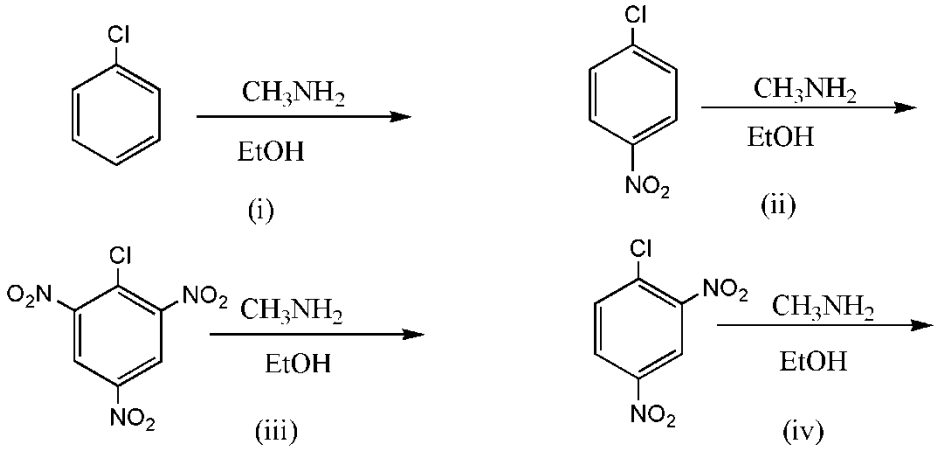
3. Which one of the options is true regarding the product formation in the following reaction?



(a) (i) (b) (ii)

(c) (iii) (d) (i), (ii) & (iii)

4. Which one the reactions proceed at room temperature?



(a) (i) (b) (ii)

(c) (iii) (d) (iv)

5. Which one of the type of aromatic nucleophilic substitution reactions proceeds with the formation of benzyne intermediate?

(a) S_NAr2 (Addition-elimination) (b) S_NAr2 (Elimination-Addition)

(c) S_N1 (d) $S_{RN}1$

6. Which one of the halogen atom easily substituted by nucleophile in elimination-addition reaction (S_NAr2)?

(a) F (b) Cl

(c) Br (d) I

7. Which one of the halogen atom easily substituted by nucleophile in addition-elimination reaction (S_NAr2)?

(a) F (b) Cl

(c) Br (d) I

8. Why aryl halide gives nucleophilic substitution reaction under drastic conditions?

(a) Halide is ring activating (b) Aryl ring act as an electrophile

(c) Aryl ring act as a nucleophile (d) All are correct

9. In aromatic nucleophilic substitution reaction, substrate should have

(a) Ring activating substituent (b) Ring deactivating substituent

(c) Both activating or deactivating substituents (d) None of them

10. The order of elimination-addition (S_NAr2) reaction ?

(a) 1 (b) 0

(c) 2 (d) 1.5

7.10.2 Fill in the blanks and True/False:

(1) Aromatic nucleophilic substitution reactions of diazonium salts with nucleophiles operate via _____order.

(2) Unimolecular Radical-Nucleophilic aromatic Substitution or $S_{RN}1$ reactions proceeds with the formation of intermediary _____

(3) Substituents at *ortho* and *para* positions lead to one type of benzyne intermediate compared to *meta* in elimination-addition aromatic nucleophilic substitution reactions (S_NAr2).

(4) 2,4-dinitro-fluorobenzene undergoes faster compared 2,4-dinitro-chlorobenzene in addition-elimination reaction (S_NAr2).

(5) In S_N1 Nucleophilic Aromatic Substitution reaction, benzenediazonium chloride lead to the formation of intermediate benzonium cation.

(6) *p*-chlorotoluene with strong base ($NaNH_2$) lead to the formation of *para*- and *meta*-substitution products.

(7) "Meisenheimer" complex is an intermediate in the_____ reactions.

(8) The Sommelet-Hauser reaction is highly favoured in _____solvents.

(9) Aromatic nitro compounds with potassium cyanide giving carboxylation at_____ to the position of the former nitro group.

(10) $S_{RN}1$ reactions can be proceed by photo stimulation .

7.10.3 Very short answer questions:

(1) Define nucleophile?

(2) Draw the structure of benzyne?

(3) Write the order of F, Cl, Br and I substitution in addition-elimination aromatic nucleophilic substitution reactions (S_NAr2)?

(4) Write the order of F, Cl, Br and I substitution in elimination-addition aromatic nucleophilic substitution reactions (S_NAr2)?

(5) Write down the order of reactivity of chlorobenzene, *ortho*-nitrochlorobenzene, *Para*-nitrochlorobenzene, *ortho-para*-dinitrobenzene in addition-elimination aromatic nucleophilic substitution reactions (S_NAr2)?

(6) Draw the structure of product formed in the reaction of *meta*-chlorotoluene with strong base ($NaNH_2$) in liquid ammonia?

(7) Why there is no product formed when 2,6-dimethylchlorobenzene reacts with strong base ($NaNH_2$) in liquid ammonia?

(8) Draw the structure of benzenediazonium chloride?

(9) When *4*-nitrochlorobenzene reacts with potassium cyanide will give carboxylation at *ortho* or *para* to the position of the former nitro group?

(10) Why electron withdrawing group promotes aromatic nucleophilic substitution reactions?

Answer key: 1-a, 2-c, 3-d, 4-c, 5-b, 6-d, 7-a, 8-c, 9-a, 10-c

Answer key: (1)Fast, (2)Benzene radical, (3)True, (4)True, (5)True, (6)True, (7)Addition-elimination S_NAR2, (8)Polar, (9)meta, (10) True

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7.12 SUGGESTED READINGS

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7.13 TERMINAL QUESTIONS

7.13.1 Short answer questions:

(1) Describe, why 2,4,6-Trinitrochlorobenzene reacts with NaOH just in warm water while chlorobenzene do not ?

(2) Write down the product formed in reaction of benzyne with furan?

(3) Write down the reaction between 2,4,6-trinitrophenetole and sodium amide ($NaNH_2$)?

(4) Explain why para-nitrofluorobenzene reacts with sodium methoxide quickly in methanol compared para-nitrochlorobenzene?

(5) What product will be formed if anthracene reacts with benzyne? Write down the reaction.

(6) Write down the reaction of bezenediazonium chloride with water.

(7) Rank the aryl halides in each group in order of increasing reactivity in nucleophilic aromatic substitution by an addition–elimination mechanism.

a. chlorobenzene, *p*-fluoronitrobenzene, *m*-fluoronitrobenzene

b. 1-fluoro-2,4-dinitrobenzene, 1-fluoro-3,5-dinitrobenzene, 1-fluoro-3,4-dinitrobenzene

c. 1-fluoro-2,4-dinitrobenzene, 4-chloro-3-nitrotoluene, 4-fluoro-3-nitrotoluene

8. Explained why *p*-nitrochlorobenzene reacts with aqueous sodium bicarbonate at 100 ^oC but *m*- nitrochlorobenzene do not?

9. What product will be formed if benzyne reacts and methanol?

10. What product will be formed if 1, 2-dinitrobenzene reacts with aqueous sodium bicarbonate at 100 ^{o}C ?

7.13.2 Long answer question:

(1) Describe the reaction mechanism of addition-elimination aromatic nucleophilic substitution reactions (S_NAr2).

(2) Describe the mechanism of m-chlorotoluene reaction with sodamide in liquid ammonia.

(3) Describe the reaction mechanism of 4-iodo-1, 2, 4-trimethylbenzene with a strong base such as KNH_2 in presence of NH_3.

(4) Describe the reaction mechanism of S_N1.

(5) Describe the smile rearrangement.