M.Sc. Previous Year

Chemistry, MC-02

ORGANIC CHEMISTRY

मध्यप्रदेश भोज (मुक्त) विश्वविद्यालय – भोपाल
MADHYA PRADESH BHOJ (OPEN) UNIVERSITY – BHOPAL

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SYLLABI-BOOK MAPPING TABLE

Organic Chemistry

Syllabi	Mapping in Book
I **Nature of Bonding in Organic Molecules** Delocalized chemical bonding-conjugation, cross conjugation, resonance, hyper conjugation, bonding in fullerenes, tautomerism. Aromaticity in benzenoid and non-benzenoid compounds, alternant and non-alternant hydrocarbons. Huckel's rule, energy level of π-molecular orbitals, annulenes, anti-aromaticity, ψ-aromaticity, homoaromaticity PMO approach. Bonds weaker than covalent - addition compounds, crown ether complexes and cryptands, inclusion compounds, cyclodextrins, catenanes and rotaxanes. **Stereochemistry** Conformational analysis of cycloalkanes, declaims, effect of conformation on reactivity, conformation of sugars, steric strain due to unavoidable crowding. Elements of symmetry, chirality, molecules with more than one chiral centre, thero and erythro isomers, methods of resolution, optical purity, enantiotopic and diastereotopic atoms, groups and faces, stereospecific and stereoselective synthesis. Asymmetric synthesis, Optical activity in the absence of chiral carbon (biphenyls, allenes and spiranes), chirality due to helical shape. Stereochemistry of the compounds containing nitrogen, sulphur and phosphorus.	**Unit-1:** Nature of Bonding in Organic Molecules and Stereochemistry **(Pages 3-108)**
II **Reaction Mechanism: Structure and Reactivity** Types of mechanisms, types of reactions, thermodynamic and kinetic requirements, kinetic and thermodynamic control, Hammond's postulate, Curtin-Hammett principle. Potential energy diagrams, transition states and intermediates, methods of determining-mechanisms, isotope effect. Hard and soft acids and bases. Generation, structure, stability and reactivity of carbocations, carbanions, free radicals, carbenes and nitrenes. Effect of structure on reactivity - resonance and field effects, steric effect, quantitative treatment. The Hammett equation and linear free energy relationship, substituent and reaction constants. Taft equation. **Free Radical Reactions** Type of free radical reactions, free radical substitution mechanism, mechanism of an aromatic substrate, neighbouring group assistance. Reactivity for aliphatic and aromatic substrates at a bridgehead. Reactivity in the attacking radicals. The effect of solvents on reactivity. Allylic halogenation (NBS), oxidation of aldehydes to carboxylic acids, auto-oxidation, coupling of alkyenes and arylation of aromatic compounds by diazonimum salts. Sandmeyer reaction. Free RADICAL rearrangement. Hunsdiecker reaction.	**Unit-2:** Reaction Mechanism: Structure and Reactivity **(Pages 109-180)**
III **Aliphatic Nucleophilic Substitution** The S_N2, S_N1, mixed S_N1 and S_N2 and SET mechanism. The neighbouring group mechanism, neighbouring group participation by π and σ bonds, anchimeric assistance. Classical and nonclassical carbocations, phenonium ions, norbornyl system, common carbocation rearrangements. Application of NMR	**Unit-3:** Substitution Reactions **(Pages 181-252)**

	spectroscopy in the detection of carbocations. The S_N1 mechanism. Nucleophilic substitution at an allylic, aliphatic trigonal and a vinylic carbon. Reactivity effects of substrate structure, attacking nucleophile, leaving group and reaction medium, phase transfer catalysis and ultrasound, ambident nucleophile, regioselectivity. **Aliphatic Electrophilic Substitution** Biomolecular mechanisms - S_E2 and S_E1 and S_E1 mechanism, electrophilic substitution accompanied by double bond shifts. Effect of substrates, leaving group and the solvent polarity on the reactivity. **Aromatic Electrophilic Substitution** The arenium ion mechanism, orientation and reactivity, energy profile diagrams. The orthopara ratio, ipso attack, orientation in other ring systems. Quantitative treatment of reactivity in substrates and electrophiles. Diazonium coupling, Vilsmeir reaction, Gattermann-Koch reaction. **Aromatic Nucleophilic Substitution** The S_NAr, S_N1, benzyne and $S_{RN}1$ mechanisms. Reactivity - effect of substrate structure, leaving group and attacking nucleophile. The von Richter, Sommelet Hauser, and Smiles rearrangements.	
IV	**Addition to Carbon-Carbon multiple Bonds** Mechanistic and stereochemical aspects of addition reactions involving electrophiles, nucleophiles and free radicals, regio and chemoselectivity, orientation and reactivity. Addition to cyclopropane ring. Hydrogenation of double and triple bonds, hydrogenation of aromatic rings. Hydroboration. Michael reaction. Sharpless asymmetric epoxidation. **Addition to Carbon-Carbon Hetro Bonds** Mechanism of metal hybrid reduction of saturated an unsaturated carbonyl compounds, acids, esters and nitriles. Addition of Grignard reagents, organozinc and organolithium reagents to carbonyl and unsaturated carbonyl compounds. Wittig reaction. Mechanism of condensation reaction involving enolates - Aldol, Knoevenagel, Claisen, Mannich, Benzoin, Perkin and Stobbe reactions. Hydrolysis of esters and amides, ammonolysis of esters. **Elimination Reactions** The E2, E1 and E1 cB mechanisms and their spectrum. Orientation of the double bond. Reactivity - effects of substrate structures, attacking base, the leaving group and the medium. Mechanism and orientation in pyrolytic elimination.	**Unit-4:** Addition and Elimination Reactions **(Pages 253-302)**
V	**Pericyclic Reactions** Molecular orbital symmetry, Frontier orbitals of ethylene, 1, 3 - butadiene, 1, 3, 5 - hexatriene and allyl system. Classification of pericyclic reactions. Woodward-Hoffmann correlation diagrams. FMO and PMO approach. Electrocyclic reaction - conrotatory and disrotatory motions, 4n, 4n + 2 and allyl systems. Cycloadditions - antarafacial and suprafacial additions, 4n and 4n + 2 systems, 2 + 2 addition of ketenes, 1, 3 dipolar cycloadditions and cheleotropic reactions. Sigmatropic rearrangements - suprafacial and antarafacial shifts of H, sigmatropic shifts involving carbon moieties, 3,3 - and 5, 5- sigmatropic rearrangements. Chlaisen, Cope and aza-Cope rearrangements. Fluxional tautomerism. Ene reaction.	**Unit-5:** Pericyclic Reactions **(Pages 303-328)**

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INTRODUCTION

NOTES

Organic chemistry is the study of the structure, properties, composition, reactions, and preparation of carbon-containing compounds, which include not only hydrocarbons but also compounds with any number of other elements, including hydrogen (most compounds contain at least one carbon–hydrogen bond), nitrogen, oxygen, halogens, phosphorus, silicon, and sulfur. This branch of chemistry was originally limited to compounds produced by living organisms but has been broadened to include human-made substances such as plastics. The range of application of organic compounds is enormous and also includes, but is not limited to, pharmaceuticals, petrochemicals, food, explosives, paints, and cosmetics.

Organic compounds are all around us. The great abundance of organic compounds, their fundamental role in the chemistry of life, and their structural diversity have made their study especially challenging and exciting. Organic chemistry is the largest area of specialization among the various fields of chemistry. The range of application of organic compounds is enormous and also includes, but is not limited to, pharmaceuticals, petrochemicals, food, explosives, paints, and cosmetics. Many modern, high-tech materials are at least partially composed of organic compounds.

Carbon can form covalent bonds with itself and other elements to create an array of structures. In organic chemistry, we learn about the reactions chemists use to synthesize carbon based structures, as well as the analytical methods to characterize them. Organic reactions are chemical reactions involving organic compounds.The basic organic chemistry reaction types are addition reactions, elimination reactions, substitution reactions, pericyclic reactions, rearrangement reactions, photochemical reactions and redox reactions. Stereochemistry, is also subdiscipline of organic chemistry, it involves the study of the relative spatial arrangement of atoms that form the structure of molecules and their manipulation. The study of stereochemistry focuses on stereoisomers.

This book, is divided into five units which will help to understand the basic concepts of organic chemistry, nature of bonding in organic molecules, stereochemistry, elements of symmetry, chirality, types of mechanisms, types of reactions, thermodynamic and kinetic requirements, kinetic and thermodynamic control generation, structure, stability and reactivity of carbocations, carbanions, free radicals, carbenes and nitrenes,type of free radical reactions, aliphatic nucleophilic substitution reactions, aliphatic electrophilic substitution reactions, aromatic electrophilic substitution reactions, aromatic nucleophilic substitution reactions, addition to carbon-carbon multiple bonds, addition to carbon- multiple hetro bonds, mechanism of condensation reaction, elimination reactions, pericyclic reactions, cheleotropic reactions, and sigmatropic rearrangements.

UNIT 1 NATURE OF BONDING IN ORGANIC MOLECULES AND STEREOCHEMISTRY

NOTES

Structure

1.0 INTRODUCTION

A chemical bond is a lasting attraction between atoms, ions or molecules that enables the formation of chemical compounds. The bond may result from the electrostatic force of attraction between oppositely charged ions as in ionic bonds or through the sharing of electrons as in covalent bonds. The strength of chemical bonds varies considerably; there are strong bonds or primary bonds such as covalent, ionic and metallic bonds, and "weak bonds" or "secondary bonds" such as dipole–dipole interactions, the London dispersion force and hydrogen bonding.

Chemical bonding, any of the interactions that account for the association of atoms into molecules, ions, crystals, and other stable species that make up the familiar substances of the everyday world. When atoms approach one another, their nuclei and electrons interact and tend to distribute themselves in space in such a way that the total energy is lower than it would be in any alternative arrangement. If the total energy of a group of atoms is lower than the sum of the energies of the component atoms, they then bond together and the energy lowering is the bonding energy.

Stereochemistry, a subdiscipline of chemistry, involves the study of the relative spatial arrangement of atoms that form the structure of molecules and their manipulation.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. An important branch of stereochemistry is the study of chiral molecules. Stereochemistry spans the entire spectrum of organic, inorganic, biological, physical and especially supramolecular chemistry.

In this unit, you will study about nature of bonding in organic molecule conjugation, cross conjugation, resonance, hyper conjugation, bonding in fullerenes, tautomerism. aromaticity in benzenoid and non-benzenoid compounds, alternant and non-alternant hydrocarbons, huckel's rule, energy level of pi molecular orbitals, annulenes, anti-aromaticity, y-aromaticity, homoaromaticity pmo approach, bonds weaker than covalent, crown ether complexes and cryptands, inclusion compounds, cyclodextrins, cateranes and rotaxanes, and stereochemistry

1.1 OBJECTIVES

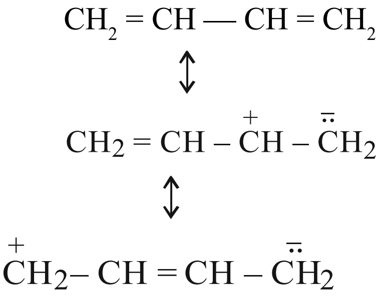
After going through this unit, you will be able to:

- Understand nature of bonding in organic molecules
- Explain conjugation, cross conjugation, resonance, hyper conjugation,
- Explain bonding in fullerenes and tautomerism
- Discuss aromaticity in benzenoid and non-benzenoid compounds
- Explain alternant and non-alternant hydrocarbons
- Discuss energy level of pi molecular orbitals
- Discuss bonds weaker than covalent
- Explain conformational analysis of cycloalkanes
- Analyze optical activity in the absence of chiral carbon
- Discuss stereochemistry of the compounds containing nitrogen, sulphur and phosphorus

1.2 DELOCALIZED CHEMICAL BONDING

When an organic molecule contain alternate single and double bonds, the system is called conjugated system and the occurrence of conjugated system is called conjugation. In such a situation the double bond behave abnormally and shows a behavior different from an isolated double bond. The π bond electrons are not localised of two atoms but they are spread over the other atoms. As a result of delocalisation the molecules behave differently and undergoes abnormal addition locations.

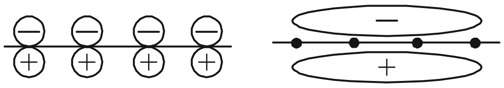
Example of 1, 3 butadiene



$$CH_2 = CH - CH = CH_2$$
$$\updownarrow$$
$$CH_2 = CH - \overset{+}{C}H - \overset{\overline{..}}{C}H_2$$
$$\updownarrow$$
$$\overset{+}{C}H_2 - CH = CH - \overset{\overline{..}}{C}H_2$$

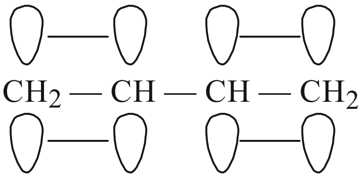
Resonance structure

Structure of 1, 3 butadiene is a conjugation of single and double bond. According the molecule orbital theory each carbon atom is trigonally hybridised.

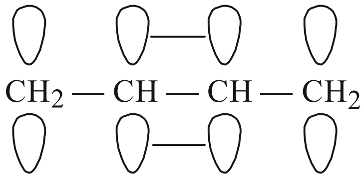


Overlapping of the P atomic orbitals on adjacent carbon atoms gives two localised π bonds:

(i)



(ii)



Interaction is alo possible between two central carbon atoms. As a result of this a π (bond) molecular orbital containing four π electrons is formed which coveres all the four carbon atoms. The electrons in the π molecular orbital on said to be delocalised as they are now spread over and held in common by all the four carbon atoms.

There are three main type of structures that exhibit delocalisation

(a) Double (or triple) bonds in conjugation i.e. alternate single and double bonds.

Example – acrolein, butadiene

(b) Double (or triple) bond in conjugation with a P-orbital on adjacent atoms.

Example – Vinyl Chloride

(c) Double (or triple) bond in conjugation with a C – H bond.

Example – Propylene

1.2.1 Conjugation, Cross Conjugation, Resonance, Hyperconjugation

Let us study them in detail.

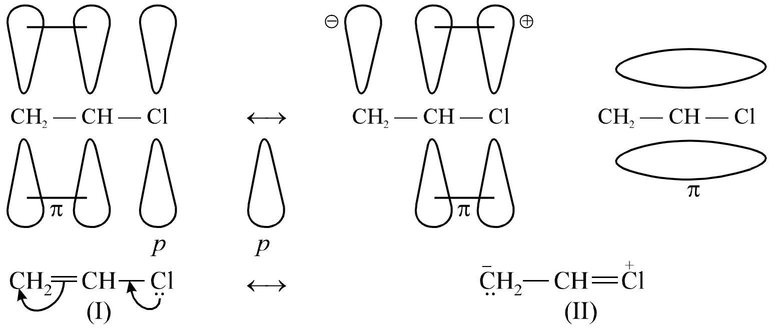
NOTES

- **Conjugation**

If the single and double bonds are present alternately in a molecule, it is said to contain double bonds in *conjugation* and the molecule is called a conjugated molecule. For example in 1,3-butadiene the double bonds are in conjugation.

$$CH_2 = CH — CH = CH_2 \text{ (1,3-Butadiene)}$$

Alternatively the double (or triple) bonds may be in conjugation with a lone pair of electrons (or non-bonding electrons) on an adjacent atom. Thus in vinyl chloride the double bond is in conjugation with the lone pair of electrons at chlorine.



It has been observed that in butadiene or vinyl chloride and other similar conjugated compounds the double bond does not behave as an isolated double bond. In case of butadiene the addition of a molecule of bromine results in a mixture of 1,2 and 1,4-addition products, whereas its structure explains only 1,2-addition.

$$CH_2—CH—Cl \xrightarrow{Br_2} \underset{\text{(Theoretical product)}}{\underset{\text{1,2-Dibromo derivative}}{CH_2=CH—CHBr—CH_2Br}}$$

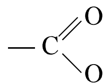
$$\downarrow Br_2$$

$$\underset{\text{1,2-Dibromo derivative}}{CH_2=CH—CHBr—CH_2Br} + \underset{\text{(Actually obtained)}}{\underset{\text{1,4-Dibromo derivative}}{CH_2Br—CH=CH—CH_2Br}}$$

On the other hand, the chlorine in vinyl chloride is very firmly bound and cannot be replaced by usual substitution reactions as in the case with C_2H_5Cl. *Thus we see that conjugation effect in molecules results in large deviations from their usual behaviour.*

To explain such differences in the actual and expected behavior of conjugated molecules and the fact that many such compounds can be represented by two or more electronic structures, which are capable of explaining some or several properties of these compounds, Robinson and Ingold (1933) gave the concept of **mesomerism** or **mesomeric effect**.

- **Mesomerism**

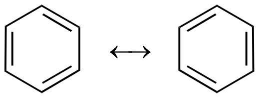
The early successes of classical structural theory led to the generally followed practice of representing the molecules by structural formulae. It has been observed that when a compound is conjugated such classical structural formulae are inconsistent with all the properties of that compound. For example a carboxylic group is represented as  $-C\begin{array}{l} /\!\!/ O \\ \diagdown O \end{array}$ and therefore, should exhibit the reactions of > C═O and — OH groups, which is evident from the structural formula but it is not so. Similarly the structure of benzene given by Kekule does not explain the important features of the molecule. To account for the properties of benzene it was suggested by Robinson and Ingold that when a molecule (like benzene) can be represented by two or more electronic structures satisfying all the valency rules and all of which are capable of explaining some but not all the properties of the compound the molecule is having neither of these structures but the real structure of the molecule lies in between these structures. The real structure cannot be represented on paper because of the limitations of the classical structural theory. This concept is known as **concept of mesomerism**.

Thus benzene can be represented as having two structures shown here.

To show that the structure of the real molecule lies in between these structures a double headed arrow (↔) is placed between the possible structures. Since the real structure of the molecule lies in between these two structures the energy corresponding to real structure is lower than the energies of either of these. Such structures can be written by simply shifting the electrons from one position to another, hence it can be said that the electrons of the molecule have acquired a greater degree of freedom or electrons are now *delocalised.* The difference in the energy of the real molecule of benzene and that of the structures shown above is known as **delocalization energy** or **stabilization energy due to conjugation** or **energy of mesomerism**. This lowering of energy makes the actual molecule more stable than represented by either of these structures. This delocalization energy may be obtained from the difference in the values for heat of combustion or heat of hydrogenation of the actual molecule and those calculated for the above structures.

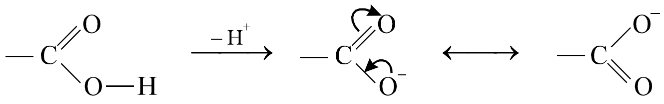
- **Resonance**

Simultaneous to the development of the concept of mesomerism, Heisenberg (1926) gave the theory of *resonance* based on quantum mechanics. This was applied qualitatively to organic compounds by Pauling as the concept of resonance. The concept of resonance practically says more or less the same thing as mesomerism but it is a consequence of valence bond method of representing molecular parameters. The problem in case of benzene and other conjugated systems is that no single classical structure adequately represents the molecule and several structures must be written for it. None of these structures completely describe the molecule but each contributes, to the total picture or behaviour of the molecule and the actual molecule is considered as a hybrid of all these structures. This crudely parallels the mathematical expression written for the molecule in V.B. method. Thus the above two Kekule structures for benzene having localized bonds do not represent benzene but a resonance hybrid of the two (or more) will represent the molecule more accurately. All the bonds which are double in one structure are single in the other structure. Thus the actual bonds in benzene are intermediate between double and single bonds.

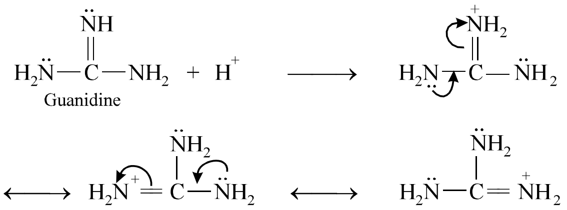


Such a qualitative, empirically based concept, bearing resemblance to V.B. approach and developed by Pauling, is called *Theory of Resonance.* It states that a molecule for which several classical structural formulae may be written, cannot be satisfactorily represented by any one of these formulae known as **limiting structures** or **canonical structures** but only by the superposition of the whole set. The limiting structures are considered to be in resonance and the real molecule as a resonance hybrid of these. The resonance in a molecule is depicted by writing a double headed arrow between limiting structures. The limiting structures do not correspond to real ground state. These contributing limiting structures can only be selected on the basis of chemical consideration. At this point the resonance and V.B. concepts may be distinguished because the mathematics provides no basis for selecting one or the other resonance structure as is done in resonance representation. In V.B. scheme the wave function of the molecule can be obtained not only as a linear combination of wave functions with appropriate coefficients. *In this respect, the concept of resonance coincides with the concept of mesomerism.*

Usually the significance of various physical phenomenon is explained by assuming various limiting structures as responsible for specific properties of a compound. Thus the acidic properties of —COOH group are explained by assuming that the carboxylate anion obtained by dissociation of a proton is stabilized by resonance.



Similarly the basicity of guanidine is explained in terms of resonance stability acquired by resulting cation due to resonance.



However, one should be careful that from illustration given above it is extremely easy to misunderstand that such structures are real or there is some such phenomenon as electron resonance.

The concept of resonance is used to describe long range delocalization of electrons leading to an extra stability. In a conjugated molecule the conjugated electrons can get delocalized. Hence such electrons must either be non-bonding electrons or loosely bonded π (pi) electrons hereafter called molecule electrons.

In order to get localized there should be some vacant orbital (or an orbital which can accept a pair of electrons after some adjustment in another part of the molecule) where the mobile electrons may be shown to be moving.

The essential condition of conjugation is that there must be a gap of one bond between mobile electrons and the vacant orbital. Thus, resonance is not possible in following molecule as there is a gap of two bonds between mobile electrons

$$CH_2{=}\,CH\underset{\uparrow}{—}CH_2\underset{\uparrow}{—}CH = CH_2 \quad \text{(Resonance not possible)}$$

Gap of two bonds

but is possible in $CH_2{=}\,CH—\overset{\oplus}{C}H_2$ as there is a gap of only one bond between mobile electrons and vacant orbital at positively charged carbon.

Conditions and Rules for Resonance

Wheland has suggested following conditions for resonance:

(1) The positions of all the atomic nuclei in limiting structures must be same or very nearly same.

(2) The limiting structures must have the same number of paired and unpaired electrons.

(3) The limiting structures must not exhibit large differences in the average positions of the electrons.

(4) The energies of the various limiting structures must be same or nearly the same.

(5) All the limiting structures must be written in accordance with usual structural scheme.

(6) All the limiting structures do not contribute equally to the real molecule but each structure contributes in proportion to its stability. Equivalent limiting structures contribute equally. Usually all the atoms taking part in the resonance lie in a plane and the stability of a structure depends on following factors:

  (*a*) Structures with more covalent bonds are more stable than those with lesser covalent bonds. Limiting structures having same number of sigma and pi bonds are known as isovalent structures. If the number is different then the structures are called *heterovalent*. In general, isovalent structures are more important than heterovalent structures, for example,

Isovalent structures

$$\underset{\text{(I)}}{CH_2 = CH—\ddot{\underset{\cdot\cdot}{Cl}}\!:} \leftrightarrow \underset{\text{(II) Significant contribution}}{\overset{\ominus}{C}H_2 —CH = \overset{\oplus}{Cl}\!:}$$

Heterovalent structures

$$\underset{\text{(III)}}{CH_2{=}CH—CH{=}CH_2} \longleftrightarrow \underset{\text{(IV) Insignificant contribution}}{\overset{\oplus}{C}H_2 —CH = CH — \overset{\cdot\cdot\,\ominus}{C}H_2}$$

  (*b*) Stability decreases if there are isolated charges or there is increase in charge separation. Structures with similar charges on adjacent atoms are not significant.

(*c*) Structures with a negative charge on more electronegative atom are more stable than those in which the negative charge is on less electronegative atom. Amongst heterovalent structures those having negative charge on more electronegative atom (like oxygen or chlorine) are important contributing structures, e.g.

$$\mathrm{CH_2{=}CH{-}CH{=}\ddot{\underset{\cdot\cdot}{O}}} \longleftrightarrow \mathrm{\overset{\oplus}{C}H_2{-}CH{=}CH{-}\overset{\ominus}{\ddot{\underset{\cdot\cdot}{O}}}{:}}$$

(V) (VI) Significant contribution

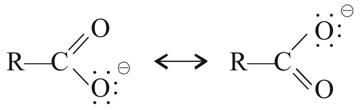
(*d*) Structures with strained bond angles or bond lengths are less stable.

For writing resonance contributing structures only electrons may be shifted from one place to another within the molecule but not the atoms.

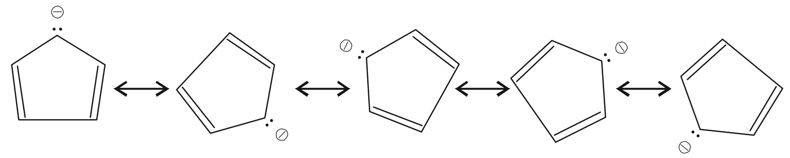
Resonance Energy

The extra stabilization of a molecule because of resonance or delocalization is expressed in terms of resonance or delocalization energy. The magnitude of resonance energy is large when

(a) Limiting structures are identical, for example, in carboxylate anion.



(b) Number of limiting structures of comparable energy is large



Cyclopentadienyl anion (All limiting structures are of identical energy)

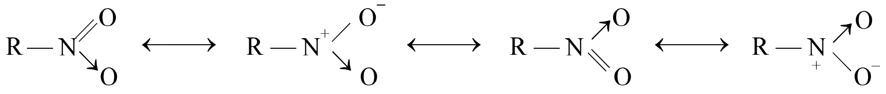
(c) Number of conjugated pi-electrons in a planar cyclic compound is $(4n + 2)$ where 'n' may have values of 0, 1, 2... etc. For $n = 1$ the most important case is benzene which has extra resonance stabilization due to aromaticity.

The resonance energy is generally equal to the difference in enthalpy of combustion of actual compound and that calculated for the most important limiting structure.

Applications

As has been seen the concept of resonance is most useful in explaining the unusual behaviour like stability of the conjugated systems. The resonance representation of some such molecules is given below:

(*i*) *Nitroalkane*



(*ii*) *Butadiene*

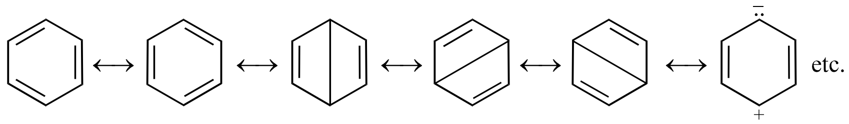
$$CH_2{=}CH{-}CH{=}CH_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}\overset{-}{C}H_2 \longleftrightarrow \overset{-}{C}H_2{-}CH{=}CH{-}\overset{+}{C}H_2$$

(*iii*) *Diazomethane* $CH_2{=}\overset{+}{N}{=}\overset{+}{N} \longleftrightarrow \overset{-}{C}H_2{-}\overset{+}{N}{\equiv}N$

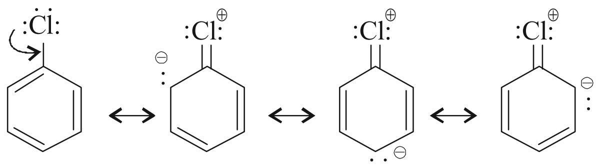
NOTES

(*iv*) *Allyl cation* $CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2$

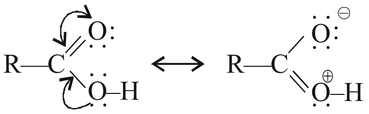
(*v*) *Benzene*



(*vi*) *Chlorobenzene*



(*vii*) *Carboxylic acids*



There are two important features which may be observed in the above representation of resonance structures:

1. The electrons are not necessarily present where they are expected to be but are delocalized giving the molecule an extra stability.
2. A more significant case is that of chlorobenzene and vinyl chloride. Normally chlorine withdraws electrons towards itself by –*I* effect but in its limiting structures chlorine has get a positive charge and seems to be donating electrons towards carbon skeleton.

   Does this mean that chlorine has lost its –*I* effect? No, as the –*I* effect is a permanent effect but in addition it now has an electron donating resonance effect (called +*R* or +*M* effect) due to conjugation.

   In carboxylic acids oxygen of the — OH group has given its electron pair towards carbon (+*R* or +*M* effect) due to conjugation despite the –*I* effect of the oxygen.

   Since in both the above cases inductive and resonance effects are operating in opposite direction one of them will prevail in deciding the overall electron density distribution in the molecule. In case of chlorobenzene, chlorine has a –*I* effect and also a +*R* effect such that –*I* > +*R*. Thus chlorine withdraws electron density from benzene ring by –*I* effect but comparatively increases the electron density at *o*- and *p*- positions of benzene ring by +*R* effect.

Although both mesomerism and resonance are used to explain the molecular properties in terms of electronic structural formulae yet the *concept of mesomerism has evolved from purely chemical considerations, whereas the resonance* *concept has been developed by analogy to quantum and wave mechanics, and applied to organic structural representations.* However both these terms are used somewhat interchangeably by organic chemists.

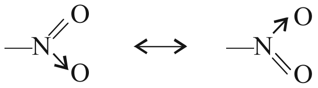
The concept of mesomerism and resonance may be distinguished from each other by taking the example of ethylene molecule. Its structural formula $CH_2 = CH_2$ is capable of explaining its properties satisfactorily. Therefore the concept of mesomerism cannot be applied to ethylene. On the other hand in the concept of resonance certain rules are provided for writing the contributing structures whether or not there is a discrepancy in its properties and the structure written for it. Thus ethylene may be considered as resonance hybrid of following contributing structures:

$$CH_2 = CH_2 \leftrightarrow \overset{\oplus}{C}H_2 - \overset{\ominus}{C}H_2 \leftrightarrow \overset{\ominus}{C}H_2 - \overset{\oplus}{C}H_2$$

Some important applications of resonance effect are given below:

1. ***Effect on bond lengths:*** In resonance description of molecules very often a bond between two particular atoms in represented as a single bond in one limiting structure and as a double bond in another limiting structure.

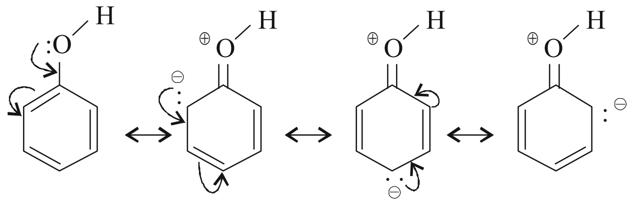
   Since the molecule is a hybrid of these structures such a bond acquires partial single and partical multiple bond character. Hence the bond length is somewhere between that of the single and multiple bond. For example all C—C bonds in benzene are equal to 1.39Å whereas the usual bond length for single and double bonds are 1.54Å and 1.33Å respectively. In carboxylate anion both C—O bonds are equal to 1.27Å and this value lies in-between the lengths for C—O single and double bonds. In 1, 3-butadiene C_1 to C_2 and C_3 to C_4 bond length is 1.35Å (greater than 1.3 Å expected for a double bond) and C_2—C_3 bond length is 1.47Å (less than expected value of 1.54Å for a single bond.) In nitro compounds the two N—O have identical bond lengths due to two identical contributing structures.

   Thus the shortening of single bond distances and lengthening of multiple bond distances in most of the conjugated molecules are explained on the basis of resonance concept.

2. ***Effect on stability*:** Resonance hybrid is always more stable than any of the limiting structures. Thus benzene molecule is about 36 kcal mol^{-1} more stable as compared to contributing Kekule structures. The difference of energy of actual molecule from limiting structures is called resonance energy.

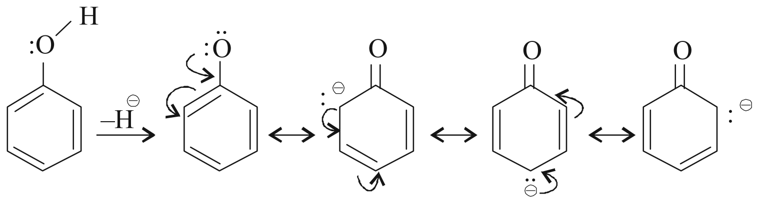
3. ***Effect on strengths of acids and bases*:** Compounds with —OH group in alcohols are neutral and act as nucleophiles but when —OH group is attached to a conjugated system as in phenol it acquires acidic character due to resonance involving limiting structures having +ve charge on oxygen which results in easy loss of $H^{\oplus}$



Resonance contributing structures of phenol

Also the phenoxide ion formed as a result of loss of proton is more stabilized by resonance as compared to phenol because:

(a) only one kind of charge is there on all the limiting structures unlike phenol which has dipolar limiting structures



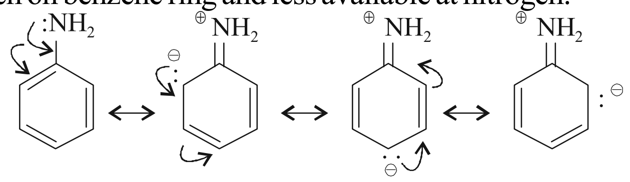
Resonance contributing structures of phenoxide ion

(b) phenoxide ion has negative charge on oxygen and ring carbon atoms while phenol has positive charge on oxygen –an electronegative atom.

The basic character of amines is due to the lone pair of electrons at nitrogen. Usually the base strength of amines increases with increase in number of alkyl groups attached to nitrogen due to their +*I* effect (except in case of tertiary amines which are weaker bases due to steric factor).

$NH_3 < R—NH_2 < R_2NH > R_3N$ (Abnormal due to steric factor)

If —NH_2 is attached to a conjugated system like benzene, the lone pair at nitrogen gets delocalized over the benzene ring due to +*R* effect of —NH_2 group, making aromatic amines much less basic than aliphatic amines. Resonance structure of aniline shows delocalization of electron pair of nitrogen on benzene ring and less available at nitrogen.

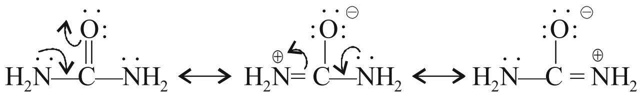


Resonance contributing structures of aniline

As the number of aryl group increases, the basic character of aromatic amines decreases. Thus,

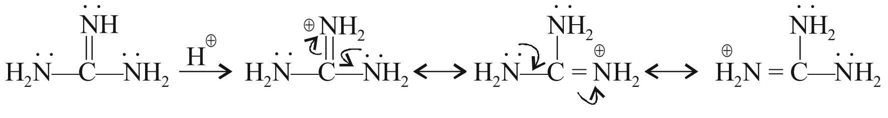
$$C_2H_5NH_2 > C_6H_5NH_2 > (C_6H_5)_2\,NH > (C_6H_5)_3\,N$$

Urea is a monoacid base though it has two nitrogens with lone pairs. The resonance structure of urea shows that both the nitrogens of urea are somewhat deficient in electrons and oxygen is rich in electrons. Since there is only one oxygen it behaves as a monoacid base.



Resonance contributing structures of urea

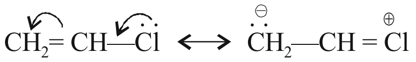
Guanidine is a strong base due to greater resonance stabilization of its conjugate acid.



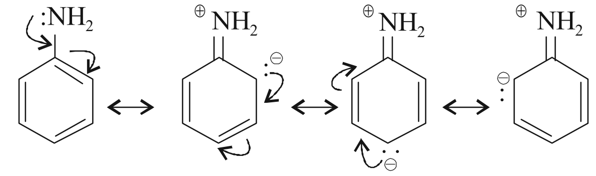
Guanidine Conjugate acid of Guanidine (more stable)

4. ***Effect of resonance on electron displacement*:** While writing the resonance limiting structures, it is customary to show shift of electrons from one position to another but since the limiting structures have no real existence the movement of electrons is not taking place. Electrons in a molecule occupy a definite position which is not completely defined by any limiting structure.

   Some groups when linked to a conjugated system release electrons because of resonance (regardless of their inductive effects) and are said to have +*R* or +*M* effect. Examples of such groups are –X (halogen), — OH, and — NH_2. All these groups have –*I* but –*R* effect. The essential feature of such groups is that they have a lone pair at the atom directly linked to conjugated system which participates in resonance, for example:

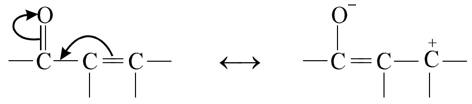
+ R effect: (i) 

$CH_2{=}CH{-}\ddot{Cl} \longleftrightarrow \overset{\ominus}{\ddot{C}H_2}{-}CH{=}\overset{\oplus}{Cl}$

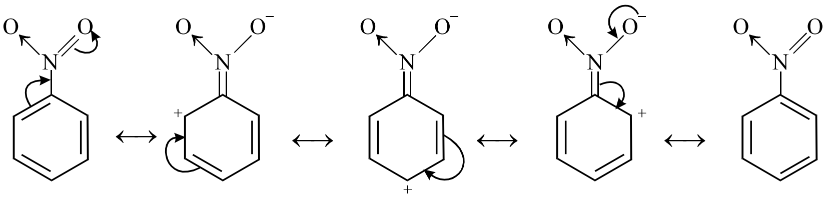
(ii) 

In both these examples of +*R* effect, the usual inductive effect (–*I*) is opposing the resonance effect (+*R*). In contrast those groups which when linked to a conjugated system withdraw electrons due to resonance are said to have –*R* or –*M* effect, for example, — NO_2, — CN, > CO, — SO_3H etc. The important feature of these groups is that the atom directly linked to the conjugated system does not have a lone pair and is attached to a more electronegative atom by a multiple bond.

–R effect:

(*i*) 

α,β-Unsaturated carbonyl compounds

(ii) 

Nitrobenzene

Steric Inhibition of Resonance

The word steric is derived from 'stereos' meaning space. Steric effect essentially arises because of the fact that each atom of molecule occupies some space. If two atoms are brought closer, then their van der Waal's radii, their electron clouds repel each other and this process in energetically unfavourable. Steric effect plays an important role in organic chemistry. Consider the example shown in Figure 1.1.

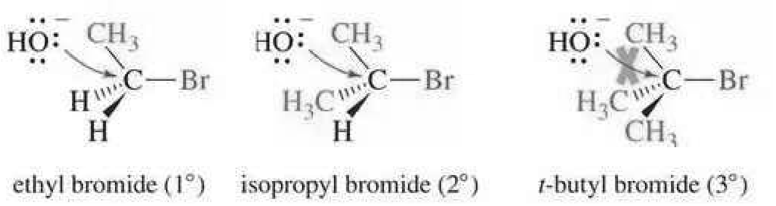


Fig. 1.1 *S_N2 Reaction*

Figure 1.1 shows the S_N2 reaction in which there are three substrates. Hydroxide ion is attacking carbon which is attached to bromine. Bromine leaves as hydroxide attacks on the central carbon atom.

In the first substrate central carbon is attached to two hydrogens and one methyl group and in the second substrate two methyl groups and one hydrogen. In the third substrate three methyl groups. Methyl group occupies significant space, so when hydroxide ion approaches the central carbon atom, methyl group starts repelling the hydroxide ion. Presence of two methyl groups makes the compound more stable. In the case of three methyl groups, reaction hardly occurs. So one can say that Methyl group has steric effect on the hydroxide ion. This steric effect sometimes leads to low reaction rates.

Steric Enhancement of Resonance

The rate constants and the activation energies for the alkaline hydrolysis of some substituted ethyl benzoates provide evidence for the phenomenon of steric enhancement of resonance. For example, for 3-substituted-4-alkoxybenzoic esters the rate constants can be evaluated on the basis of the principle of additivity of substituent effects, which can be significantly higher as compared to the observed values. It indicates that the 3-substituent does not sterically inhibit the resonance interaction of the alkoxy and ester groups but it actually enhances it. The observed rate constants of 4-alkoxy-3-methyl-N, N-dimethylanilines are considerably higher than the predicted values on the basis of additivity of group effects. As a result there is enhanced resonance interaction of the alkoxy group with the dimethylamino group increasing the nucleophilicity of the dimethylamino group. A similar steric enhancement of resonance is also possible for 3-methyl-4-methylthio-N, N-dimethylaniline.

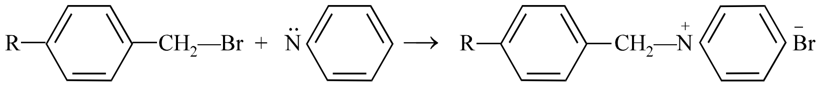
- **Hyper Conjugation**

When an H — C bond is attached to an unsaturated carbon atoms, the σ (sigma) elecrons of this H — C bond enter into conjugation with unsaturated system. Such conjugation between electrons of single and multiple bonds is known as *hyperconjugation.* However since σ electrons are less polarizable than π or *n* (nonbonding) electrons, the contribution of the ionic forms involving σ bonds will be less significant than that of ionic forms involving π and *n*-electrons.

The concept of hyperconjugation was developed on the discovery of anomalous electron releasing pattern of alkyl groups. The inductive (+*I*) effect of alkyl groups is normally in the order

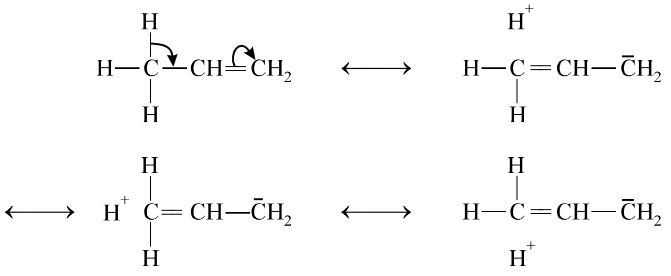
$$-CH_3 < -CH_2-CH_3 < -CH(CH_3)_2 < -C(CH_3)_3$$

However, Baker and Nathan observed that when alkyl groups are attached to an unsaturated system, the order of inductive effect is disturbed and in some cases actually reversed. For example in the following reaction:



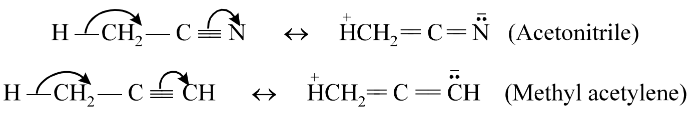
the rate of reaction should increase in the order of the increase in inductive effect of group — R but surprisingly the rate of reaction actually decreases in that order. Thus alkyl groups are capable of releasing electrons by a mechanism different from the inductive effect and the methyl group is the most successful exponent of this electron release phenomenon.

The dipole moment of propylene (0.4 D) and its greater stability than ethylene can be explained by considering the resonance contributions of structures such as:



in which no covalent bond is shown between a carbon and hydrogen atom. The hyperconjugation is therefore, also known as *no-bond resonance.* The hydrogen is taken as the positive end because of its smaller electronegativity. At this point it must be emphasized that the hydrogen does not actually become free or leave the molecule because if it moved from its original position one of the necessary condition, for resonance to occur, will be violated. Since the hyperconjugation depends on the presence of hydrogen at α-carbon, this appears to be the reason for the reversal of electron releasing ability of alkyl groups in the order $CH_3— > C_2H_5— > (CH_3)_2CH > (CH_3)_3C$ due to hyperconjugation. The number of α-hydrogens is maximum in methyl group and nil in *t*-butyl group.

Other application of hyperconjugation is the explanation of shortening of C—C single bond adjacent to a triple bond, for example, in acetonitrile and methyl acetylene:



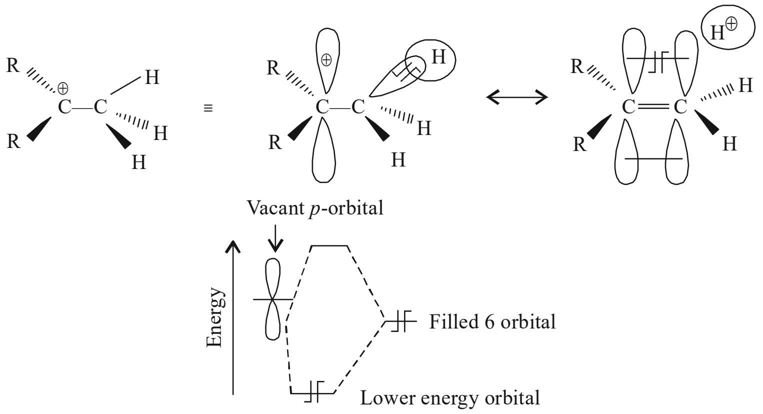
$$H-CH_2-C\equiv \ddot{N} \leftrightarrow \overset{+}{H}CH_2=C=\overset{\cdot\cdot}{\bar{N}} \quad \text{(Acetonitrile)}$$

$$H-CH_2-C\equiv CH \leftrightarrow \overset{+}{H}CH_2=C=\overset{\cdot\cdot}{C}H \quad \text{(Methyl acetylene)}$$

Similarly the heat of combustion or heat of hydrogenation of 1-butene (with two α-hydrogen atoms) is higher than of isobutylene (with six α-hydrogen atoms).

Orbital Picture of Hyperconjugation

It appears that the vacant p-orbital on adjascent carbon interacts with sigma electrons of C—H bond as shown here. The stabilization arises because the orbital interaction leads to electrons being in lower energy orbitals. Alternatively methyl group may act as a compound atom.



1.2.2 Bonding in Fullerenes

Fullerenes are forth allotropic form of carbon. Fullerenes are spherical molecules which have solebility in various organic solvents.

A fullerene is a carbon cage structure having fused ring system which consists of pentagons and hexagins. C_{60} and C_{70} are most accessible members of this family [Fig. 1.2]

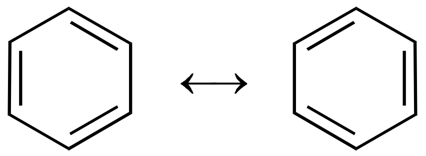


Fig. 1.2 *Different Fullerene Derivative*

The high symmetry found in this molecule is an important property C_{60} molecule is composed of 60 carbon atoms which are arrange as 12 pentagons and 20 hexagons. All rings are fused and double bonds are highy conjugated. The reason for high symmetry of this molecule is 120 symmetrical operations fund in molecule like rotation around the axis and reflection in plane which maps the molecule onto itself. When a carbon atom is placed at each vertex of molecule which all valences satisfied by two single bonds and one double bond, stabilised by resonance gives structure of C_{60} molecule, appears to be aromatic.

Table 1.1 *Types of Fullerenes*

Sr.	Type	Description
[1]	Fullerenes	C_{60} molecules is composed of -60 carbon atoms.
[2]	Buckyball clustes	Smallest number is C_{20} and common is C_{60}. Because sphere of buckyball is hollow, other atoms can traped with in it.
[3]	Nanotubes	Hollow tubes of very small dimensions with single or multiple walls.
[4]	Megatubes	Varing in dimension than nanotubes as larger in dimeter with walls of different-thickness.
[5]	Polymer	Chain, formed under high pressure and temp.
[6]	Nano "Onions"	Spherical particles having multiple layer which surrounds buckyball care.
[7]	Linked "ball and chain" dimer	To bucky ball linked by a caron chains.

General Properties

Pure fullerenes have better close packing than impure one. Fullerenes have low density (1.65 g/cc) relative to diamond [3.51 gn/cc]. Fullerenes are stables upto temperature of 1000°C. As the cage is entirly of sp^2 hybridijation carbon it gives electron withdrawing negative inductive effect (–I).

So fullerenes are strongly electron attracting i.e. (that is) fullerenes can readily react with nucleophiles. High strain energies contribute to reactivity.

1.2.3 Tautomerism

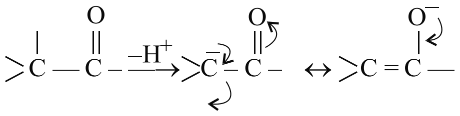
Tautomers are isomers of a compound, which differ only in the position of the protons and electron. The carbon skeleton of the compound is unchanged but tunctional groups are different. A reaction which involves simple proton transfer in an intra molecular fashion is called a tautomerism keto-enol. tautomerism is very common.

Cause of Tautomerism

Aldehydes and kelones are week acids and have abnormally law pk_a value. Therefore they can behave as a Bronsted acid in an acid-base reaction with a string base.

As there is hardly any electronegatively difference between hydrogen and carbon, C–H bones in alkans are not polarijed. Therefore, hydrogens in alkanes are non-acidic.

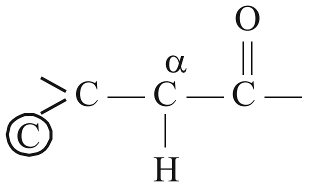
But in case of ketones and aldehydes the α-hydrogen 0/- carbonyl compound is directly bound to the electron withdrawing group. Due to resonance, the negative charge is mostly dispersed between the α-carbon and the carbons oxygens, by resonance, which leads to the stabilisation of the otherwise highly carbanion. The α-carbon and the carbonyl oxygen are the two nucleophilic and basic centres of the enolate arions.



$$>\overset{|}{C}-\overset{O}{\overset{||}{C}}-\xrightarrow{-H^+}>\bar{C}-\overset{O}{\overset{||}{C}}-\ \leftrightarrow\ >C=\overset{O^-}{\overset{|}{C}}-$$

[α-Carbonion] [enolation]

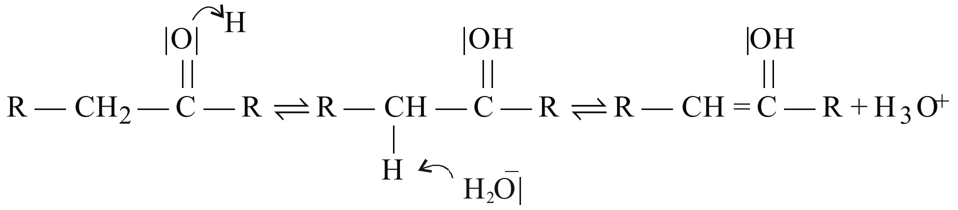
The acidities of these α-hydrogen atoms is enhanced if an electron withdrawing group is attached to the α- carbon atom.



Electron withdrawing group

On the otherhand, the acidity of the α-hydrogen atoms decreases if an electron donating group is attached to the α-carbon atom.

The keto form and enolic form are in equilibrium called as keto-enol tautomerism.



$$R-CH_2-\overset{|O|}{\overset{||}{C}}-R \rightleftharpoons R-\underset{H}{\underset{|}{CH}}-\overset{|OH}{\overset{||}{C}}-R \rightleftharpoons R-CH=\overset{|OH}{\overset{||}{C}}-R+H_3O^+$$

The keto and enolic form of a carbonyl compound are constitutional isomers.

1.3 AROMATICITY

Originally the term *aromatic* was coined for odiferous compounds and referred to a classification of organic compounds based on the physiological property of odour. Many of these organic compounds resemble benzene in their chemical behaviour particularly in undergoing substitution reaction despite unsaturation in the molecule and are said to exhibit aromatic character or aromaticity. It was also realized that the molecules of most of these organic compounds possess a benzene ring or a condensed system of benzene rings. Thus the term aromatic was synonymous to *benzenoid* (meaning the presence of benzene ring) and it was considered that the concept of aromatic character or aromaticity would be clear as soon as the problem of the structure of benzene was finally solved. However in recent years it has been pointed out that compounds other than benzene or its derivatives resemble them in chemical behaviour. Compounds such as azulenes, tropolones etc. are called '*non-benzenoid*' aromatics. The important characteristics observed for aromatic compounds are:

(1) They are usually cyclic compounds. Their molecules have been shown to be planar by X-ray and electron diffraction methods.

(2) Inspite of high degree of unsaturation these compounds are resistant to usual addition reactions of unsaturated compounds.

(3) Despite unsaturation these compounds undergo substitution reactions. Important of these substitution reactions are *electrophilic substitution reactions* like those of benzene, for example, halogenation, nitration, sulphonation, Friedel Craft alkylation and acylation reactions.

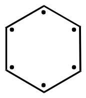
(4) They show unusual stability as shown by their low heat of hydrogenation and heat of combustion.

These distinctive properties of aromatic compounds must be somehow related to their structural features, some of which at least should be common to all compounds exhibiting aromaticity.

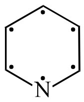
Theories of Aromaticity

The earliest attempts to explain aromaticity date back to 1865 when Kekule assigned a dynamic formula to benzene involving interconversion of the two Kekule forms. In 1890 E. Bamberger suggested that aromatic character was associated with compounds having six residual affinities. He argued that a hexacentric system alone was capable of this stability. He could explain the aromaticity of compounds like pyridine, pyrrole and furan by assuming that in case of pyrrole and furan, lone pair of nitrogen was considered to be contributing to the six residual affinities.

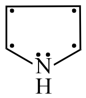
1. **Aromatic Sextet Theory:** In 1925 *Robinson* proposed sextet theory to explain aromaticity. According to this theory if there were six electrons more than required to link together the atoms of a planar system (carbocyclic or heterocyclic), then this closed group resists disruption. This closed group of six electron was called the '*sextet*' and this was responsible for *aromatic character* or *aromaticity*. Such a group is possible in benzene and heterocyclic compounds and therefore they exhibit aromatic character.



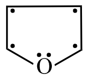
Benzene



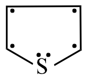
Pyridine



Pyrrole



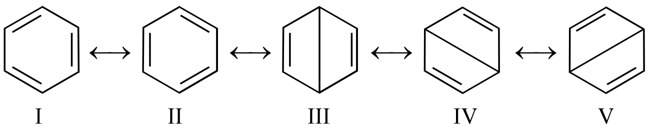
Furan



Thiophene

2. **Valence Bond Theory:** Benzene molecule has been found to be flat hexagon where C—C bond length is 1.397 Å and C—C—H valency angle is 120°. The value of bond length lies between the value for single bond (1.54 Å) and that of a double bond (1.33 Å). Hence the bonds in benzene have double bond character. The regular hexagon structure accounts for all the bonding electron except six. All this data satisfies the condition for a molecule to have resonating structure. V.B. theory calculation showed that there could be five canonical structures for benzene. Out of these five hypothetical structures, the Kekule structures (I and II) contribute 80% and the Dewar structures (III to V) 20% to the resonance hybrid structure of benzene. The heat of hydrogenation of the hypothetical cyclohexatriene would be –359 kJ mol^{-1} but the observed value for benzene is –

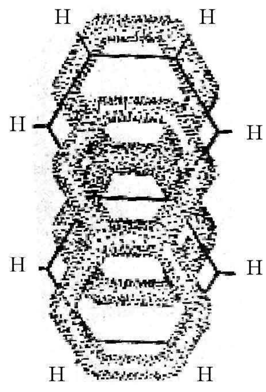
200.5 kJ mol^{-1}. Hence benzene is more stable than the triene by 150.5 kJ mol^{-1}. This value is the resonance stabilisation energy of benzene which gives its stability and the aromaticity. There are other compounds which have resonance energy and stability somewhat similar to benzene. The resonance energy of such compounds is given in the brackets.



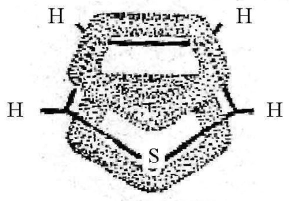
Naphthalene	(255.2 kJ mol^{-1})	Pyrrole	(88.2 kJ mol^{-1})
Anthracene	(351.5 kJ mol^{-1})	Furan	(67.2 kJ mol^{-1})
Azulene	(193.2 kJ mol^{-1})	Thiophene	(123.5 kJ mol^{-1})
Tropolone	(109.2 kJ mol^{-1})	Pyridine	(125.5 kJ mol^{-1})

3. **Molecular Orbital Theory:** The molecular orbital structure of benzene shows benzene to be a hexagon sandwiched between two delocalised 6 π electron orbitals. Delocalisation of the three localised molecular orbitals lowers the energy of the molecule by an amount which is called the energy of delocalisation. This delocalisation energy is the same as resonance energy of the valence bond theory.

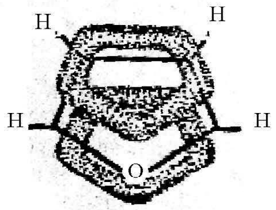
Hence it was concluded that a cyclic system having a delocalised 6 π electron molecular orbital will show stability and aromatic character similar to naphthelene and heterocyclic compounds like pyridine, thiophene, furan and pyrrole.



(1)



(2)



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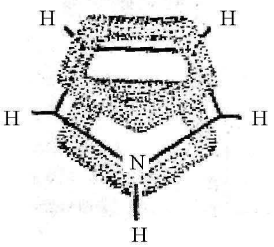

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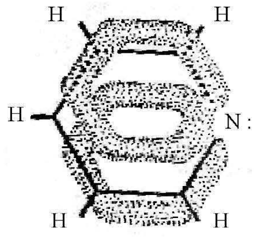
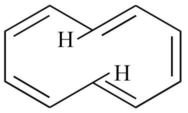


(5)

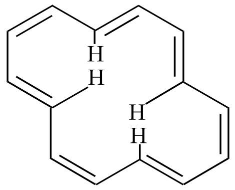
Huckel's Rule for Aromaticity

E. Huckel (1937) carried out M.O. calculation for monocyclic systems where each carbon atom contributed one π electron and came to the conclusion that stability and aromatic character is based on the presence of $(4n + 2)\pi$ electron in such systems, where 'n' is a positive integer. For value of $n = 1$ the Huckel's number is 6. The rule holds good in case of compounds like naphthalene (10π electron), pyridine (6π electron), furan, thiophene and pyrrole.

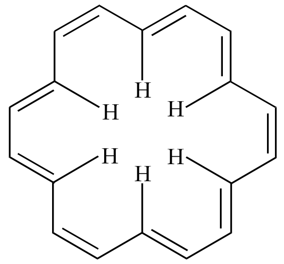
Sondheimer *et al.* (1962) prepared *annulenes* (conjugated monocyclic polyenes) with molecular formula C_nH_n, having 10, 12, 14, 16, 18, 20, 24 and 30 π electrons. Of these only those having 10, 14, 18 and 30 π electron come under the $(4n + 2)\,\pi$ electron Huckel rule. Their aromatic character was studied by NMR which revealed that they had no aromatic character. Of these [10] and [14] annulenes were not planar.



[10] Annulene



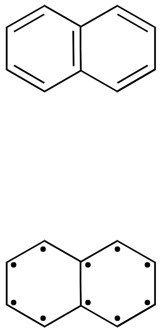
[14] Annulene



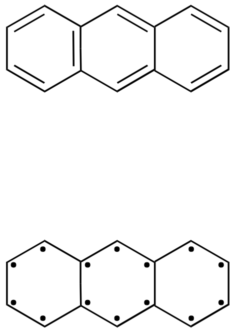
[18] Annulene

[No aromatic character]

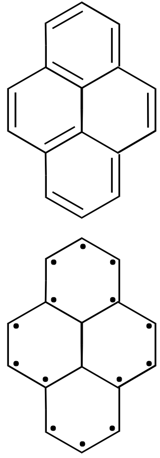
Huckel's $(4n + 2)\,\pi$ rule when applied to polycentric system was not successful in all cases. It was suggested that $(4n + 2)\,\pi$ rule should be applied to peripheral conjugated π electrons. *Naphthalene* has 10 and *anthracene* 14 π electrons which are all peripheral but *pyrene* has 16π electrons of which only 14 are peripheral. All the three compounds show aromatic character.



Naphthalene
(10 π electrons)



Anthracene
(14 π electrons)

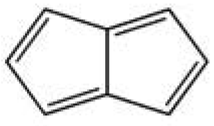


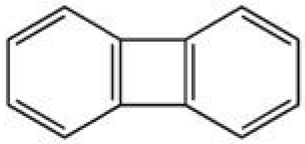
Pyrene
(14 π electrons-peripheral)

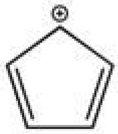
Aromatic compounds are as follows:

(i) Antiaromatic compounds

Antiaromaticity is a characteristic of a cyclic molecule with a π electron system that has higher energy due to the presence of 4n electrons in it. Unlike aromatic compounds, which follow Hückel's rule ([4n+2] π electrons) and are highly stable, antiaromatic compounds are highly unstable and highly reactive. To avoid the instability of antiaromaticity, molecules may change shape, becoming non-planar and therefore breaking some of the π interactions. In contrast to the diamagnetic ring current present in aromatic compounds, antiaromatic compounds have a paramagnetic ring current, which can be observed by NMR spectroscopy.


A


B

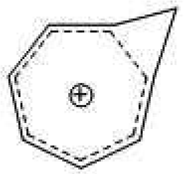

C

A: Pentalene *B: Biphenylene* *C: Cyclopentadienyl Cation*

Examples of antiaromatic compounds are pentalene (A), biphenylene (B), cyclopentadienyl cation (C). The prototypical example of antiaromaticity, cyclobutadiene, is the subject of debate, with some scientists arguing that antiaromaticity is not a major factor contributing to its destabilization.

(ii) Homoaromatic compounds

Homoaromaticity, in organic chemistry, refers to a special case of aromaticity in which conjugation is interrupted by a single sp^3 hybridized carbon atom. Although this sp^3 center disrupts the continuous overlap of p-orbitals, traditionally thought to be a requirement for aromaticity, considerable thermodynamic stability and many of the spectroscopic, magnetic, and chemical properties associated with aromatic compounds are still observed for such compounds. This formal discontinuity is apparently bridged by p-orbital overlap, maintaining a contiguous cycle of π electrons that is responsible for this preserved chemical stability.

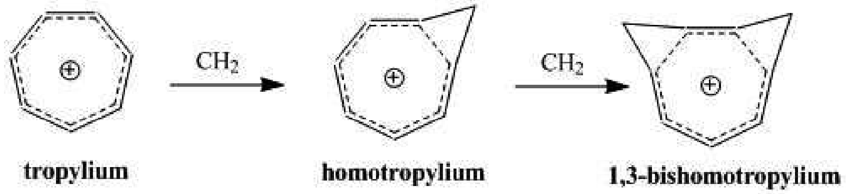


Homoaromatic homotropylium cation ($C_8H_9^+$)

The concept of homoaromaticity was pioneered by Saul Winstein in 1959, prompted by his studies of the 'tris-homocyclopropenyl' cation. Since the publication of Winstein's paper, much research has been devoted to understanding and classifying these molecules, which represent an additional class of aromatic molecules included under the continuously broadening definition of aromaticity. To date, homoaromatic compounds are known to exist as cationic and anionicspecies, and some studies support the existence of neutral homoaromatic molecules, though these are less common. The 'homotropylium' cation ($C_8H_9^+$) is perhaps the best studied example of a homoaromatic compound.

The term 'homoaromaticity' derives from the structural similarity between homoaromatic compounds and the analogous homo-conjugated alkenes previously observed in the literature. The IUPAC Gold Book requires that Bis-, Tris-, etc. prefixes be used to describe homoaromatic compounds in which two, three, etc. sp^3 centers separately interrupt conjugation of the aromatic system.

NOTES



IUPAC naming system illustrated by the Homotropylium cation derivatives

(iii) Non-aromatic compounds

Hydrocarbons are mixes made out of carbon and hydrogen alone and they are classified into two main groups, aromatic and non-aromatic compounds. The aromatic hydrocarbons contain ring or cyclic system with delocalised electron cloud while the non-aromatic hydrocarbons do not contain such ring/ cyclic system. A nonaromatic is found to be either non-cyclic or not in a planar form. These incorporate basically the alkanes, which are immersed hydrocarbons, alkenes which are saturated hydrocarbons, alkenes which contain one or more double bonds and finally the alkenes which contain one or more triple bonds.

The non-aromatic compounds without ring structure are named aliphatic though those with a ring structure like cyclohexane are named alicyclic. The aromatic hydrocarbons regularly comprise of fused rings as in case of benzo pyrene.

Properties of Non-aromatic Compounds

Some of the properties of non-aromatic compounds are as follows:

- **Stability:** The nonaromatic compounds are more stable than an antiaromatic compound but is considered to be less stable than aromatic compounds.
- **Reactivity Index:** In case of reactivity - the nonaromatic compounds are more reactive than aromatic compounds. The reason behind the less reactivity of aromatic compound the presence of delocalised electron cloud below and above the plane in aromatic compound but it is not present in nonaromatic.

Examples

A nonaromatic is found to be either non-cyclic or not in a planar form. Lots of non-aromatic compound exist like 1-octyne, 1-nonyne, 1, 4-cyclohexadiene, 1, 3, 5-cyclo heptatriene, etc.

1.3.1 Alternant and Non-Alternant Hydrocarbons

An alternant hydrocarbon is any conjugated hydrocarbon system which does not possess an odd-membered ring. For such systems it is possible to undertake a starring process, in which the carbon atoms are typically divided into two sets such that all the carbons in one set are marked with a star so that no two starred or unstarred atoms are bonded to each other. Here the starred set contains the highest number of atoms. When this condition is fulfilled, then the secular determinant in the Hückel approximation has a simpler form, since cross-diagonal elements between atoms in the same set are essentially 0.

NOTES

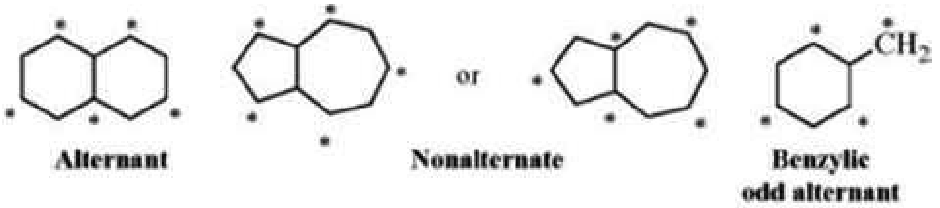
Alternant hydrocarbons show the following three very interesting properties:

- The molecular orbital energies for the π system are paired, that is for an orbital of energy $E = \alpha + x\beta$ there is one of energy $E = \alpha - x\mathbf{b}$.
- The coefficients of two paired molecular orbitals are similar at the same position, except for a sign change in the unstarred set.
- The population or electron density at all sites is equal to unity in the ground state, so the distribution of ð electrons is uniform across the whole molecule.

Moreover, if the alternant hydrocarbon contains an odd number of atoms then there must be an unpaired orbital with zero bonding energy (a non-bonding orbital). For this orbital, the coefficients on all the orbitals belonging to the smaller (unstarred) set are 0, and the sum of the coefficients of the (starred) orbitals around them must also be 0. The most-widely accepted method to molecular orbital calculations on planar hydrocarbons is possible due to Hückel. Following is the most significant distinctions made at the Hückel level between alternant (1) and non-alternant hydrocarbons (2).

Non-alternant hydrocarbons always feature at least one ring constructed with an odd number of carbon atoms, whereas alternant hydrocarbons have no such rings.

Fundamentally, the aromatic hydrocarbons can be divided into alternant and non-alternant hydrocarbons. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets in such a manner that no two atoms of the same set are directly linked. For convenience, one set may be starred. Naphthalene is an alternant and azulene a non-alternant hydrocarbon as shown below:



In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; that is, for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$. Even-alternant hydrocarbons are those with an even number of conjugated atoms, that is, an equal number of starred and unstarred atoms. For these hydrocarbons all the bonding orbitals are filled and the (electrons are uniformly spread over the unsaturated atoms. Figure illustrates 'Energy Levels' in odd-alternant hydrocarbon (odd a h) and even-alternant hydrocarbon (even a h) in which the arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

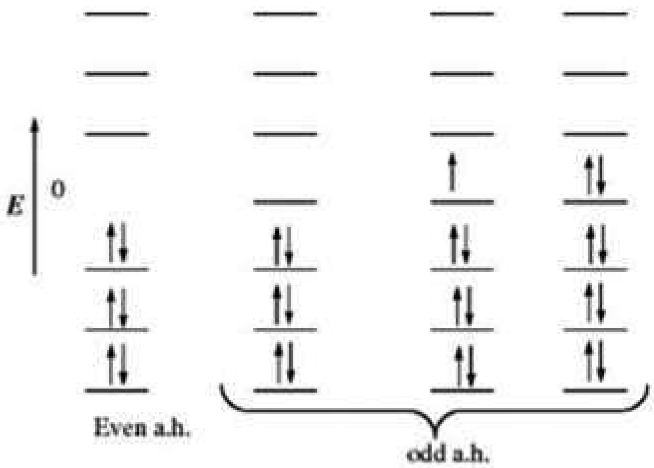


Fig. 1.3 *Energy Levels in Odd- and Even-Alternant Hydrocarbons*

As with the allylic system, odd-alternant hydrocarbons (which must be carbocations, carbanions, or radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in +*E* and +*E* pairs, one orbital can have no partner and must therefore have zero-bonding energy. For example, in the benzylic system the cation has an unoccupied nonbonding orbital, the free radical has one electron there and the carbanion has two (Refer Figure 1.4). As with the allylic system, all three species have the same bonding energy. The charge distribution (or unpaired-electron distribution) over the entire molecule is also the same for the three species and can be calculated by a relatively simple process. Figure 1.4 illustrates the 'Energy Levels for the Benzyl Cation, Free Radical and Carbanion'. Since á is the energy of a *p* orbital, the nonbonding orbital has no bonding energy.

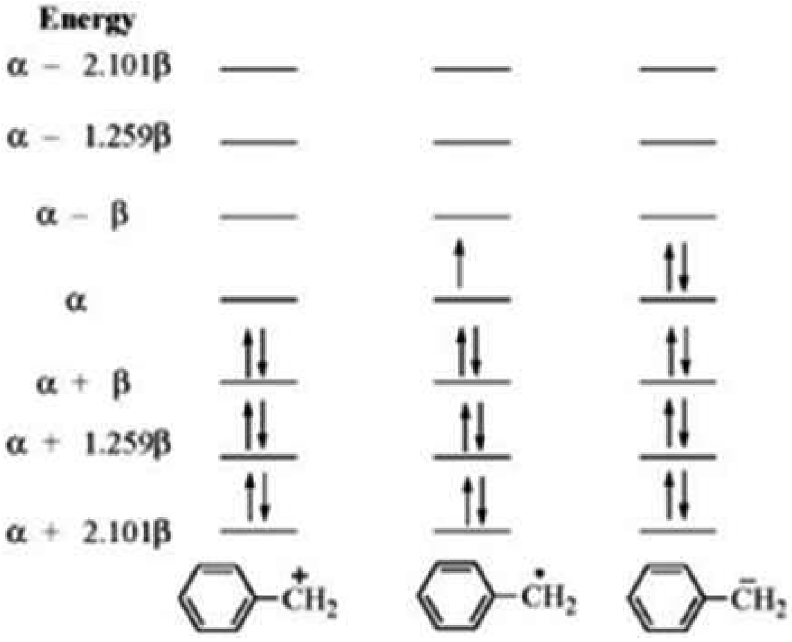


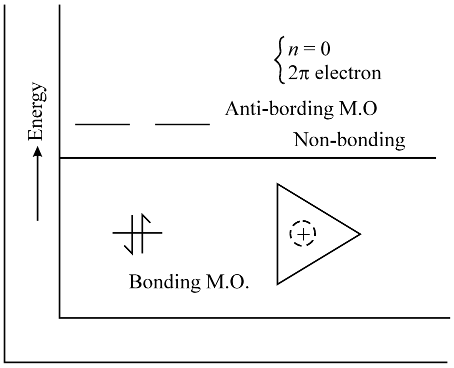
Fig. 1.4 *Energy Levels for the Benzyl Cation*

For non-alternant hydrocarbons, the energies of the bonding and antibonding orbitals are not equal and opposite and charge distributions are not the same in cations, anions, and radicals.

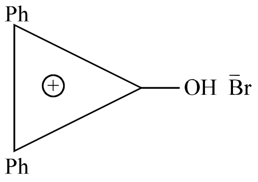
1.3.2 Aromaticity of Non-Benzenoids: Cyclopentadienyl Anion, Ferrocene and Azulene

Let us study them in detail.

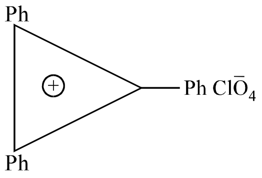
The compounds which do not contain any benzene ring are called non-benzenoids. Various non-benzenoid systems or compounds are known which contain 2, 6 or 10 pi electrons and show aromatic character.



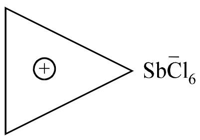
(*i*) 2π *Electron System*: A number of cyclo-propenium salts have been prepared which contain 2π electron cyclopropenyl cation. The cation correspond to the value $n = 0$ in the Huckel's formula of $(4n + 2)\pi$ electron.



Hydroxy diphenyl-
cyclopropenyl bromide

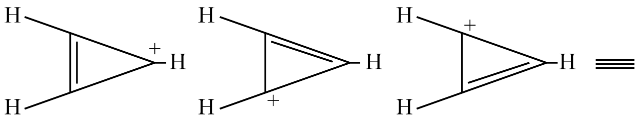


Triphenylcyclopropenyl
perchlorate

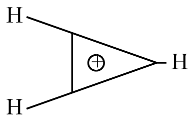


Cyclopropenyl
hexachloroantimonate

This cation is formed by the transfer of an electron from antibonding M.O. to the anion. The cation can be represented as a resonance hybrid (V.B. theory) which explains the stabilisation and aromaticity. From M.O. theory, the empty $2p_z$ orbital from which the electron has been lost overlaps the two single electron orbitals to form a closed orbital containing two electrons.

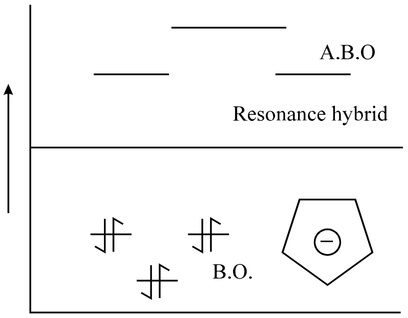


Resonating structures of cyclopropenyl cation



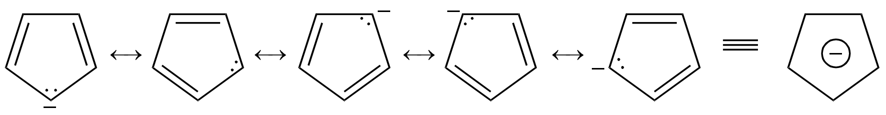
Resonance hybrid

(*ii*) 6π *Electron Systems*: We have discussed the aromatic character of benzene and other heterocyclic compounds possessing 6π electron. Benzene has three bonding and three antibonding orbitals. Six π electron fill the three bonding orbitals completely to form a closed system of π electron.



Cyclopentadienyl anion

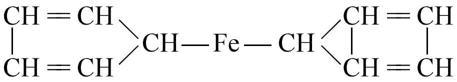
The 5π electrons system with a planar or nearly planar structure can get an electron to become a 6π electron system. Cyclopentadienyl anion formed (from potassium cyclopenta dienide) in this manner is stabilised by resonance.



Resonating structures of cyclopentadienyl anion

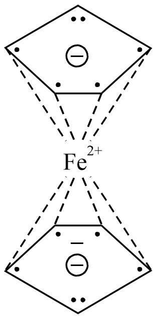
Resonance hybrid

Dicyclopentadienyl iron (**ferrocene**) is another compound which has aromatic properties.

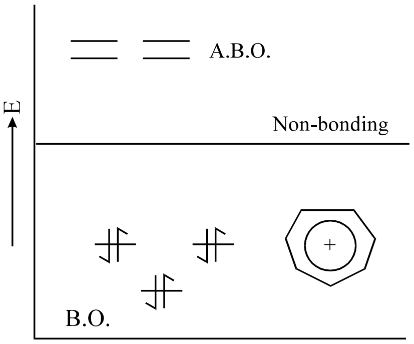


$$\begin{array}{l}CH=CH\\ |\\ CH=CH\end{array}\!\!>CH-Fe-CH<\!\!\begin{array}{l}CH=CH\\ |\qquad\quad |\\ CH=CH\end{array}$$

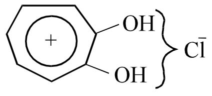
In tropylium salts one π electron is lost from anti bonding orbital to give the tropylium cation (cycloheptatrienyl) which thus is left with only 6π electrons. This ion is a resonance hybrid of seven canonical structure. Several tropylium derivatives are known which all show aromatic properties.



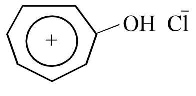
Azulene is a non-benzenoid containing a seven-membered ring fused into a five-membered ring. It has 10 π electrons in all, two being common to both rings. Now if one π electron is transferred from the seven π electron ring to five π electron ring then the molecule will have a dipole structure, each ring containing six π electrons. Azylene also behaves chemically as an aromatic compounds.



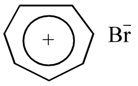
Tropylium cation



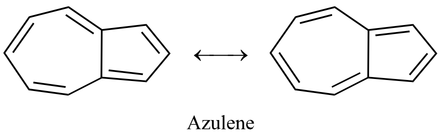
1,2-Dihydroxy tropylium chloride



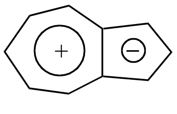
Hydroxy tropylium chloride



Tropylium bromide

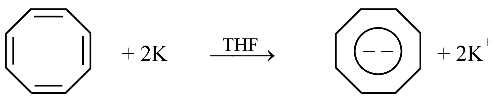


Azulene



Dipolar structure

(*iii*) 10 π *Electron System*: Cyclo-octatetraene has 8π electrons and is a very reactive compound like olefins. However, if it is made to react with potassium in tetrahydrofuran (THF) dipotassium cyclo-octatetraenide is formed which has the cyclo-octatetetraenyl dianion. In the formation of the dianion two π electrons are gained, one to each non-bonding M.O. and a close shell having 10 π electrons is formed. NMR studies have confirmed its aromatic character.



Cyclo-octateraenyl dianion

It is now realised that energetic stabilisation of a molecule does not necessarily have any relationship with low chemical reactivity because the chemical reactivity depends on the free energy difference between that of the reactants and the transition state. Thus a molecule might be stable or aromatic and yet highly reactive. Therefore J.A. Elvidge in 1965 pointed out that Huckel's rule refers only to the energy (or stability) in the ground state of the molecule and the term aromaticity should be applied to the ground state properties of the molecule. *Perhaps the best way to ascertain the aromaticity of a compound is the study of its NMR spectra. The protons of aromatic compounds show the same chemical shift in NMR as the protons of benzene. Thus an aromatic compound will sustain an induced current in NMR.*

On the basis of the foregoing discussion the criteria for aromaticity is as follows:

(*i*) The compounds must have high degree of unsaturation yet unusual stability due to large delocalisation or resonance energy.

(*ii*) It must have the property of undergoing electrophilic substitution reaction instead of addition reaction.

(*iii*) The molecule must have cyclic clouds of delocalised $(4n + 2)\pi$ electrons.

(*iv*) The compounds must have the ability to sustain an induced current in NMR.

NOTES

1.3.3 Aromaticity in Benzoid Compounds

Let us study some compounds in detail.

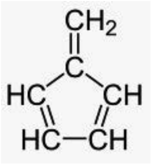
- **Tropolone**

It is an example of non-benzenoid compound which is aromatic in nature but does not have any benzene ring. The aromaticity is due to conjugated pi-electron system in the molecule.

Tropolone

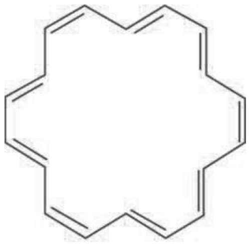
- **Fulvene**

It is one of several hydrocarbons with the same formula as benzene, C_6H_6. The fulvenes are the class of molecules based on this simple hydrocarbon frame, the parent chemical, fulvene itself, is rarely encountered.



- **Annulenes**

Benzene has 6 electrons; an aromatic compound, but cyclobutadiene with 4 pi-electrons and cyclooctatraene with 8 pi-electrons are non-aromatic compounds. Conjugated polyenes which are also called as annulenes follow Huckel's rule and aromatic compounds. For example, 10-annulene and 18-Annulene follow Huckel's rule so aromatic in nature.



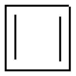
[18]- annulene

Annulenes are monocyclic compounds containing substituting ring double bonds, for example benzene, but of various sizes. As indicated by methodical terminology, benzene is a [6]annulene, while cyclobutadiene is [4]annulene, though cyclooctatetraene is a [8]annulene.

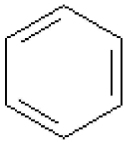
The general formula annulenes compound is C_nH_n (when n is an even number) or C_nH_{n+1} (when n is an odd number).

NOTES

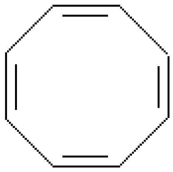
The initial three annulenes are cyclobutadiene, benzene, and cyclooctatetraene ([8]annulene). Some annulenes, in particular cyclodecapentaene or [10]annulene, cyclododecahexaene or [12]annulene and cyclotetradecaheptaene ([14]annulene)



[4]An-nu-lene.



[6]An-nu-lene.



[8]An-nu-lene.

Electron System in Annulenes

(a) ***Two Electron System:*** Huckel rule predicts cyclopropenyl cation to be aromatic. It has two electrons (n=0) engaged in cyclic delocalization. Example: trichloro, diphenyl

(b) ***Four Electron System:*** 4n systems in a closed loop which is antiaromatic, less stable than the relating open chain counterpart.

(c) ***Six Electron System:*** 6n systems in a closed loop which is antiaromatic, less stable than the relating open chain counterpart like benzene.

- **Aromaticity on Larger Annulene**

None of the larger annulenes are as steady as benzene, as their reactivity more closely resembles a conjugated polyene than an aromatic hydrocarbon like [18]annulene. [18]-annulene is relatively planar, with CC bonds between 137-143 pm. It responds more like a polyene than benzene and it undergoes addition reaction with H_2 and Br_2.

While the total aromatic stabilization energies (ASE) of the [n]annulenes, from C_6H_6 to $C_{66}H_{66}$, meet to ca. 22 kcal/mol, the ASEs per σ-electron diminish especially. When the Bond length increases it reduces stabilization of the annulene compounds and it also changes the magnetic properties of a compound also.

Example: Cyclodocosahendecaene ([22]-annulene)

Cyclodocosahendecaene ([22]-annulene)

- **Hetero Annulenes**

On the basis of molecular structure and their energy classification, a range of monocyclic and bridged annulenes and hetero-annulenes chemical compound will come in to frame. In aromatic heterocyclic compounds or molecules, it is not only the structure of carbon atoms' orbitals that participate in the formation of the aromatic π system. Orbitals of the heteroatom(s) also participate in the π system here too. Pyridine, for example, is such an aromatic heterocyclic compound. Each of the six ring atoms is sp^2-hybridized, while the molecule possesses six π electrons. The lone electron pair of pyridine's nitrogen atom occupies an sp^2 orbital. These electrons are thusly not π electrons. The staying two sp^2 orbitals of the nitrogen cover with sp^2 orbitals of the contiguous carbons, shaping two σ bonds. The π framework is the aftereffect of the covering of the nitrogen's and carbons' p orbitals, which are perpendicular to the ring plane. So the annulenes compound having hetero formation are called hetero annulene compound.

- **Fullerenes (C_{60})**

Fullerenes are a family of carbon compounds having at least 60 carbon atoms forming carbon spheres, where carbon atoms are arranged in semi-regular polyhedra distributed over the sphere. The fullerene family was discovered in 1985 by Smalley, Curl and Kroto and are extremely plenteous at the Earth's surface and in the universe. They are the third allotropic type of carbon after diamond and graphite. Fullerenes have the property of shaping shut pens (with the C_{60} molecule) with a structure like that of a football.

The C60 molecule has 60 carbon atoms arranged at the summits of 0.7 nm distance across customary polyhedron with hexagonal and pentagonal countenances.

Types of fullerene

(a) ***Buckyball clusters:*** Smallest member is C_{20} (unsaturated version of dodecahedrane) and the most common is C_{60}.

(b) ***Nanotubes:*** These are very small hollow tubes having single or multiple walls.

(c) ***Megatubes:*** Having bigger diameter than nanotubes and prepared with walls of different thickness.

(d) ***Polymers:*** Long Chain of one dimension, two-dimensional and three-dimensional polymers are formed under high-pressure high-temperature conditions.

(e) ***Nano "Onions":*** Multiple carbon layers having spherical structures surrounding a buckyball core.

1.3.4 Bonds Weaker than Covalent

Basically, the bonds possess bond dissociation energy in the range of 200-400 kJ mol^{-1}, that is the covalent bonds. However, some of the bonds have very low bond dissociation energies, such as in the range of 10-40 kJ mol^{-1}. Following are some of the bonds that are weaker than the energy range of typical covalent bonds.

Ion-Ion Interaction

Ion-ion interactions can be defined as an attractive force between ions having opposite charges. The ion-ion interactions are described as ionic bonds having the forces that hold together ionic compounds. Since each ion contains some charge, either positive or negative, therefore as per the electron attraction and repulsion theory the like charges repel each other while the opposite charges attract each other. Even though the ionic bonds or the ion-ion interactions are considered as compared to the typical covalent bonds, the ion-ion interaction between a cation and an organic anion is slightly weaker in comparison to the typical covalent interaction due to the bond energy in the range of 100-350 kJ mol^{-1}. These Coulombic forces function over relatively long distances in the gas phase. The Force (F) depends on the product of the charges (Z_1, Z_2) divided by the square of the distance of separation (d^2). The equation can be given as:

$$F \alpha \frac{-Z_1 Z_2}{d^2}$$

Two oppositely charged particles in a vacuum can be attracted towards each other and the force becomes more stronger as they approach until ultimately, they stick together or attach to each other. The bond is very strong, and a considerable amount of energy is required for separating them.

An ion pair is formed which contains a positively charged region and a negatively charged region. There are reasonably strong interactions between these ion pairs and free ions.

Ion-Dipole Interactions

An ion-dipole interaction is the result of an electrostatic interaction between a charged ion and a molecule that has a dipole. It is an attractive force that is commonly found in solutions, especially ionic compounds dissolved in polar liquids. A cation can attract the partially negative end of a neutral polar molecule, while an anion attracts the positive end of a polar molecule. Ion-dipole attractions become stronger as the charge on the ion increases or as the magnitude of the dipole of the polar molecule increases. In the following figure sodium (Na$^+$) only attracts the negatively charged end of water molecules (H_2O), the orientation is shown below.

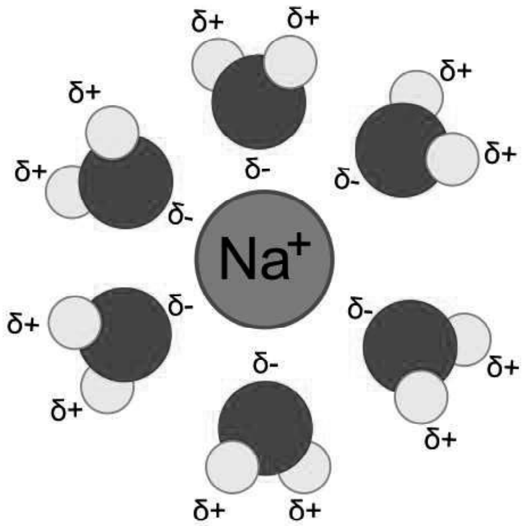


Fig. 1.5 *Sodium Attracts the Negatively Charged End of Water Molecules*

Dipole-Dipole Interactions

Dipole-dipole forces are defined as attractive forces between the positive end of one polar molecule and the negative end of another polar molecule. Dipole-dipole forces have strengths ranging from 5 kJ to 20 kJ per mole. The dipole-dipole forces are weaker as compared to ionic bonds or covalent bonds and have a significant effect only when the molecules involved are very close together.

Figure 1.6 illustrates two arrangements of polar iodine monochloride molecules that produce dipole-dipole attractions.

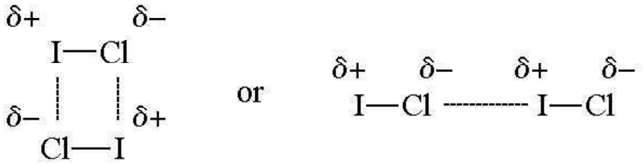


Fig. 1.6 Polar Iodine Monochloride Molecules showing Dipole-Dipole Attractions

The polar molecules have a partial negative end and a partial positive end. The partial positive end of a polar molecule is attracted to the partial negative end of another polar molecule.

1.4 ENERGY LEVEL OF π-MOLECULAR ORBITALS

Let us study energy level in the following compounds in this section.

1.4.1 π-Molecular Orbitals

Bonding and energy in homonuclear and hetronuclear molecules may be understood by following molecular orbital diagrams.

1. **Hydrogen Molecule:** Hydrogen molecule is having two hydrogen atoms containing one electron each ($1s^1$). Its M.O. diagram is as given in Figure 1.7.

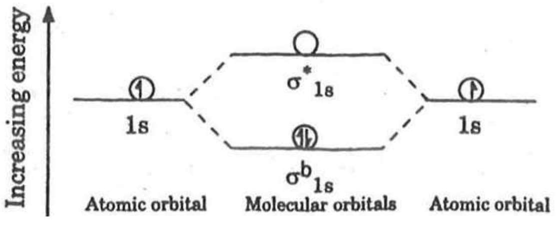


Fig. 1.7 M.O Energy Level Diagram of H_2 Molecule

(a) M.O. configuration of $H_2 = (\sigma_{1s})^2 (\sigma^*_{1s})^0$

(b) Bond Order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[2 - 0] = 1$ (Single Bond)

(c) Stability = As bond order is one, the molecule is quite stable.

(d) It is diamagnetic in nature as all the electrons in molecular orbital are paired.

NOTES

2. **H_2^+ Ion:** It is made up of H atom containing one electron and H^+ ion containing no electron. M.O. diagram for H_2^+ ion is given in Figure 1.8.

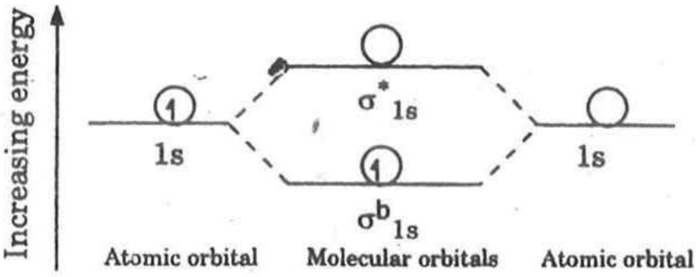


Fig. 1.8 *Energy Level Diagram of* H_2^+

(a) M.O. configuration of H_2^+ ion = $(\sigma_{1s})^1(\sigma^*_{1s})^0$

(b) Bond order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[1 - 0] = \frac{1}{2}$

(c) Stability = Its bond order is less than the bond order for H_2 molecule. Therefore, it is less stable than H_2 molecule.

(d) It is paramagnetic in behavior as it possess one unpaired electron $(\sigma_{1s})^1$.

3. **H_2^- Anion or He_2^+ Cation or H-He Molecule:** These species are having three electrons in all which are arranged in M.O. diagram as shown in Figure 1.9.

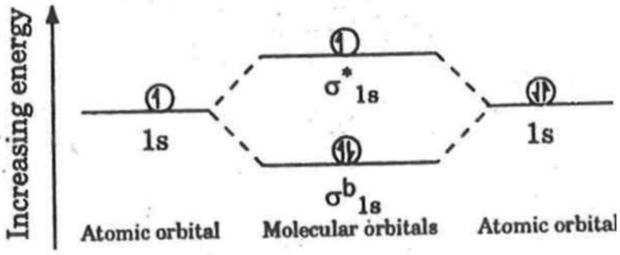


Fig. 1.9 *M.O Energy Level Diagram of H-He*

(a) M.O. configuration of H_2^- or He_2^+ or H-He = $(\sigma_{1s})^2(\sigma^*_{1s})^1$

(b) Bond order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[2 - 0] = \frac{1}{2}$

(c) Stabiliy = Its stability is equal to H_2^+ as in both cases the bond order is 0.5.

(d) It shows paramagnetic nature as it has one unpaired electron (σ^*_{1s}).

Table 1.2 *Characteristics of* H_2^+, H_2 *and* H_2^-

	Properties of Ions or Molecule	H_2^+	**H2**	H_2^-
1	Bond Order	$\frac{1}{2}$	1	$\frac{1}{2}$
2	Bond Length	$H_2^+ > H_2$	Minimum	$H_2^- > H_2$
3	Stability	Somewhat Stable	Quite Stable	Somewhat Stable
4	Magnetic Character	Paramagnetic	Diamagnetic	Paramagnetic
5	Dissociation Energy	$H_2^+ < H_2$	Maximum	$H_2^- < H_2$

4. **Helium Molecule (He_2):** Each helium atom contains 2 electrons. Therefore, He_2 molecule will have 4 electrons. These 4 electrons will be arranged in M.O. diagram as given below in Figure 1.10.

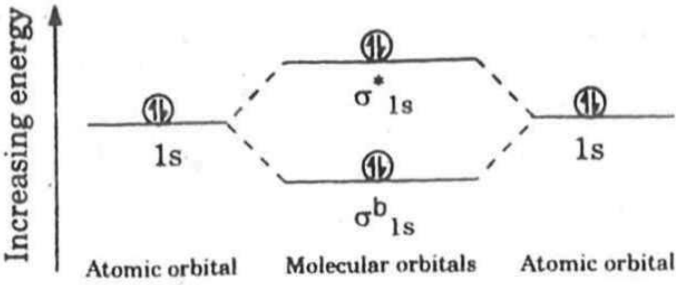


Fig. 1.10 *M.O. Energy Level Diagram of* He_2

(a) M.O. configuration of $He_2 = (\sigma_{1s})^2 (\sigma^*_{1s})^2$

(b) Bond order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[2 - 2]$ = Zero

Bond order zero indicates that there is no linkage between two atoms. Hence the He_2 molecule does not exist.

(c) Stability = The molecule is highly unstable and there is no experimental proof for its existence.

(d) It is diamagnetic in nature as all the electrons in M.O. are paired.

5. **Lithium Molecule (Li_2):** Each lithium atom has electronic configuration of $1s^2\,2s^1$ and so the Li_2 molecule has total of six electrons. In the molecular orbital formation, the electrons of the inner shell (K shell) do not enter in bonding and so remain in their atomic orbitals. The orbitals which do not enter into bonding are called nonbonding orbitals. Thus we infer that only the valence electrons are involved in bond formation. The M.O. energy level diagram of Li_2 is shown in Figure 1.11.

NOTES

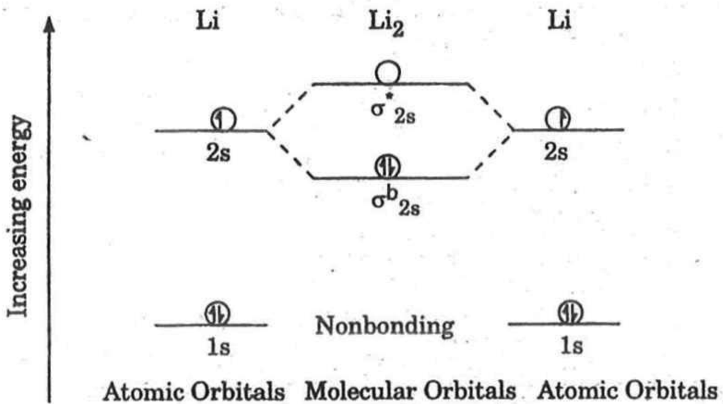


Fig. 1.11 *M.O. Energy Level Diagram of* Li_2

(a) M.O. configuration $Li_2 = (KK)\,(\sigma_{2s})^2\,(\sigma^*_{2s})^0$

(b) Bond order = $\frac{1}{2}\,[N_b - N_a] = \frac{1}{2}\,[2 - 0] = 1$

(c) Stability= The σ bond in lithium molecule is comparatively longer and weaker than that of H_2 molecule as being formed by overlapping of 2*s* orbitals = Bond dissociation energy of Li_2 kJ/mol which is less than that of H_2 molecule (431.4 kJ/mol).

(d) It is diamagnetic in nature as all electrons in M.O. are paired.

6. **Nitrogen Molecule (N_2):** Nitrogen molecule has 14 electrons and thus its M.O. energy level diagram may be shown as in Figure 1.12.

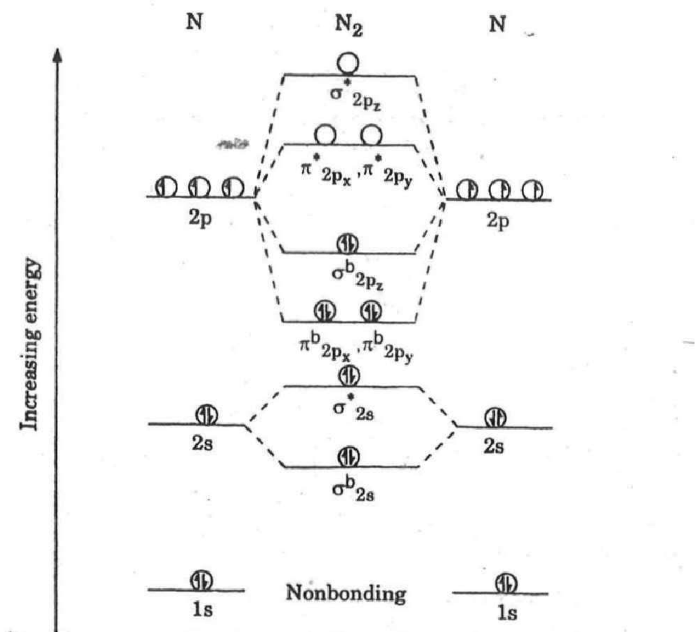


Fig. 1.12 *M.O. Energy Level Diagram for* N_2 *Molecule*

(a) M.O. configuration of $N_2 = (KK)\,(\sigma_{2s})^2\,(\sigma^*_{2s})^2\,(\pi_{2p_x})^2\,(\pi_{2p_y})^2\,(\sigma_{2p_z})^2$

(b) Bond order = $\frac{1}{2}$ [N_b - N_a] = $\frac{1}{2}$ [8 - 2] = 3

i.e., a triple bond exists between two nitrogen atoms.

(***Note**:* Electrons of K shell do not involve in M.O. formation. Therefore, these electrons remain as nonbonding electrons. Hence these are neither considered as bonding nor as anti-bonding.)

(c) Stability = Since the bond order of N_2 molecule is 3, it is highly stable molecule. It is evident from its bond dissociation energy (940 kJ/mol).

(d) All the electrons in M.O. are paired so it is diamagnetic in nature. This has also been proved experimentally.

7. **N_2^+ Cation:** N_2^+ ion shows that it is formed by the loss of one electron from N_2 molecule.

Thus M.O. electronic configuration of N_2^+ ion will be,

$$N_2^+ = KK\,(\sigma_{2s})^2\,(\sigma^*_{2s})^2\,(\pi_{2p_x})^2\,(\pi_{2p_y})^2\,(\sigma_{2p_z})^1$$

The characteristic properties of the cation will be:

(a) Bond order = $\frac{1}{2}$ [N_b - N_a] = $\frac{1}{2}$ [7 - 2] = $2\frac{1}{2}$

(b) The bond order of cation is smaller than that of N_2 molecule. Therefore, it is less stable than N_2 molecule.

(c) It has one unpaired electron in its M.O. electronic configuration. So, it is paramagnetic in nature.

8. **Oxygen Molecule (O_2):** Oxygen molecule has 16 electrons in all, in which each oxygen atom has contributed 8 electrons. The molecular orbital energy level diagram of O_2 molecule is as given below in Figure 1.13.

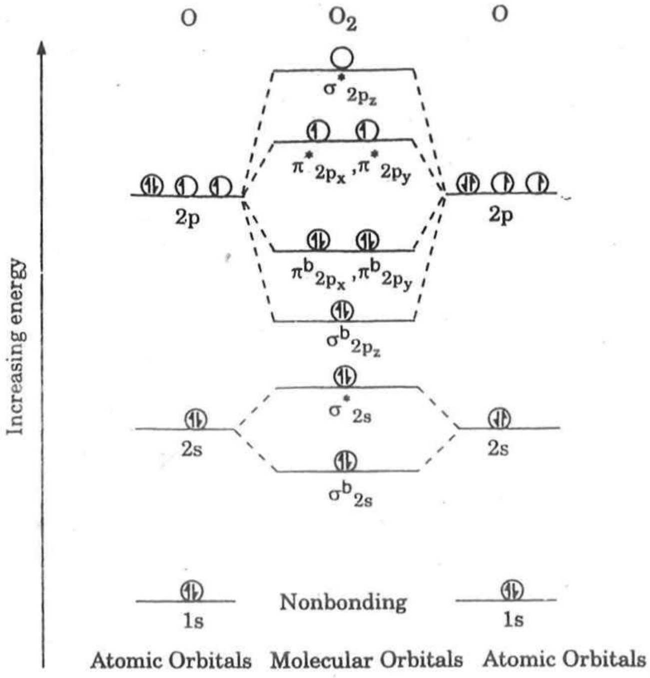


Fig. 1.13 *M.O. Energy Level Diagram for O_2 Molecule*

(a) M.O. electronic configuration =

$$\text{KK}\left(\sigma_{2s}\right)^2\left(\sigma *_{2s}\right)^2\left(\sigma_{2p_z}\right)^2\left(\pi_{2p_x}\right)^2\left(\pi_{2p_y}\right)^2\left(\pi *_{2p_x}\right)^1\left(\pi *_{2py}\right)^1$$

(b) Bond order = From M.O. diagram of O_2, the $N_b = 8$ and $N_a = 4$.

Therefore, bond order = $\frac{1}{2}[8-4] = 2$, i.e., it has double bond.

(c) Stability = Since the bond order of O_2 molecule is 2, therefore the O_2 molecule is quite stable. It is confirmed by its high dissociation energy (443 kJ/mol).

(d) Magnetic character = From its M.O. diagram it is clear that the oxygen molecule has two unpaired electrons $\left(\pi *_{2p_x}\right)^1\left(\pi *_{2p_y}\right)^1$. So, it is paramagnetic in nature as confirmed by experiments.

9. **Fluorine Molecule (F_2):** When two fluorine atoms (each having 9 electrons) combine to give F_2 molecule then the total 18 electron occupy the molecular orbitals according to Aufbau's rule. It results in the following M.O. electronic configuration (Refer Figure 1.14).

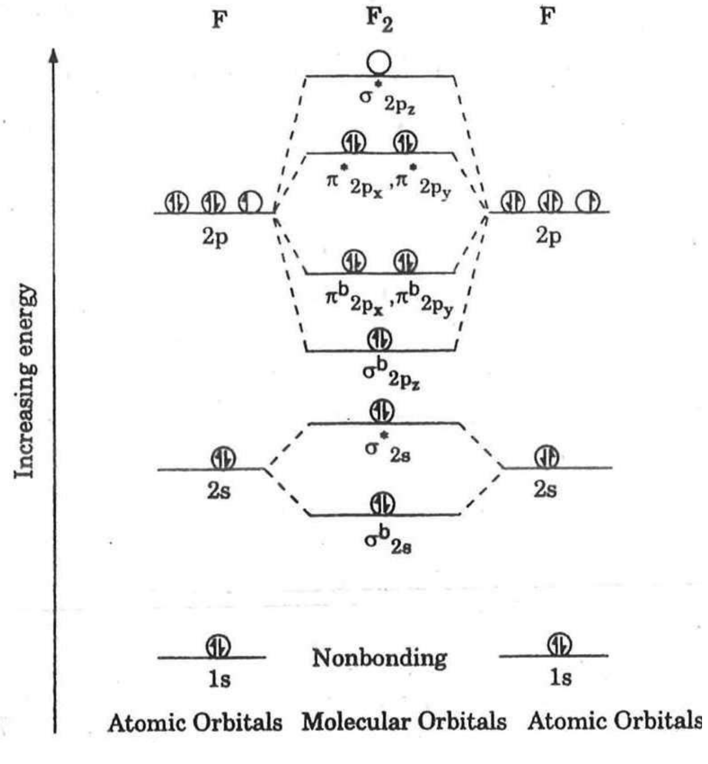


Fig. 1.14 *M.O. Energy Level Diagram for F_2 Molecule*

(a) M.O. Configuration,

$$F_2 = \text{KK}\left(\sigma_{2s}\right)^2\left(\sigma *_{2s}\right)^2\left(\sigma_{2p_z}\right)^2\left(\pi_{2p_x}\right)^2\left(\pi *_{2p_x}\right)^2\left(\pi *_{2p_y}\right)^2$$

(b) Bond order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[8-6] = 1$ (i.e., single bond between two fluorine atoms).

(c) Stability = Since the bond order of F_2 molecule is one therefore, it is a stable molecule.

(d) Magnetic nature = It shows diamagnetic behaviour as all the electrons in F_2 molecule are paired.

10. Neon Molecule (Ne_2): It shall have 20 electrons in its molecule, which will be occupying the M.O. in increasing energy level as shown below.

$$Ne_2 = KK\left(\sigma_{2s}\right)^2\left(\sigma *_{2s}\right)^2\left(\sigma_{2p_z}\right)^2\left(\pi_{2p_x}\right)^2\left(\pi_{2p_y}\right)^2\left(\pi *_{2p_x}\right)^2\left(\pi *_{2p_y}\right)^2\left(\sigma *_{2p_z}\right)^2$$

This electronic configuration of Ne_2 molecule will indicate for the following inference.

(a) Bond Order $= \frac{1}{2}\left[N_b - N_a\right] = \frac{1}{2}\left[8-8\right] =$ Zero, i.e., no bond exists between two Ne atoms.

(b) Stability = As the bond order is zero, the molecule is highly unstable and exists only in atomic state.

(c) Magnetic character = All the electrons in Ne_2 molecule are paired. So, it is diamagnetic in nature.

Heteronuclear Molecules

A hetero-nuclear molecule is a molecule composed of atoms of more than one chemical element. For example, a molecule of water (H_2O) is hetero-nuclear because it has atoms of two different elements, hydrogen (H) and oxygen (O). Similarly, a hetero-nuclear ion is an ion that contains atoms of more than one chemical element. For example, the carbonate ion (CO_3^{2-}) is hetero-nuclear because it has atoms of carbon (C) and oxygen (O). The lightest hetero-nuclear ion is the helium hydride ion (HeH^+). This is in contrast to a homo-nuclear ion, which contains all the same kind of atom, such as the di-hydrogen cation, or atomic ions that only contain one atom such as the hydrogen anion (H^-).

In the foregoing discussion, we have studied the M.O. diagrams for homonuclear diatomic molecules and their related properties. We may now apply the same method to heteronuclear diatomic species such as CO, *NO^+, CN^- and NO. Due to difference in electronegativities of the two hetero atoms, the molecular orbitals become polarized. It results in higher stabilization of MO's of more electronegative atom compared to other atom. This can best be illustrated taking the example of CO.

- **Carbon Monoxide:** It possesses 10 valence electrons (4 contributed by carbon and 6 by oxygen atom) which may be accommodated in five M.O. The M.O. energy level diagram of CO is given in Figure 1.15.

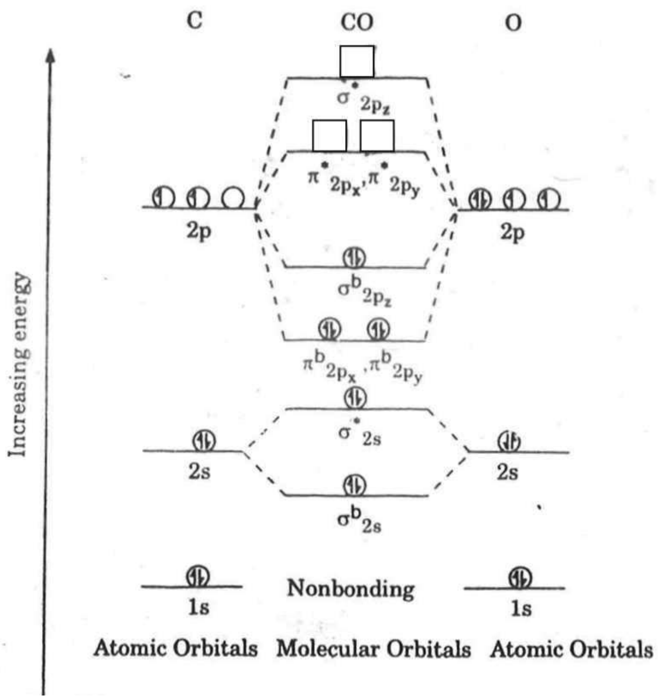


Fig. 1.15 *M.O. Energy Level Diagram for Carbon Monoxide*

(a) Electronic Configuration = $KK(\sigma_{2s})^2(\sigma*_{2s})^2(\pi_{2p_x})^2(\pi_{2p_y})^2(\sigma_{2p_x})^2$

(b) Bond Order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[8-2] = 3$ (Triple bond)

(c) Stability = As the bond order is three, the CO molecule is highly stable molecule.

(d) Magnetic properties of carbon monoxide (CO) = All electrons in M.O. are paired. Hence CO is diamagnetic in nature.

- **Nitric Oxide (NO):** Nitric oxide has 11 valence electrons and so its M.O. electronic configuration will be,

$$NO = KK(\sigma_{2s})^2(\sigma*_{2s})^2(\pi_{2p_x})^2(\pi_{2p_y})^2(\pi*_{2p_x})^1$$

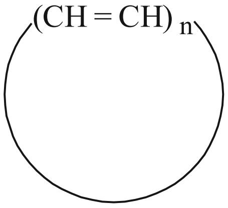
(a) Bond order = $\frac{1}{2}[N_b - N_a] = \frac{1}{2}[8-3] = 2\frac{1}{2}$

(b) Stability = It is less stable than NO^+ ion (bond order = 3) because bond order of NO is smaller than that of NO^+ ion. This is manifested by quick oxidation of NO to NO^+ iron by the loss of one $(\pi*_{2p_x})$ electron.

(c) Magnetic nature of nitric oxide = It is paramagnetic, as it possesses one $(\pi*_{2p_x})$ unpaired electron.

1.4.2 Annulenes

Annulenes are the completely conjugated monocyclic hydro carbons containing an even numbers of carbon atoms.

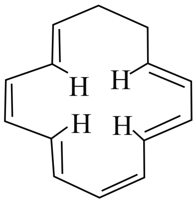


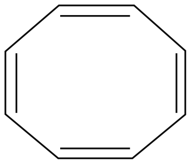
General Formula
C_nH_n
Alternatively
$(CH = CH)_n$

Annulenes with 7 or more number of carbon atoms are named as [*n*] annulene, *n* represents the number of carbon atoms in the

[8] Annulene = cyclooctatelraene

[14] Annulene = cyclotelradecaheptaene





Annulenes cond be aromatic, anti/non-aromatic [8] annulene is non aromatic [6] annulene is aromatic.

Cyclooctatetraene is a planar cyclic conjugated system which has 4 nπe$^-$. It behaves like a typical alkene and undergoes addition reaction with electrphillic reagent like Br and HCl oxidation by $KMnO_4$.

Its non aromatic behavior explained by the molecular orbital theory.

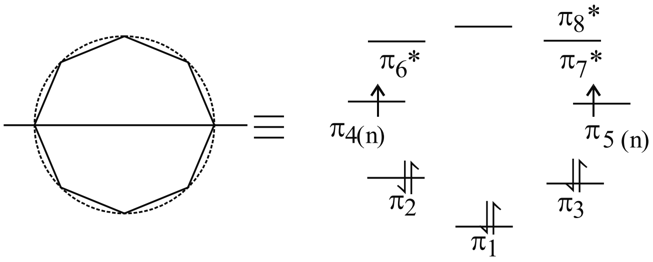
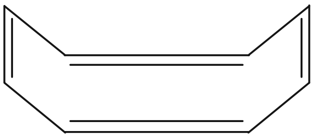


***Fig. 1.16** MO Diagram for [8] Annulene*

Energy level of various molecular orbital according to which there are three bonding two non bonding and three antibonding molecular orbitals since non-bonding π^h orbitals are half filled so it should be predicted to be non aromatic.

Cyclooctatetraene is not plane, but a tube shaped molecule.



C = C — C = 126.1°
C = C — H = 117.6°

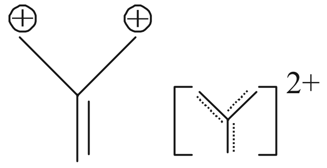
The p orbitals of one sp^2 hybridized carbon are is not coplanar with these of the neighbouring ones, therefore no effective overlapping of the orbitals take place for delocalioation.

[14] Annulene (14 $\underline{p}e^-$ system) i.e. $(4n + 2)\ \pi e^-$ does not undergo substitutive nitration and sulphonation reaction indicative of its now aromatic behavior. In [14] Annulene 'H' present at the interior of the using interfere with each other, and X-ray analysis shows that the moleculus is not planner.

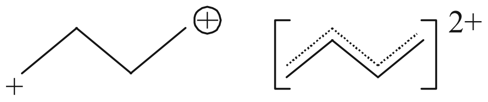
Y-Aromaticity

In organic chemistry, the term Y aromaticity is used to describe a y shaped, planar (flat) molecule with resonance bonds that exhibits more stability than other geometric or connective arrangement with the same set of atom.

It is developed to explain the extraordinary stability of guanidern cation and high basicily of Guanide. Guanidimium is not a ring molecule, and is cross conjugated rather than a linear π system but is reported to have its six π electrons delocalized over the whole molecule.



Trimethylenemethane dication



Butadienyl dication

Trimethylene methandication has extraordinary stability than the Butadienyl dication. High energy of resonance stablize the trimethylene methane dication.

Ψ-Aromaticity

Aromaticity also occurs in compounds that are not carbocyclic or heterocyclic; inorganic six-membered-ring compounds analogous to benzene have been synthesized. The aromaticity of planar Ψ 6-5 rings occurring in the Zintl phase Li12Si7 was experimentally evinced by Li solid-state NMR. Metal aromaticity is believed to exist in certain clusters of aluminium and gallium.

1.5 PMO APPROACH FOR AROMATICITY

Aromaticity from PMO approach the energy of an open chain-system will change, when it is converted into a cyclic system. If the energy decrease in the process the ring is aromatic, if the energy increase it is antiaromatic, both aromatic and antiaromatic compounds always contain even number of electrons. Open chain conjugated π-system having even number of electrons can be classified into the following two catagories:

1. A system in which HOMO has m-symmetry and LUMO has C_2 symmetry.
2. A system in which MOMO has C_2- symmetry and LUMO has m symmetry

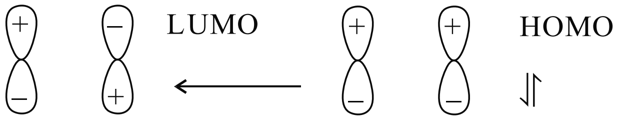
(HOMO – Highest Occupied Molecular Orbital)

(LUMO – Lowest Unoccupied Molecular Orbital)

Goldstein and Haffmann have named these two system as mode 2 and mode O respectively.

Example of Mode:

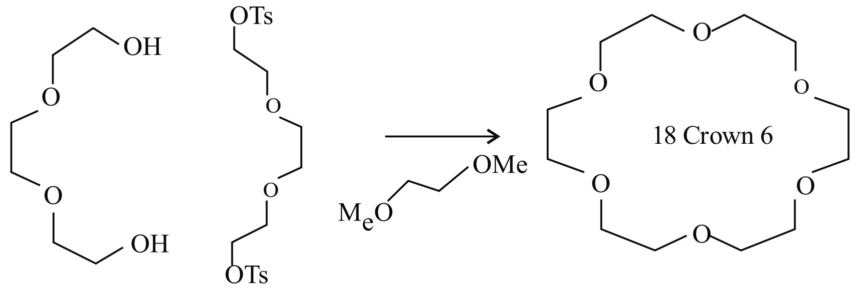
Such system have always $(4n + 2)\pi$ conjugated even number of electrons.



Ψ_2 (C_z - symmetry) Ψ_2 (m - symmetry)

Crown ether complexes and Cryptends

Crown ethers are cyclic compounds that have several ether linkage. A crown ether specifically binds certain metal ions or organic molecules, depending on the size of its cavity.

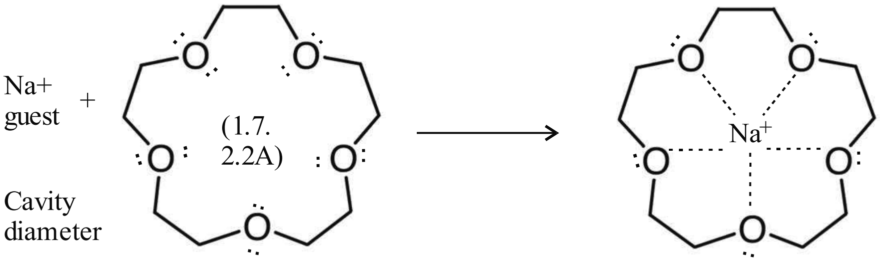


Cyclic aligomess

16 Crown-6 has an eighteen membered ring with six evenly spaced oxygen atoms. These cross ethers have cavities ideal for complex formation with metal ions. They can even carry metal ion into solution in organic solvents.

h depicts the ring size, m is the number of ethereal oxygen atoms, the cross either can thus be abbreviated nCm.

Application of Crown ether– (i) Crown ether guest complex is called an inclusion compound.



[15] Crown-5 Inclusion Compound

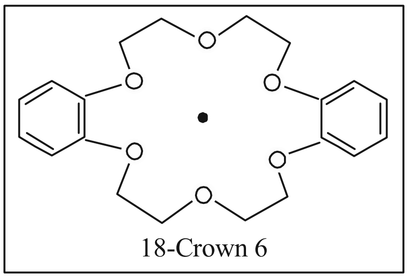
(ii) Acting as a phase transfer catalyst.

In presence of [18] Crown-6 potassium acetate can be dissolve in a non polar solvent (Benzene).

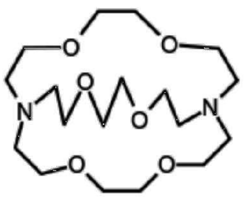
Cryptands

Cryptands are macro bi or poly [Football liquids] cycles able to encapsulate an ions by providing it higher protection because of their cagelike structure. They are more potent stronger and selective complexing agents for alkali metals. Crypts contain nitrogen, Oxygen and sometimes phosphorus and sulphure atoms in their core structure. They are for the same reason considered as the 3D equivalents of crown ethers. The molecules are cross linked approximately with donor atoms correctly positioned in the bridging group in order encapsulate metal ion in structure having cage like formation.

A typical crypt is the molecule called crypt 222 (222 denotes the no. of ethernal oxygen atom in each N–N bridge). Cryptates (hidden) are so called because they wrap around and hide the cation.

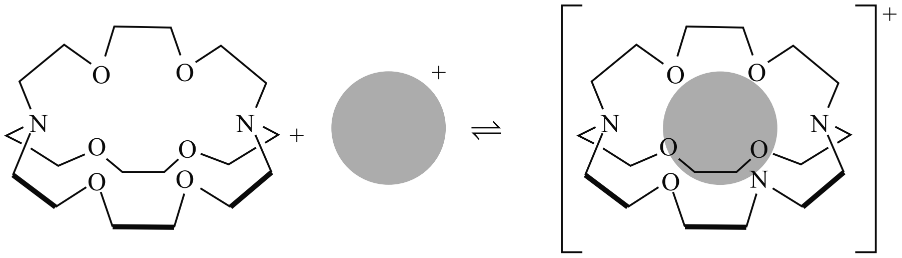


18-Crown 6



[Crypl-222]

The two rings of cryptand provide extra strength to hold the ion. This ion capturing capability of a cryptand can reach upto a hundred thousand times more than that of 18 cross-6.



A cryptand A cations A cryptate complex

Fig. 1.17 *Cryptand Capturing on Ion.*

Crypts and crown ethers constitute an important and interesting class of complexing ligands.

Inclusion Compounds

Several types of inclusion compounds are known. In all these compound molecules of one constituents called the guest molecules are physically imprisoned in cavities of crystal structures of the other constituents called the host molecules. In these compounds host molecules from crystal lattices which have sufficient large space for the guests to fit into. There is no bonding between hosts and guests except vander waal's forces.

These compounds are of two types, which are as follows:

(1) Channel complexes (Canal Compound)

In which host crystallise almost in parallel cylinderical channels along the inside length of which guest molecules are confined. Vandes Waal's forces are essential for importing stability to the structure, which molecules can be guests is determined only by their shapes and size. Usually no internal molar ratio exists between the guest and host molecules X-ray analysis of channel complexes has shown that the diameter of the channel is about 5A°.

Urea and thiovrea usually forma structure which is closely packed. Molecular formula of channel complexes is usually A_nB (A = Urea) and n generally not being a whole number.

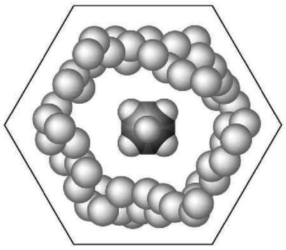


Fig. 1.18 *Guest molecules in a urea lattice is 4 or more than it.*

(2) Clathrate Complexes (Cage Compound)

Noble gases are enclosed in the cavities of crystal lattices of certain organic and inorganic compounds. Resulting compounds thus formed are called cage compounds. Such as organic and inorganic substances as has cavities in its lattice is called he host, where as molecules of noble gases trapped in carities are called guest. These compounds do not have any type of chemical bonding and non-stoicheometric. On heating the crystals or dissolving them in suitable solvents, guest can escape the host and more out.

Quinol and urea joined by hydrogen bonds. Where compounds on crystallisation with other constituent, they do not act so in their normal state. Dimensions of cages Limits the sige especially the lengths of those molecules which function as the other constituents Ar, Kr and Xe, all the three noble gases, fit into the clathrate structure formed by quinol.

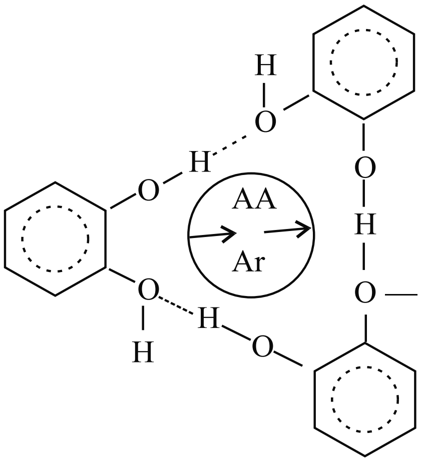


Fig. 1.19 *Clathrate – Compound* $[C_6H_4(OH)_2]_3$ *Ar*

Stability of Clathrate compounds are attributed to:

(a) Formation of hydrogen bonds.

(b) Formation of rigid eages of suitable shapes and siges by the host molecules

(c) Vander Waal's forces and sometimes weak charge transfer interactions between the inert gases and the host molecules.

Some of the common uses of clathrate compounds are as follows:

(a) They are used for the separation O helium and neon from Ar, kr and Xe.

(b) They are used in the strorage of inert gases.

(c) kr 58 clathrates used as a source of energy for mini atomic batteries and useful sources of β-radiations.

Cyclodextrins

Cyclodextrins (CDs) are a family of cyclic oligomers obtained by enzymatic digestion of strach. Cyclodextrins nomenclature depends on the number of glucose units in the structure.

α- Cyclodextrins (α-CDs) = 6 unit of glucose (nexame)

β- Cydodextrins (β-CDs) = 7 units of glucose (neptame)

γ- Cydodextrins (γ-CDs) = 8 units of glucose (octame)

They are cyclic oligosaccharides consisting of α-1, 4 glycosidic bonded d-glucopyranose unit. They belong to the family of cage molecule. Cyclodextrin molecule one shaped like a truncated cone or torus with two open ends because of their chair conformation of glucopyranose unit.

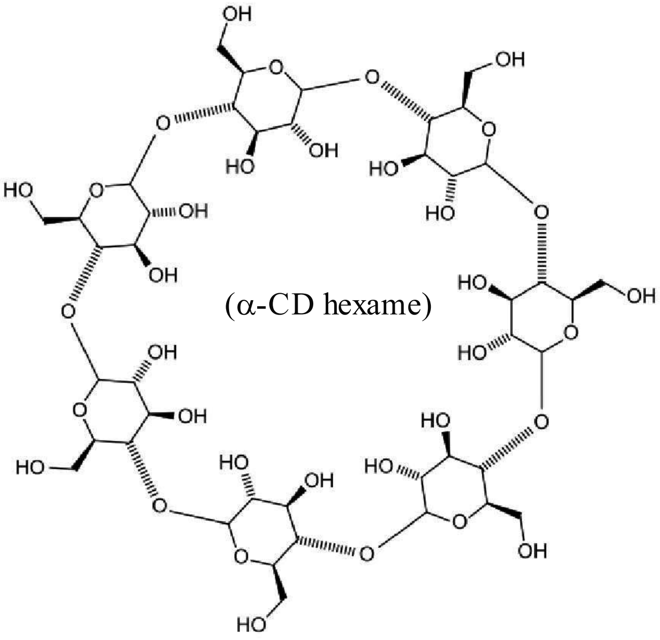


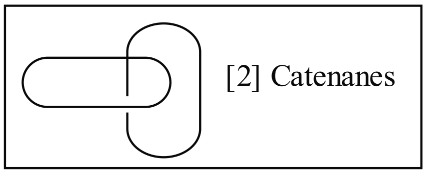
Fig. 1.20 *6-Glucopyranose Units*

Rotaxanes and Catenanes

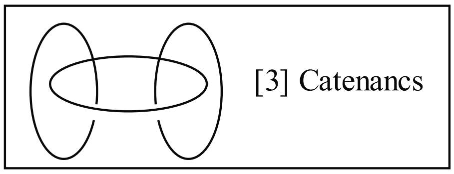
Rotaxanes and Catenanes are examples of interlocked molecules. They consists of two or more separate components which are non connected by chemical bond like covalent bonds but linked with mechanical bond.

Catenanes

In catenanes structure two or more macro cyclic ring interlocked or linked without any valence forces. The schematic representation of catenanes is as below.

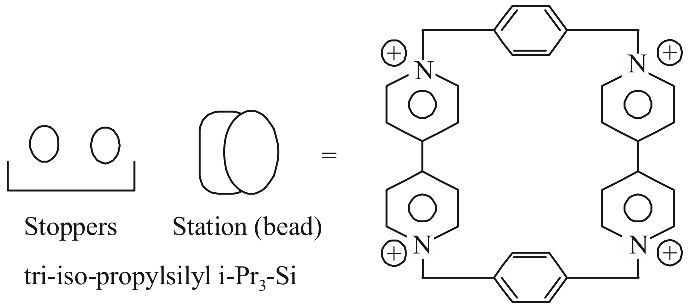


The prefix in square brackets indicate the number of mechanically interlocked compounds



Rotaxanes

They consist of macro cyclic rings trapped on to a linear unit by two bulley substituents.



In the above examples of rotaxanes, the bulky end groups or slopper and chain consists a series of – O – CH_2 – CH_2 – O group but also contain two benzene rings. The ring or bead around the chain is a macrocycle containing two benzene rings and four pyridine rings in the chain. It is symmetric rotoxane.

Synthesis of catenanes and rotaxanes by useing templated (synthesis) interaction method such as hydrogen bond metal ligand interaction π–π change transfer interaction or hydrophobic forces.

The necessity for interaction between components naturally places restriction on the simetural and functional make-up of the final product.

For the synthsisis of [2] rotaxanes, the following two methaels were used:

(a) **Clipping Strategy:** In clipping strategy, the macrocyclic component assembles around a preformed thread molecule. When the tread is present the newly bonds begin to form between the bed and stopper.

(b) **Metal-Ligand Interaction:** In metal ligand interaction, the completed macrocycle and a thread precursors are first form complex with metal ion [Cd^{2+}] in orthogonal fashion. Covalent bond forming reactions then attach the two buinky stopper groups to complete the rotaxanes.

Check Your Progress

1. What is a conjugated molecule?
2. Define cross conjugation.
3. Write the formula and structure of fulvene.
4. What are the types of fullerenes?
5. Define tautomerism.

1.6 STEREOCHEMISTRY

Structural isomerism depends on the mode of linking of atoms which gives rise to the following four types signifying the main difference in their structural features:

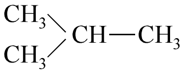
1. Skeletal or Chain Isomerism

Isomers differing in the structure of carbon chains are known as skeletal or chain isomers and the phenomenon as skeletal or chain isomerism. The simplest compound exhibiting this type of isomerism is of molecular formula C_4H_{10} (butane).

There are two compounds corresponding to this formula which differ only in the nature of carbon skeleton.

$CH_3.CH_2CH_2.CH_3$

n-Butane (B.P. = –0.5°C)
Straight Chain Carbon Skeleton



Isobutane (B.P. = – 10.2°C)
Branched Chain Carbon Skeleton

Similarly, pentane (C_5H_{12}) exists in three isomeric forms because the five carbon atoms can be linked in three different forms of chains. The number of chain isomers goes on increasing with increase in the number of carbon atoms (*cf.* Alkanes) in the chain.

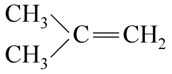
It is also possible that one of the isomer may have an open chain skeleton while the other may have a closed chain or ring (cyclic) skeleton. Thus C_4H_8 may have the following skeletal isomers all of which are known:

Straight Chain

$CH_3.CH_2.CH{=}CH_2$

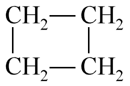
1-Butene (*n*-Butylene)

Branched Chain



2-Methyl-2-propene
(Isobutylene)

Closed Chain or Ring

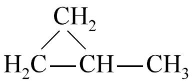


Cyclobutane

and

$CH_3.CH{=}CH.CH_3$

2-Butene

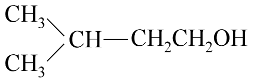


Methyl cyclopropane

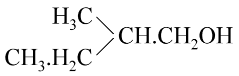
This type of isomerism is also shown by other classes of compounds besides the hydrocarbons, e.g., *n*-amyl alcohol, isoamyl alcohol and *ter*-amyl alcohol, all have the same molecular formula ($C_5H_{12}O$) and are skeletal or chain isomers. Thus:

$CH_3.CH_2CH_2.CH_2CH_2OH$

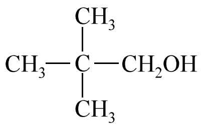
1-Pentanol (*n*-Amyl alcohol)



3-Methyl-1-butanol
(Isoamyl alcohol)



2-Methyl-2-butanol



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2OH$$

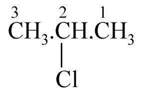
2,3-Dimethyl-1-propanol
(*ter*-Amyl alcohol)

2. Position Isomerism

In compounds containing similar carbon chain, the difference in position occupied by a particular atom or group in the carbon chain, gives rise to position isomerism. These isomers which differ only in the position of a group or atom in the carbon chain are known as *position isomers*. Thus the molecular formula C_3H_7Cl represents following position isomers.

$\overset{3}{C}H_3.\overset{2}{C}H_2.\overset{1}{C}H_2.Cl$

1-Chloropropane
(*n*-Propyl chloride)



$\overset{3}{C}H_3.\overset{2}{C}H(Cl).\overset{1}{C}H_3$

2-Chloropropane
(Isopropyl chloride)

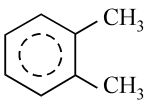
The unsaturated hydrocarbons also exhibit this type of isomerism because of difference in the position of the double or triple bond. Thus:

Mol. Formula

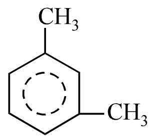
C_4H_8 $CH_3.CH_2.CH{=}CH_2$ 1-Butene; $CH_3.CH{=}CH.CH_3$ 2-Butene

C_4H_6 $CH_3.CH_2.C{\equiv}CH$ 1-Butyne (Ethyl acetylene); $CH_3.C{\equiv}C.CH_3$ 2-Butyne (Dimethyl acetylene)

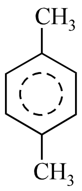
The disubstituted benzene exists in three isomeric forms—*ortho*, *meta* and *para*, which are position isomers differing only in the position of the two substituents. The three xylenes (mol. formula C_8H_{10}) exhibit this type of isomerism and are given below:



ortho-Xylene
(1,2-Dimethylbenzene)



meta-Xylene
(1,3-Dimethylbenzene)



para-Xylene
(1,4-Dimethylbenzene)

3. Functional Isomerism

Isomerism exhibited by compounds differing in functional groups is known as functional isomerism. As the functional group largely determines the properties of a compound, such compounds differ in their physical and chemical properties. Compounds exhibiting this type of isomerism are called *functional isomers.*

(*i*) Dimethyl ether and ethyl alcohol both have the same molecular formula (C_2H_6O) but belong to two different classes of compounds.

$CH_3.O.CH_3$ Methoxymethane (Dimethyl ether)

C_2H_5OH Ethanol (Ethyl alcohol)

(*ii*) Propionaldehyde and acetone both have the same molecular formula (C_3H_6O) but propionaldehyde has an aldehydic group (— CHO) whereas acetone has a ketonic group ($>C{=}O$).

$CH_3.CH_2.CHO$ Propionaldehyde

$CH_3.CO.CH_3$ Acetone (Propanone)

(*iii*) Propionic acid and methyl acetate are functional isomers (mol. formula $C_3H_6O_2$) having acid and ester functional groups respectively.

$CH_3.CH_2.COOH$ Propionic acid

CH_3COOCH_3 Methyl acetate

4. Metamerism

Compounds of the same homologous series show this type of isomerism because of unequal distribution of carbon atoms (or difference in size of alkyl groups) on either side of the functional group in the molecules. Only those compounds which have a polyvalent functional group can exhibit metamerims. Thus diethyl ether and methyl propyl ether, both having the same molecular formula and the same functional group (*i.e.* ether linkage) are metamers because of difference in alkyl groups on either side of ether linkage.

$C_2H_5O.C_2H_5$ Diethyl ether	$CH_3.O.C_3H_7$ Methyl propyl ether

Ketones as well as amines also *exhibit metamerism.*

Mol. formula		
$C_5H_{10}O$ (Ketone)	$C_2H_5.CO.C_2H_5$ Diethyl ketone	$CH_3.CO.C_3H_7$ Methyl propyl ketone
$C_6H_{15}N$ (Amine)	$C_3H_7.NH.C_3H_7$ Dipropyl amine	$C_2H_5.NH.C_4H_9$ Butyl ethyl amine

1.6.1 Stereoisomerism

Compounds having the same atoms or groups with a different spatial arrangement are called stereoisomers. This type of isomerism is called stereoisomerism and is of two kinds:

(A) Geometrical Isomerism

As early as in 1874, **Le Bel** and **van't Hoff** had suggested that the valencies of carbon atoms are distributed symmetrically in spaces and are directed towards the corners of the regular tetrahedron with carbon at its centre. The angle between these valencies is 109°28¢. Accordingly any saturated compound having two carbon atoms may be picturised as having the two carbon tetrahedra joined corner to corner. In such a case the tetrahedra are capable of rotating freely on their axes (bond) with respect to each other. *This is known as the concept of free rotation around carbon to carbon single bond.*

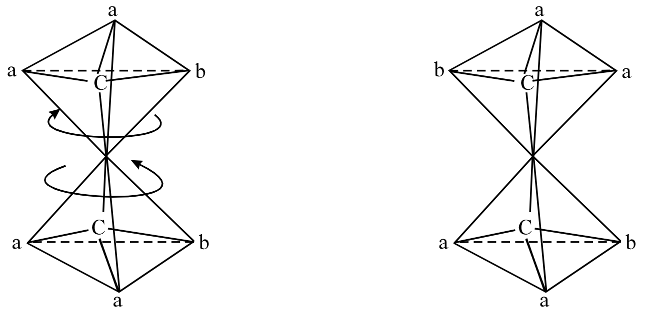


Fig. 1.21 *Showing two tetrahedral carbon atoms linked to each other through a single bond. Because of freedom of rotation around C—C bond axis both of the above structures are indentical molecules.*

Actually, there is only one compound corresponding to above different structures and the molecule can assume either of these structures by simple rotation on its axis. Structures which may be wirtten by simple rotation of one carbon with respect to the other, resulting in different configuration or spatial arrangement of atoms or group within the molecule and which may not be isolated are known *as conformers.*

On the other hand if the two carbon atoms are joined through a double bond then the freedom of rotation ceases to exist. In other words the two carbon atoms are fixed with respect to each other and rotation can only be brought about by rotating the molecule as a whole. *This is known as the concept of restricted rotation around carbon to carbon double bonds.* As a result of this restricted rotation two different arrangements, of the substituent groups attached to these two carbon atoms, become possible.

Such isomers, which posses the same structural formula but differ in spatial arrangement of the groups around the double bond or some other similar feature (e.g. a ring) are known as geometrical isomers and the phenomenon is known as geometrical isomerism. The isomer which has similar groups on the same side of the double bond is called '*cis*', (Latin, *cis* = same side) and the other which has similar groups on the opposite side of the double bond is known as '*trans*' (Latin, *trans* = across) isomer. *This type of isomerism is, therefore, also known as cis-trans isomerism.*

In modern concept a *single bond is considered to be an axially symmetrical σ bond permitting free rotation about its axis. The double bond is considered to be consisting of a σ and a π bond*. The presence of a π bond is capable of explaining the rigidity or restricted rotation associated with a multiple bond (shown in Fig.1.22). *If the carbon atoms are rotated with respect to each other π molecular orbital is distorted. The two 'p' atomic orbitals remain no longer parallel and no orbital overlap can occur. It is this energy barrier which prevents the rotation and substituents are held in a rigid planar geometrical conformation.*

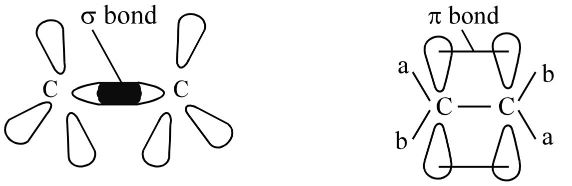
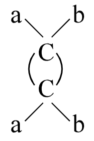


Fig. 1.22 *Modern Concept of Single and Double Bond*

A simple and convenient method of representing the geometrical isomers is to use a planar model rather than the tetrahedral model. Thus the above models may be represented as:



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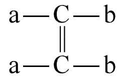
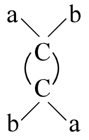
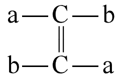
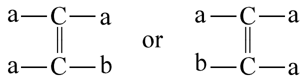


or

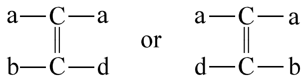




It is essential to point out here that if the two groups attached to any carbon atom are identical then both the structures would be one and the same and no isomers will be possible. For example:

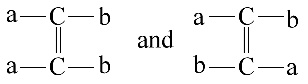


Identical structures
(One different substituent)

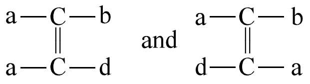


Identical structures
(Two different substituent
on same carbon atoms)

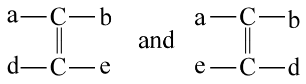
In all other cases where the carbon atoms joined by a double bond have different substituents, geometrical isomerism is possible.



Non-identical structures
(Two different substituent on
different carbon atoms)



Non-identical structures
(Three different substituents)

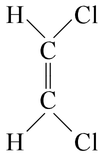


Non-identical structures
(Four different substituents)

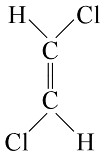
Thus compounds like 1,2 disubstituted alkenes, unsaturated dibasic acids, oximes (having carbon to nitrogen double bond) are capable of exhibiting geometrical isomerism. However, it should be pointed out that in cases where all the four substituents are different (abC = Cde) it is not possible to decide the *cis* and *trans*-configurations.

Examples

(*i*) *1,2-Dichloroethane*

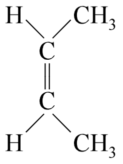


cis-

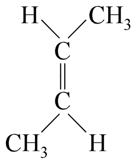


trans-

(*ii*) *2-Butene*

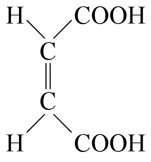


cis-

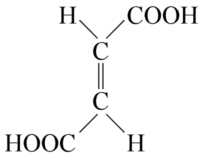


trans-

(*iii*) *Maleic and Fumaric acids*

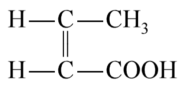


Maleic acid (*cis-*)



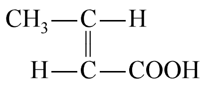
Fumaric acid (*trans-*)

(*iv*) *Crotonic and Isocrotonic acids*



$$\begin{array}{rcl} H- & C & -CH_3 \\ & \| & \\ H- & C & -COOH \end{array}$$

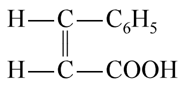
Isocrotonic acid (*cis*-)



$$\begin{array}{rcl} CH_3- & C & -H \\ & \| & \\ H- & C & -COOH \end{array}$$

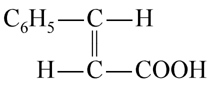
Crotonic acid (*trans*-)

(*v*) *Cinnamic and Allocinnamic acids*



$$\begin{array}{rcl} H- & C & -C_6H_5 \\ & \| & \\ H- & C & -COOH \end{array}$$

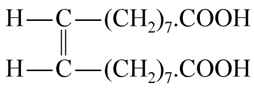
Allocinnamic acid (*cis*-)



$$\begin{array}{rcl} C_6H_5- & C & -H \\ & \| & \\ H- & C & -COOH \end{array}$$

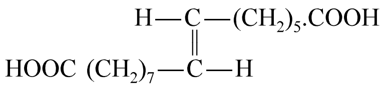
Cinnamic acid (*trans*-)

(*vi*) *Oleic and Elaidic acids*



$$\begin{array}{rcl} H- & C & -(CH_2)_7.COOH \\ & \| & \\ H- & C & -(CH_2)_7.COOH \end{array}$$

Oleic acid (*cis*-)

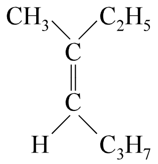


$$\begin{array}{rcl} H- & C & -(CH_2)_5.COOH \\ & \| & \\ HOOC\ (CH_2)_7- & C & -H \end{array}$$

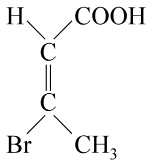
Elaidic acid (*trans*-)

E-Z System for Designating Isomeric Alkenes

As pointed out above, the use of terms *cis* and *trans* to designate isomeric alkenes becomes meaningless if the alkene is tri- or tetra-substituted. Thus in compounds shown below it is not possible to decide whether they are *cis* or *trans* because no two groups are same.



(A)



(B)

Therefore a convention for designating isomeric alkenes, known as E-Z system has been suggested which is based on the sequence or priorities of groups[1] in R-S system of Cahn, Ingold and Prelog. In this system we arrange the two groups attached to each carbon atom involved in the double bond in order of priority. Then the group of higher priority on one carbon is compared with the group of higher priority on other carbon atom. If both the groups of higher priority are on the same side of the double bond then the alkene isomer is designated as Z (from German; *Zusammen* meaning *together*) isomer, but if the groups of the higher priority are on the opposite sides of the double bond, the alkene is designated as E (German; Entgegen meaning opposite) isomer.

Thus, in compound (A) shown above the order of priority of groups will be

$$C_2H_5 > CH_3 \quad \text{and} \quad C_3H_7 > H$$

As both the groups of higher priority are on the same side of the double bond, the compound is having Z configuration.

In compound (B) the order of priority is

$$COOH > H \quad \text{and} \quad Br > CH_3$$

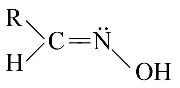
Since the groups of higher priority are on the opposite side of the double bond, the compound B is having E configuration.

NOTES

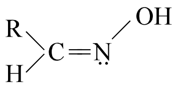
In examples given below it would be found that most *cis* isomers are designated as Z while *trans* isomers are mostly designated E. However there are many exceptions also.

(*i*) **Geometrical isomerism of oximes and related compounds:** The compounds having a carbon to nitrogen double bond (as in oximes) and nitrogen to nitrogen double bond (as in azo compounds) also exhibit geometrical isomerism because nitrogen too has the same hybridization state—as carbon *i.e.*, sp^2 in doubly bonded nitrogen.

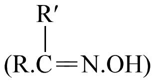
Therefore, if a carbon is replaced by nitrogen in the formation of a double bond the geometrical isomerism will be exhibited. Thus compounds of the type of oximes ($>C=N.OH$) and azo ($R.N=N.R$) in which carbon to nitrogen or nitrogen to nitrogen double bond is present show this type of isomerism because the unshared pair of electrons at nitrogen occupies a fixed position and other group attached to nitrogen lies on the other side. The terms '*syn*' and '*anti*' are used in place of '*cis*' and '*trans*' respectively to designate isomeric oximes and azo compounds. In case of aldoximes ($RCH=N.OH$) the '*syn*' isomer is the one where hydrogen and hydroxyl groups lie on the same side of the double bond whereas in the '*anti*' isomer the two groups are on the opposite side. Thus:

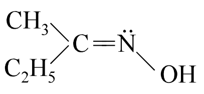


syn-Aldoxime

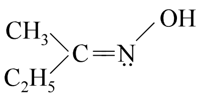


anti-Aldoxime

In the case of ketoximes  $(R.\overset{\overset{R'}{|}}{C}=N.OH)$ where two different alkyl groups[1] R and R¢ exist, the designation is arbitrary. Thus in case of methyl ethyl ketoxime:

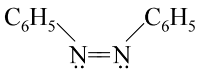


syn-Ethyl methyl ketoxime
or *anti*-Methyl ethyl ketoxime
or Z configuration

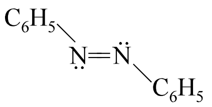


anti-Ethyl methyl ketoxime
or *syn*-Methyl ethyl ketoxime
or E configuration

The azo compounds like azobenzene exhibit geometrical isomerism as shown below:

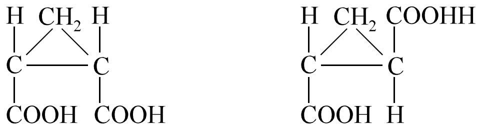


cis- or *syn*-Azobenzene



trans- or *anti*-Azobenzene

(*ii*) **Geometrical isomerism of cyclic compounds:** Just as a double bond imposes restrictions on the free rotation similarly a ring structure will also prevent free rotation of carbon atoms about their axis. The geometrical isomerism will, therefore, also arise in the cyclic or ring compounds. For example, cyclopropane-dicarboxylic acid exists in two isomeric forms — '*cis*' and '*trans*'. (Besides this it also exhibits optical isomerism.)



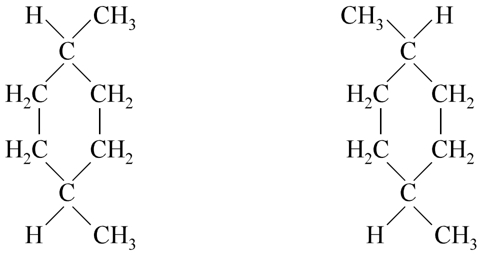
cis- *trans-*

Cyclopropane-dicarboxylic acid

Similarly cyclobutane and other higher ring systems also exhibit this type of isomerism.

cis- *trans-*

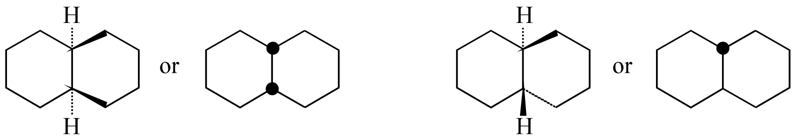
Cyclobutane-dicarboxylic acid



cis- *trans-*

1,4-Dimethyl cyclohexane

In fused ring systems the rings which are fused through adjacent carbon atoms may be fused in *cis*- or *trans*-positions giving two isomers. For example, decalin exhibits geometrical isomerism:



cis-Decalin *trans*-Decalin

(The thick line shows that the bond lies above the plane of the paper whereas dotted line shows the bond below the plane of paper).

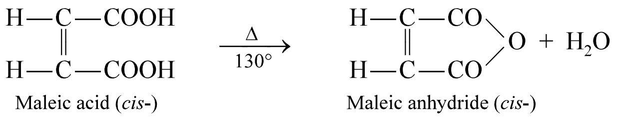
(*iii*) **Geometrical isomerism in inorganic compounds:** The coordination compounds usually exhibit geometrical isomerism. In such compounds if the geometry is square planar or octahedral the cis-trans isomerism is observed. For example:

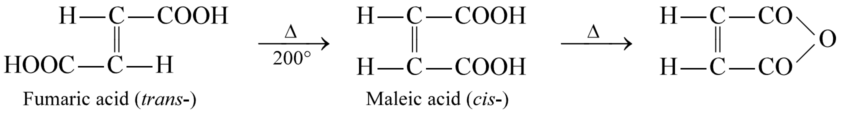
cis- *trans-*

Dichloro-diamino platinum (square planar geometry)

(*iv*) **Properties of geometrical isomers:** The geometrical isomers are generally two different compounds having appreciable difference in their physical and chemical properties—though the differences in the latter are few. Thus *cis*-isomer, in general have lower m.p. and higher values for density, refractive index, dipole moment, etc., as compared to *trans*-isomers.

If the two groups in *cis*-isomer are carboxylic groups then it may form anhydride readily losing a water molecule whereas *trans*-isomer may not form the anhydride unless it is isomerized to *cis*-form. For example, maleic acid readily forms an anhydride whereas fumaric acid first isomerizes to maleic acid at a higher temperature and then forms maleic anhydride.





(*v*) **Determination of configuration of geometrical isomers:** If a given pair of compounds shows geometrical isomerism then it is useful to find out that which one has a *cis* and which one a *trans*-configuration. This assignment of the structure to a pair of isomers is known as determination of configuration. As such, there is not standard method for finding out the configuration of geometrical isomer but by comparisons with known structures certain empirical relationships have been worked out. Determination of some of the physical and chemical properties of a pair of isomers usually gives an idea about the configuration. The following methods are in common use:

(*a*) *Study of the physical properties*: The physical properties of *cis*-*trans* isomers are usually different and show a regular behaviour. Some of these are listed in Table below:

Table 1.3 *Physical Properties of cis-trans Isomers*

Sl. No.	*Property*	*cis-Isomer*	*Trans-Isomer*[1]
1.	Melting Point	Lower	Higher
2.	Boiling Point	Higher	Lower
3.	Solubility	Higher	Lower
4.	Density	Higher	Lower
5.	Dipole Moment	Higher	Lower
6.	Refractive Index	Higher	Lower
7.	Heat of Combustion	Higher	Lower
8.	Stability	Lower	Higher

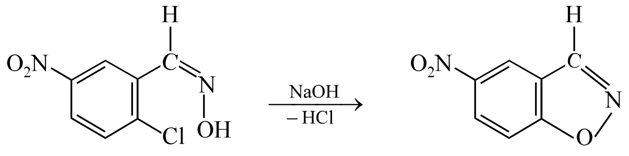
By comparison of some of these properties of the isomers, their configuration may be decided.

Besides these the spectroscopic methods, particularly ultraviolet, infrared and nuclear magnetic resonance are also used to determine the configuration. Thus in UV the *cis*-isomer always absorbs at a lower wavelength and has a lower molar extinction coefficient. In IR the stretching frequency is not shown by *trans*-isomer in general whereas *cis*-isomer shows a strong absorption in the region.

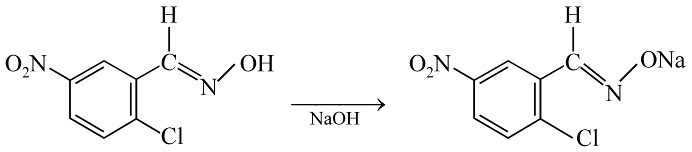
X-ray and electron-diffraction may also be used to determine the configuration of geometrical isomers.

(*b*) *Study of the chemical properties*: Although because of the similarity of the functional groups there is little difference in the chemical reactivities of the geometrical isomer—but still this minor or small chemical difference may be used for the determination of the configuration. Either the method of formation of cyclic derivatives or the method of chemical correlation is used. The former may be illustrated by taking the example of maleic and fumaric acids. The two acids are having the carboxylic groups either in *cis*- or *trans*-positions—the one which is having the two carboxylic groups in *cis*-position will readily lose a water molecule and form the anhydride whereas the isomer which has the two groups trans with respect to each other will not eliminate the water molecule to form the anhydride easily. Thus it has been found that maleic acid loses water to form maleic anhydride readily whereas the fumaric acid does not cyclize easily. Thus maleic acid must have *cis*-configuration.

Similarly out of the two isomers of 2-chloro-5-nitrobenzaldoxime one is readily cyclized on treatment with NaOH whereas the other does not. Obviously the former is *anti*- and the latter *syn*-oxime.

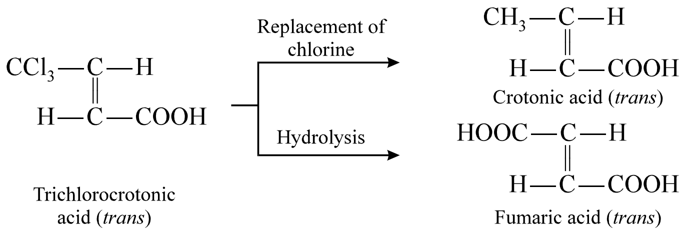


anti-Oxime Indoxazole

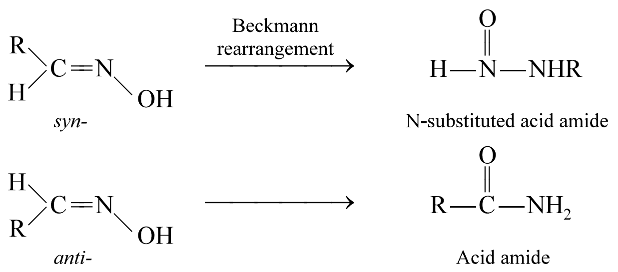


syn-Oxime Sodium salt

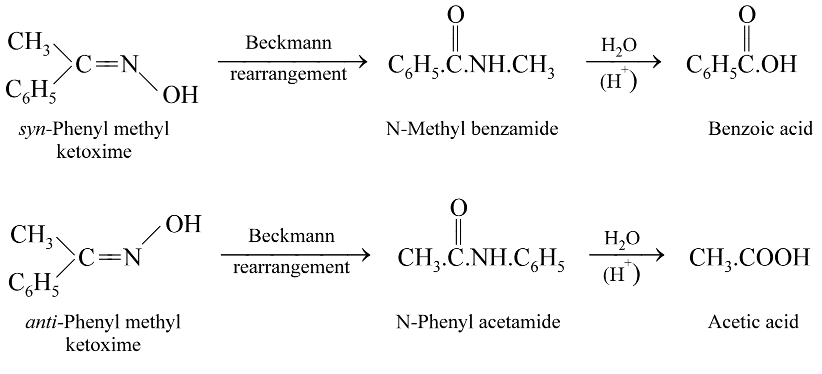
In the correlation method the compound of unknown configuration is converted to or derived from a compound of known configuration and if it is assumed that no rearrangement occurs, then the configuration of unknown compound must be the same, as that of the known compound. Thus trichlorocrotonic acid on hydrolysis gives fumaric acid, which is known to have trans-configuration, and on selective reduction gives crotonic acid. Thus both crotonic acid and trichlorocrotonic acid must have *trans*-configuration.



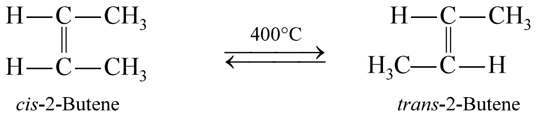
(*c*) *The configuration of oximes*: The configuration of oximes is best determined by a rearrangement reaction known as **Beckmann rearrangement** (1886). When an oxime is treated with reagents like acetic anhydride, PCl_5 etc., it is converted to an acid amide or substituted acid amide by a molecular rearrangement. It has been observed that in such rearrangements the alkyl groups, *anti*- to OH groups, migrates to nitrogen preferentially. Thus a pair of isomeric oximes will give different substituted amides.



Thus *syn*-aldoximes give N-substituted acid amides whereas *anti*-aldoximes give acid amides. In case of ketoximes two different substituted amides are obtained which may be distinguished by simple hydrolysis resulting in the formation of entirely different acids.



(***d***) ***Interconversion of geometrical isomers*:** Under suitable conditions geometrical isomers may be converted into each other. This is conveniently done by application of catalysts, heat or U.V. light. In general the ease of interconversion is in the order N == N > C == N > C == C for different types of geometrical isomers. The isomerisation is brought about by rotation around the bond axis which is only possible when the double bond becomes loose or breaks partially to allow such a free rotation. For example, maleic acid may be converted to fumaric acid on heating above its melting point. Similarly butenes can be isomerised by heating.



(B) Optical Isomerism

It has been observed that geometrical isomers show a marked difference in their physical properties accompanied with some differences in their chemical properties as well. The optical isomers, on the other hand, have same chemical and physical properties except that they show a pronounced difference in their behaviour towards *plane polarised light. The property by virtue of which the substances rotate the plane of the plane polarised light is referred to as optical activity.*

Before going into the details of optical isomerism it is necesary to discuss briefly each of the terms used in discussion and their significance in connection with optical isomerism.

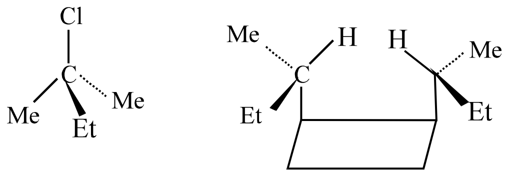
(*i*) **Symmetric, Asymmetric and Dissymmetric Molecules:** An object or molecule is considered symmetric if it possesses a **plane of symmetry, a centre of symmetry** or **an alternating axis of symmetry**. A molecule has a **plane of symmetry** if on passing a plane through it one half of the molecule is the mirror image of the other half or if a line from any atom or group on one side of the plane, drawn perpendicular to the plane and extended to an equal distance on the other side meets a similar atom or group at its end.

The **centre of symmetry** is a point in the molecule passing through which, if a line is drawn, from any atom or group and then extended to equal distance in the opposite direction, meets an identical atom, or group at its end.

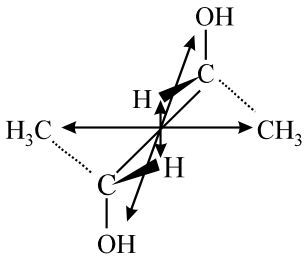
The **axis of symmetry** is an axis through which rotation of the molecule, by certain angle, will result in an arrangement indistinguishable or identical with initial molecule.

The **alternating axis of symmetry** is an axis through which if the molecule is rotated by a certain angle and then reflectd across a plane at right angles to the axis, another identical structure is obtained. One-fold alternating axis corresponds to plane of symmetry and the two-fold alternating axis to centre of symmetry.

Symmetrical objects like books, animals, eggs etc., have a plane of symmetry. sp^1, sp^2 hybridized carbon atoms and sp^3 carbons (having at least two identical substituents) too have a plane of symmetry. The sign of swastika 卐 does not have a plane of symmetry but has a centre of symmetry. Some of the molecules having a plane of symmetry, centre of symmetry or alternating axis of symmetry are shown below:



Molecules with a plane of symmetry



Butanediol-2,3

Fig. 1.23 *Molecule having centre of symmetry (Double headed arrows passing through the centre meet identical groups on either side at equal distance).*

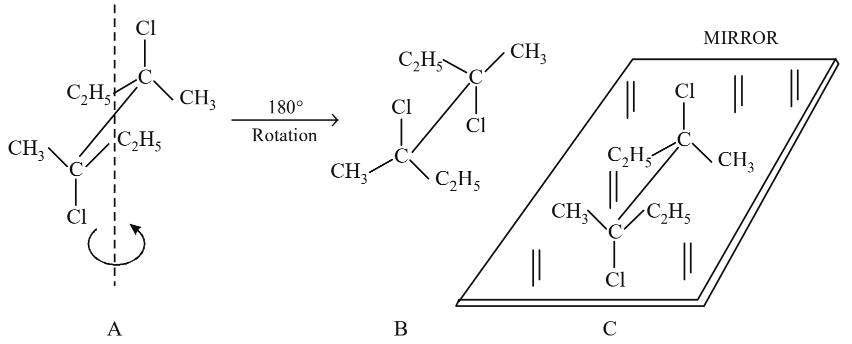
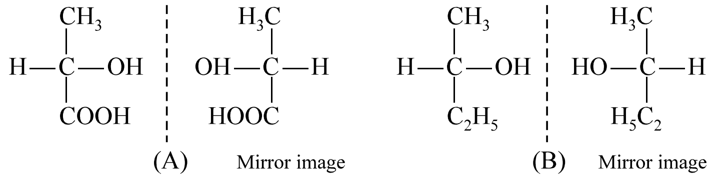


Fig. 1.24 *Molecule having a two-fold alternating axis of symmetry. (A) Line passing through the centre of 3,4-dichloro-3,4-dimethyl hexane, (B) Same as initial compound. (C) Reflection obtained in a plane perpendicular to the line passing through the centre.*

A molecule with no element of symmetry of any kind is **asymmetric**. Objects like hand, tree etc., are asymmetric. *A tetrahedral or* sp^3 *hybridized carbon attached to four different groups is asymmetric and is known as* **asymmetric carbon atom**. A molecule with no plane of symmetry is known as **dissymmetric**. Dissymmetric molecules may have an axis of symmetry but the main criterion for dissymetry is that a given molecule should not be superimposable on its mirror image. Thus all asymmetric molecules are dissymmetric but all dissymetric molecules are not necessarily asymmetric. **Non-dissymmetric** molecules are superimposable upon their mirror images.

The most commonly cited example of right and left hands is perhaps the best illustration of two objects similar in every respect expect that they are related to each other as object to its mirror image and cannot be exactly superimposed on each other. Thus an object or *a molecule which cannot be superimposed on its mirror image must be assymmetric.* Such a pair of molecules related to each other as an object to its mirror **image** are known as **enantiomorphs** or **enantiomers**.

The terms **chiral** and **achiral** are also used to designate dissymmetric and non-dissymmetric molecules respectively. A *chiral* (Greek, *cheir* meaning *hand*) molecule is not superimposable on its mirror images while *achiral* molecule is superimposable on its mirror image. The *chirality* of the molecules in most cases is due to the presence of a single *chiral* (asymmetric) atom. A chiral atom is any atom devoid of plane of symmetry and is also known as *chiral centre. Enantiomorphs exist only in case of chiral molecules.* Therefore the ultimate test for chirality is that the molecule should be non-superimposable on its mirror image. Thus a molecule will not be chiral if it possesses a plane of symmetry. Molecules shown below are chiral because they cannot be superimposed on their miror images.



$$\begin{array}{c} CH_3 \\ | \\ H-C-OH \\ | \\ COOH \end{array} \quad \vdots \quad \begin{array}{c} H_3C \\ | \\ OH-C-H \\ | \\ HOOC \end{array} \qquad \begin{array}{c} CH_3 \\ | \\ H-C-OH \\ | \\ C_2H_5 \end{array} \quad \vdots \quad \begin{array}{c} H_3C \\ | \\ HO-C-H \\ | \\ H_5C_2 \end{array}$$

(*ii*) **Optical activity:** Most of the physical and chemical properties of the optical isomers are identical. Since the phenomenon of optical isomerism is caused by the asymmetry of the molecules, the detection of the difference in the properties can be measured only when an asymmetric measuring tool is used. The most common of such a tool is plane-polarized light.

Plane polarized light

Light is propagated by a wave motion. The vibrations of the waves are perpendicular to the direction of propagation and are symmetrical about the line of propagation. Thus if an imaginary cross-section of a beam of light is examined it will be observed that these vibrations occur in all directions at right angles to the line of progagation. Ordinary light is thus having symmetry. However if such a beam of light is passed through a Nicol prism,[1] the resulting beam has all waves vibrating in the same plane. *Light, whose vibrations occur in a single plane only, is known as* **plane polarised light** *and the phenomenon is known as* **polarization**.

When plane polarized light is passed through certain substances or their solutions its plane of polarization is rotated either towards right (clockwise) or towards left (anticlockwise) by a certain angle. *The substances which rotate the plane of polarization of the plane polarized light are known as* **optically active** *and the phenomenon is referred to as* **optical activity**. Those substances which rotate the plane of polarized light to right or clockwise are called **dextro-rotatory** indicated by the sign '*d*' or (+) and those which rotate it to the left or anticlockwise are called **laevo-rotatory** indicated by sign '*l*' or (–).

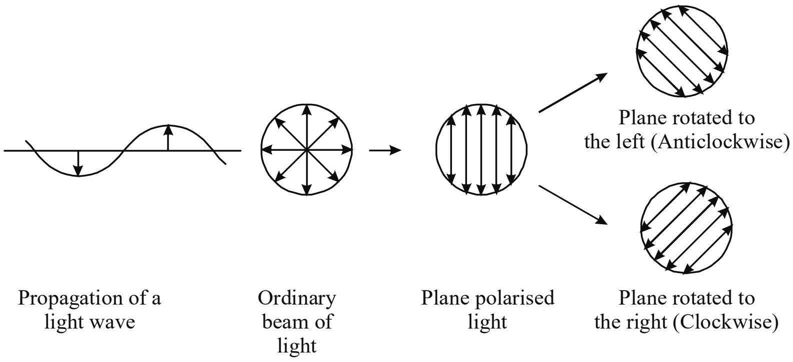


Fig. 1.25 *Imaginary Cross-Sections of Light Beams*

The extent or angle of rotation depends on the following factors:

1. Nature of the substance
2. Wavelength of the light used
3. Concentration of the solution (if substance is taken in solution)
4. Thickness of the layer or length of path through which polarised light passes
5. Nature of solvent (for solutions only)
6. Temperature of measurement

The apparatus used to measure the optical activity is known as polarimeter and has been schematically represented in Fig. 1.26.

The measurement of optical activity is reported in terms of specific rotation which is a constant; characteristic for a particular substance,

$$\text{Specific rotation } [\alpha]_{\lambda}^{t\,^{\circ}\mathrm{C}} = \frac{\alpha_{\text{obs.}}}{l \times c}$$

where α_{obs} is the rotation observed, l is the length of solution in decimetres, c the concentration is grammage of substance in 1 ml of solution.

Specific rotation is equal to observed rotation in degrees when the polarised light passes through one decimetre (or 10 cm) of the solution of the substance having the concentration of one gram per millilitre. It is calculated by the expression given above. Usually for measurement purposes the light used is the sodium D line corresponding to 589 mμ wavelength. It is also necessary to mention the solvent, if any, used for measurement. Thus the specific rotation of sucrose may be represented as:

$$[\alpha]_{\mathrm{D}}^{20^{\circ}} = +\,66.5^{\circ} \quad \text{(Water; Concn. 0.02 g/ml)}$$

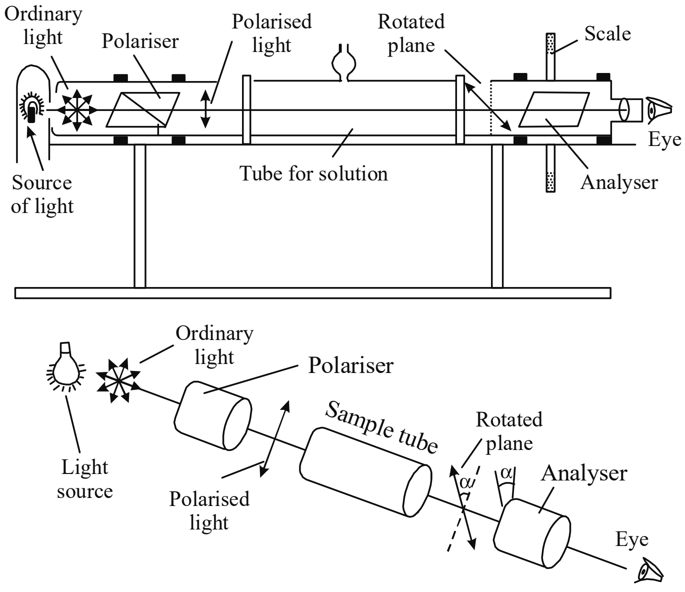


Fig. 1.26 *Schematic Representation of a Polarimeter*

Here 'D' stands for the sodium D line wavelength, 20° is the temperature of measurement in °C, the sign (+) stands clockwise or dextro-rotation and the solvent is water. The electrical effects between solute and solvent molcules may cause considerable variations in the value of specific rotation, hence the solvent and the concentration of measurement is also mentioned in parentheses. Similarly the specific rotation of the two forms of phenyl lactic acid may be written as:

$$[\alpha]_{\mathrm{D}}^{20^{\circ}} = +\,52.0^{\circ} \quad \text{(Water; Concn. 0.02 g/ml) (Dextro-rotatory)}$$

$$[\alpha]_{\mathrm{D}}^{20^{\circ}} = -\,52.0^{\circ} \quad \text{(Water; Concn. 0.02 g/ml) (Laevo-rotatory)}$$

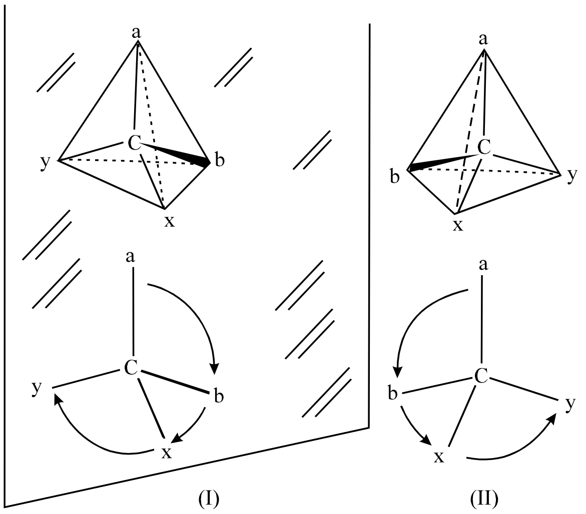
Just as (+) sign stands for dextro or clockwise rotation, the (–) sign indicated anticlockwise or laevo-rotation.

(*iii*) **Cause of optical activity:** Pasteur had suggested that optical isomerism arises from molecular dissymmetry. In 1874, the French chemist Le Bel and Dutch chemist van't Hoff almost simultaneously and independently, tried to explain the cause of optical activity.

Le Bel and van't Hoff suggested that the optical activity of substances in solutions or in liquid state depends upon the asymmetry of the molecule. According to them a carbon atom is supposed to be situated at the centre of a imaginary regular tetrahedron and its four valencies are directed towards its four corner. *Now if four different atoms or groups are attached to a carbon atom the molecule becomes asymmetric.* Hence if a substance has at least one asymmetric carbon atom it will be optically active. *However, the presence of asymmetric carbon atoms may not make a compound necessarily optically active; what is essential is the asymmetry of the molecule as a whole.*

Let there be a carbon atom having four different atoms or groups *a*, *b* and *x* and *y* attached to its valencies at the four corners of the regular tetrahedron. Obviously two arrangements are possible which will be related to one another as an object to its mirror image. They will not be superimposable upon each other.

The arrangement of groups is different in Fig. 1.27 (I) and (II). For example, if one has to go from '*a*' to '*y*' through '*b*' and '*x*', one will have to go in clockwise direction in structure I and in anticlockwise direction in structure II. Again if one tries to superimpose structure I over structure II group '*a*', '*x*' and '*b*' will overlap each other but group '*y*' from each one of the structures will go on opposite sides. Clearly the two models represent



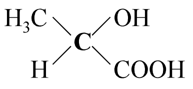
(I)
Clockwise
arrangement
of groups
a, *b*, *x*, *y*

(II)
Anticlockwise
arrangement
of groups
a, *b*, *x*, *y*

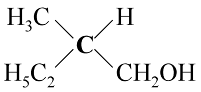
Fig. 1.27 *Two arrangements of groups at asymmetric carbon show relation as object and its mirror image.*

two isomeric spatial arrangements or two compounds having different configuration. The compounds represented by structures I and II are enantiomers.

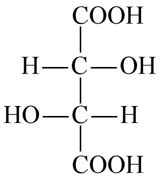
Now it has been proved beyond doubt that optical activity is due to aymmetric character of the molecule, whether the asymmetry is due to the presence of any asymmetric carbon atom or due to some other reason. The formulae of a few compounds are given below and each has at least one asymmetric carbon atom, and hence optically active. (Asymmetric carbon atoms are in thick type.)



Lactic acid

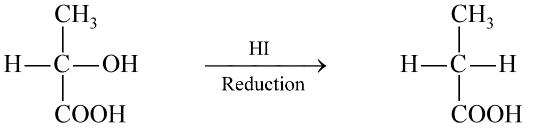


Amyl alcohol



Tartaric acid

If the asymmetric character of any of the above molecules is changed the compound becomes inactive, *e.g.*, if lactic acid is reduced it gives propionic acid, which is optically inactive.



(No asymmetry)

The number of optical isomers are given by 2^n where n is the number of asymmetric carbon atoms. Thus if there is one such carbon atom the number of isomers must be ($2^1 = 2$) two only, similarly for two asymmetric carbons the number of isomers will be ($2^2 = 4$) four and for three ($2^3 = 8$) it will be eight and so on. If the nature of asymmetic carbon atoms is same (*i.e.* the groups attached to them are same) then the number of optically active isomers is considerably less than predicted by this formula. For example, if a compound is having two dissimilar asymmetric carbons A and B then the isomers possible are as follows:

$$\begin{matrix} (1)\ +A+B & (2)\ -A-B \\ (3)\ +A-B & (4)\ -A+B \end{matrix} \quad \left\{\begin{matrix}\text{+ and – sign indicate dextro or laevo} \\ \text{rotation of asymmetric carbon atoms}\end{matrix}\right\}$$

Here + A and + B are the mirror images of – A and – B respectively. So + A + B and – A – B is a pair of enantiomorphs. Similarly + A – B and – A + B constitute another pair of enantiomorphs. But + A + B and + A – B or – A + B are not related as object and mirror images of each other—though they are isomeric and similarly – A – B and + A – B or – A + B are also not enantiomorphs. The isomers which are not related to each other as object and also not enantiomorphs. The isomers which are not related to each other as object and mirror images are known as **diastereoisomers**. These may differ in physical and chemical properties.

A compound having two similar asymmetric carbons A and A may have following isomers:

(1) + A + A (2) –A –A (3) + A –A or – A + A

Let the first one be dextro-rotatory, then the second will be laevo-rotatory. The third will have a plane of symmetry and therefore will be optically inactive despite the presence of two asymmetric carbon atoms. The optical inactivity in the molecule + A – A has arisen due to equal and opposite activity of each half of the molecule. Thus the optical inactivity has come due to the compensation of the activity of one half by the other half and this is known as the *internal compensation*. Such molecules which are optically inactive due to internal compensation are called *meso*-form (or *m*-form).

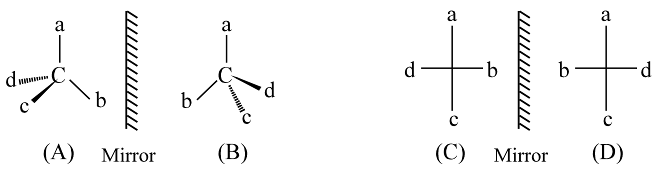
The optical inactivity could also arise due to the presence of equal amounts of the dextro and laevo forms when the compound is prepared or obtained by mixing the *d*- and *l*-forms in equal molecular proportions. This inactivity is due to equal and opposite optical activity of each isomer and therefore is regarded as arising from *external compensation.* Such a mixture is called the *dl* or (±)-form.

These two inactive forms, m- and dl-, differ in the fact that whereas the dl- form could be resolved into the ***dextro*** *and* ***laevo*** *forms, it is not possible to do so with meso-form*.

While writing the configuration of the optical isomers a three dimensional (tetrahedral) structure is represented in the planar form on the paper. The two important methods for such planar representations are (*i*) *Perspective formula* and (*ii*) *Fischer projection formula.*

In the perspective formula two groups attached to carbon atom are shown to be coplanar with it while a dotted line represents the bond and atom (or group) below the plane of the paper and a heavy thick line represents and the bond and atom (or group) above the plane.

In the representation of stereoisomers by Fischer projection formula the three dimensional molecule is considered such that the groups written to left and right of asymmetric carbon atom are projected from above the plane of paper. Similarly the groups written above and below asymmetric carbon atom are projected from beneath the plane. The two sets of formulae A, B and C, D correspond to each other and are represented in perspective and projection form.



Perspective Formula

Fischer Projection Formula

Fig. 1.28 *Representation of Asymmetric Molecules*

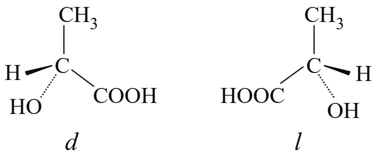
While using Fischer projection formulae the following rules must be kept in mind:

(*a*) Fischer projection formulae should not be taken out of the plane but can be rotated by 180° in the same plane. Rotation of formula by any other angle leads to change in configuration.

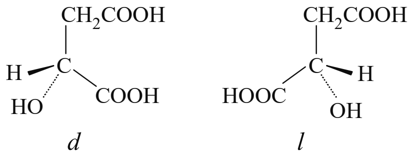
(*b*) The groups attached to asymmetric carbon atom may be interchanged clockwise or anticlockwise. The interchange of two groups changes the configuration forming enantiomer of original. Thus any odd number of interchange of groups (exchanging position of two groups is one interchange) changes the configuration while even number of interchanges do not change the original configuraton.

Perspective formulae are used for compounds having one or two asymmetic (chiral) carbon atoms but when many such atoms are present then Fischer projection formulae are more convenient.

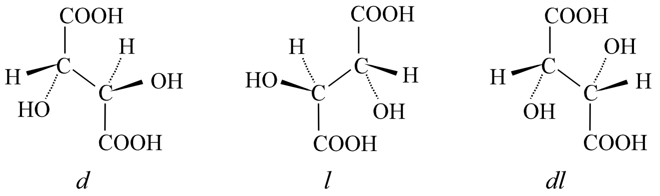
(*iv*) **Compounds with asymmetric carbon atoms:** Compounds like lactic acid, malic acid, tartaric acid, amyl alcohol, etc., possess asymmetric carbon atoms and exhibit optical isomerism because of the asymmetric carbon they possess. They may be represented as follows:



Lactic acids

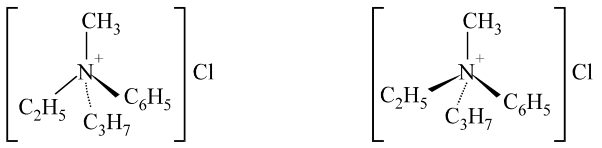


Malic acids



Tartaric acid

(*v*) **Compounds with asymmetric atoms other than carbon:** Atoms which resemble carbon in the arrangement of valencies may behave in a similar manner when four different groups are attached to them. Thus quaternary ammonium salts, compounds of phosphorus, arsenic, antimony etc., have been shown to be optically active because of the N, P, As and Sb atoms respectively. Methyl ethyl propyl phenyl quaternary ammonium chloride is an optically active compound containing tetravalent nitrogen.



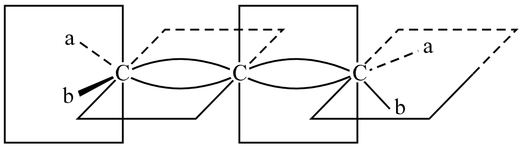
Methyl ethyl propyl phenyl quaternary ammonium chloride

(*vi*) **Compounds having no asymmetric carbon atoms:** Many compounds have no asymmetric carbon atoms, nevertheless they are optically active because the molecule as a whole is asymmetric or chiral. The condition arises because of restricted rotation in the molecule giving rise to perpendicular dissymmetric plane. For example compounds of the type of allenes, spiranes and biphenyls exhibit optical isomerism though there may not be any asymmetric carbon atom in the molecule.

(*a*) *Allenes* may be respresented by a general formula,

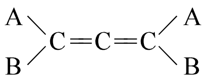
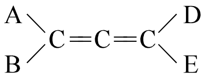
$$ab.\mathrm{C} == \mathrm{C} \;== \mathrm{C}.ab$$

where *a* and *b* are different groups. Isomeric allenes where *a* is C_6H_5 and *b* is $C_{10}H_7$ have been separated.

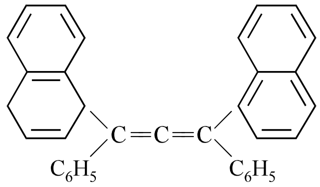


Isomeric allenes

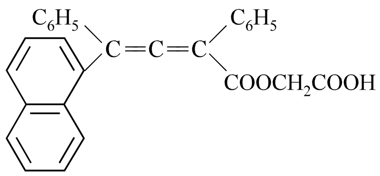
The central carbon atom of allenes is '*sp*' hybridised and has two unhybridised *p*-orbitals perpendicular to each other. Remaining two terminal carbon atoms are 'sp^2' (trigonal) hybridised, each having one unhybridised *p*-orbital. The two '*sp*' hybrid orbitals of central atom form sigma (s) bond with sp^2 hybrid orbitals of each of the two terminal carbon atoms.The remaining two *p*-orbitals (which are perpendicular to each other) of the central atom ovelap laterally with the available *p*-orbitals of the terminal carbon atoms forming two pi (π) m.o.'s which are perpendicular to each other, one lying in the plane of the paper and the other perpendicular to the plane of the paper as shown in the structure above.

Geometry of allenes of the type  $\begin{matrix}A\\B\end{matrix}\!>C=C=C<\!\begin{matrix}A\\B\end{matrix}$ or  $\begin{matrix}A\\B\end{matrix}\!>C=C=C<\!\begin{matrix}D\\E\end{matrix}$ is such that groups (A, B) at one terminal carbon become perpendicular to the groups (A, B or D, E) at the other terminal carbon atom. Therefore the mirror image of such a molecule is not superimposable on it. The molecule becomes chiral and hence it will exists in two enantiomeric forms.

Mills and coworkers (1935) resolved dinaphthyldiphenylallene (I) by catalytic asymmetric dehydration of 1,3-di-1-naphthyl-1,3-diphenylprop-2-enol. Kohler *et al*. (1935) resolved the ester of 3-(1-naphthyl)-1,3-diphenyl-allene-1-carboxylic acid (II) using brucine.

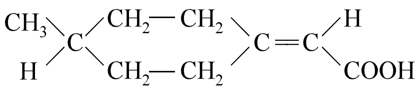


(I)



(II)

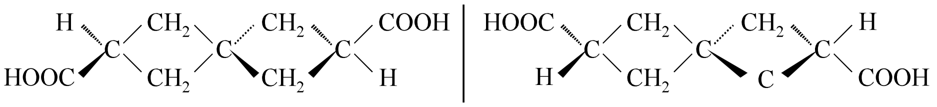
If one of the double bond of allene is replaced by a ring, the geometry of resultant molecule remains identical to that of original allene. Such a molecule is chiral and non- superimposable on its mirror image. Pope *et al.* have resolved 4-methylcyclohexylidene-1-acetic acid (III)



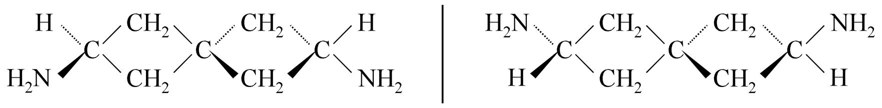
(III)

(*b*) *Spiranes* are bicyclic or polycyclic systems having one carbon atom common to two rings. (Spiranes are compounds in which a C-atom, is bound to 4 other C-atoms, in such a way that each belongs to a ring.) Again because of restricted rotation two rings of spirane become perpendicular to each other and consequently there is no element of symmentry in suitably substituted spirane. Such a molecule has no element of symmetry and is chiral and will not be superimposable on its mirror image.

Backer *et al*. (1928) resolved spiro (3.3) cycloheptane carboxylic acid (IV) and Pope *et al*. (1932) resolved 2,6-diamino dispiro (3.3) heptane (V)



(IV) Spiro (3.3) cycloheptane carboxyhc acid



(V) 2,6-Diaminospiro, (3,3)-heptane

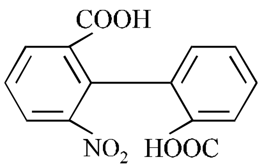
These two compounds are non-superimposable on their mirror images and hence show optical activity.

(*c*) *Biphenyls* are shown by physico-chemical studies that biphenyls are planar and the two rings are coaxial and linear.

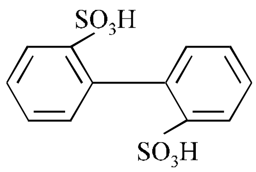
However the bulky groups in ortho position of biphenyls prevent free rotation around carbon to carbon bond joining the two benzene rings. This restricted rotation prevents the two rings from acquiring the coplanarity and a situation similar to allenes or spiranes gives rise to optical isomerism in the derivatives of biphenyls. Stereoisomers resulting from hindered rotation around a single bond (where the barrier to rotation is high enough for their isolation) are called atropisomers and the phenonenon as *atropisomerism*. Atropisomers display axial chirality and differ from other chiral compounds in that they can be equilibrated thermally. The most important class of atropisomers is biphenyls. When the two rings are suitably substituted optical activity is observed, for example, Kenner *et al*. (1927) resolved 2,2¢-dinitro-6,6¢-diphenic acid, which does not have an asymmetric carbon atom but the miolecule as a whole is chiral.

2,2′-Dinitro-6,6′-diphenic acid

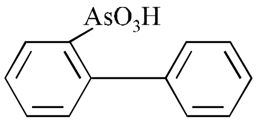
Turner *et al*. (1932) have shown that if the groups are sufficiently bulky then even tri-, di-and even monosubstituted biphenyls may have restricted rotation and hence resolvable. The following compounds have been resolved.



2-Nitro-6,6′-diphenic acid



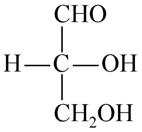
Biphenyl-2,2′-disulphonic acid



Biphenyl-2-arsonic acid

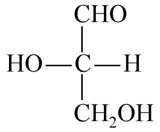
In these cases bulky, sulphonic acid group or arsonic acid group interact a with H— of the other ring to cause restricted rotation. Hence the two rings become non-coplanar and the molecules becomes non-superimposable on its mirror image and therefore are resolvable.

(*vii*) **Configuration: Relative and absolute configuration:** Arrangements of groups or atoms in space in a molecule is referred to as its configuration. It has been seen in the previous section that compounds with asymmetric carbon atoms can have different configurations—each of which belongs to different optical isomer. Thus for lactic acid dextro (*d*) and laevo (*l*) enantiomorphs are known and out of the two possible configurations one is of detro lactic acid and the other of laevo lactic acid. Fischer, however, thought that it is more important to indicate the stereochemical relationship than merely to indicate the actual direction of rotation. To solve this problem of assigining the configuration it was suggested by Rosanoff that glyceraldehyde[1] be chosen as standard and a configuation be assigned to its arbitrarily. Accordingly the two forms of glyceraldehyde were assigned the following congfigurations and labelled as 'D' and 'L' glyceraldehyde respectively.



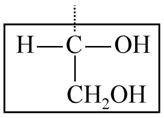
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D (+)
Glyceraldehyde



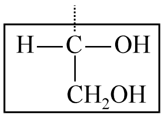
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{CH_2OH} \end{array}$$

L (–)
Glyceraldehyde



$$\boxed{\begin{array}{c} \vdots \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}}$$

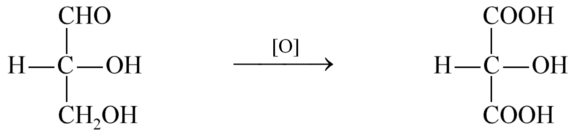
D-series



$$\boxed{\begin{array}{c} \vdots \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}}$$

L-series

All those compounds which have genetic relationship with 'D'-glyceraldehyde in configuration belong to D-series. Similarly those which have configurational similarity with standard 'L'-glyceraldehyde molecule must belong to L-series. Hence by prefixing 'D' or 'L' before the name of a compound we can immediately specify its configuration. The configuration of an optical isomer when established in relation to some compound of known configuration (as glyceraldehyde) is termed as its **relative configuration**. For example, D-gylceraldehyde can be converted to glyceric acid by simple oxidation and, therefore, the configuration of glyceric acid obtained must be 'D'.



$$\begin{array}{c}\text{CHO}\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ \text{CH}_2\text{OH}\end{array}\xrightarrow{[O]}\begin{array}{c}\text{COOH}\\ |\\ \text{H}-\text{C}-\text{OH}\\ |\\ \text{COOH}\end{array}$$

D (+)
Glyceraldehyde

D (–)
Glyceraldehyde

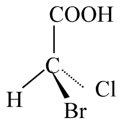
It must be borne in mind that this 'D' or 'L' prefix does not indicate the direction of rotation to be 'dextro' (+) or 'laevo' (–) but only shows the configuration at asymmetric carbon atom. The actual direction of rotation is usually written after D or L, it being (+) for dextro and (–) for laevo. Also it is not necessary that molecules with the same configuration should have the same direction (whether dextro or laevo) of rotation. Thus D-glyceric acid is laevorotatory, whereas D-glyceraldehyde is dextro-rotatory.

The *absolute configuration* of 'D' and 'L' glyceraldehydes could be verified experimentally only in 1951 by the use of asymmetric X-ray crystallography and other physical techniques. As a result, it has now been established that the arbitrary choice of Rosanoff was correct. The determination of absolute configuration is a very tedious and time-consuming affair. Therefore it is convenient to obtain the configuration of optically active compounds by relating it to known standard configuration. However, this system, of relating the configurations has a basic defect that sometimes the configuration of the same molecule may be related to both 'D' and 'L' series. Also it is difficult to apply it to molecules having complicated structures and more than one asymmetric carbon atoms.

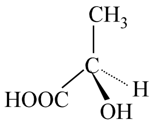
R and S System

To overcome these and such other difficulties of this system Cahn, Ingold and Prelog gave a new convention for specifying the configuration of asymmetric carbon atoms. This is also known as *Rectus* (*Latin*, meaning right) and *Sinister* (*Latin*, meaning left) system, and is often abbreviated as 'R' and 'S' system. In this system the atoms joined to the asymmetric C-atoms directly are arranged in a sequence. The important sequence rules are:

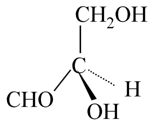
1. *The order of priority or sequence is determined on the basis of the atomic numbers of the atoms joined directly to asymmetric C, the greater the atomic number the higher the order.*



Chloro bromo acetic acid
(H = 1, C = 6, O = 8, Cl = 17, Br = 35)



Lactic acid



Glyceraldehyde

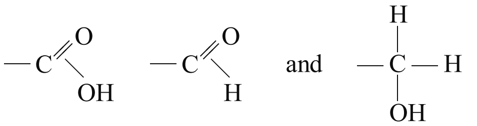
Thus in chloro bromo acetic acid the priority will be:

$$\text{Br} > \text{Cl} > \text{COOH} > \text{H}$$

2. *If two or more atoms attached to asymmetric carbon atom are same then the atoms next to those similar atoms are taken into consideration for determination of the priority order. If these are also the same then the third*

atoms are taken into consideration and so on till the ambiguity about preference is resolved. Thus for —CH_3 and —$CH_2.CH_3$, the order of priority will be — CH_2. CH_3 > — CH_3 because in methyl C— is joined to H, H, H whereas in ethyl it is joined to C, H and H.

3. *For determining order of priority, multiple bonds are treated as separate single bonds.* Thus H—C==O is regarded as carbon linked to 2 oxygen and 1 hydrogen. The order or priority of



$$-\mathrm{C}{\overset{\Large\mathrm{O}}{\diagup\!\!\diagup}}\!\!\!\underset{\mathrm{OH}}{\diagdown} \qquad -\mathrm{C}{\overset{\mathrm{O}}{\diagup\!\!\diagup}}\!\!\!\underset{\mathrm{H}}{\diagdown} \qquad \text{and} \qquad -\underset{\mathrm{OH}}{\overset{\mathrm{H}}{\mathrm{C}}}-\mathrm{H}$$

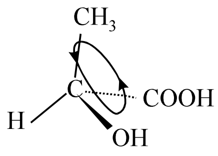
groups will be

$$—\mathrm{COOH}\,(2\mathrm{O}+1\mathrm{O}) > —\mathrm{CHO}\,(2\mathrm{O}+1\mathrm{H}) > —\mathrm{CH_2OH}\,(2\mathrm{H}+1\mathrm{O})$$

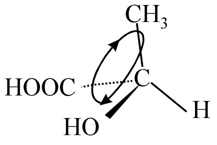
Applying these rules the order of priority of groups and atoms in lactic acid will be OH > COOH > CH_3 > H and in glyceraldehyde OH > CHO > CH_2OH > H.

After fixing the priority order of the groups joining the asymmetric C atoms the tetrahedral perspective formula of the isomer is viewed from the side opposite to the group of lowest priority and the arrangement of rest of the groups is observed. If the arrangement of groups, in going from top priority group to second and then to the third priority group, is in clockwise direction, the configuration is considered as 'R' or rectus configuration. If this arrangement is in anti-clockwise direction, the configuration is termed as 'S' or sinister configuration.

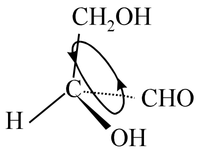
In the figures below the molecule may be visualized as steering wheel of a car with lowest priority group as steering rod and other three groups around the wheel.



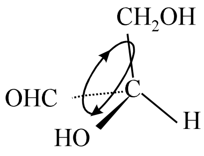
d-Lactic acid
S-Configuration



l-Lactic acid
R-Configuration



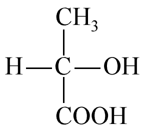
S-Glyceraldehyde



R-Glyceraldehyde

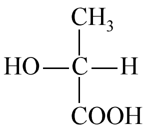
The racemic modification is termed as RS compound. This system is thus very convenient for writing the absolute configurations of the compounds, however, it does not give any indication of the actual direction of rotation.

From the above discussion it is clear that optical isomer must be represented by a tetrahedral, perspective, or projection formula as the planar representation will not give a correct idea of the molecule. However for the sake of convenience planar formulae are still extensively used for writing the configurations of optical isomers. In fact, so long as the planar formulae are kept in the plane of paper, they remain non-superimposable. Thus lactic acid may be conveniently represented as:



$$\mathrm{H}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{OH}$$

d-Lactic acid

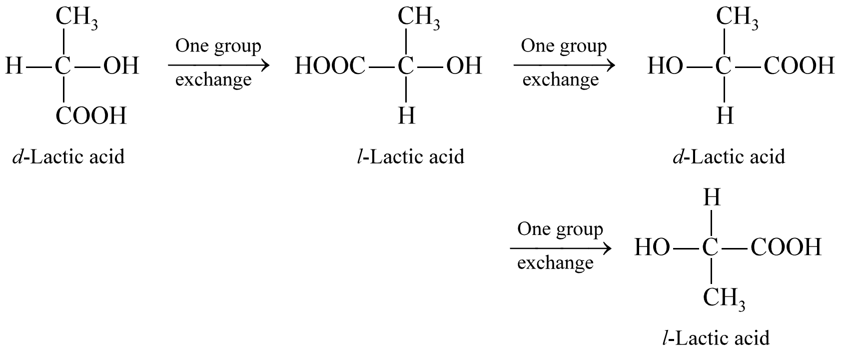


$$\mathrm{HO}-\underset{\mathrm{COOH}}{\overset{\mathrm{CH_3}}{\mathrm{C}}}-\mathrm{H}$$

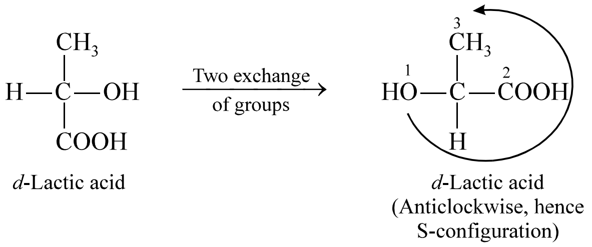
l-Lactic acid

Fischer Projection Formulae

The planar configuration of optically active compounds is referred to as Fischer projection formula. So long as these structures are not taken out of the plane of paper they serve the same purpose as perspective formulae. In Fischer projection structures the group on the left and right are considered to be projected above the plane of paper and those on top and bottom are considered to be below the plane of paper. Any odd number of interchanges of groups in these formulae results in isomeric structures while even number of exchange of groups results in the structure of same isomer. For example,

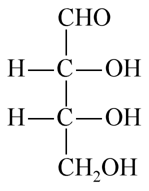


To specify RS configuration in a Fischer projection formulae exchange even number of groups to bring least priority group to the bottom and then determine the sequence of remaining groups in usual way to assign R or S configuration.

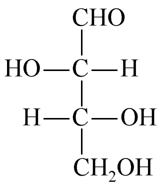


1.6.2 Erythro and Threo Nomenclature System

Erythro and threo system of specifying configuration originated from tetraldoses erythrose and threose which are diastereoisomers.

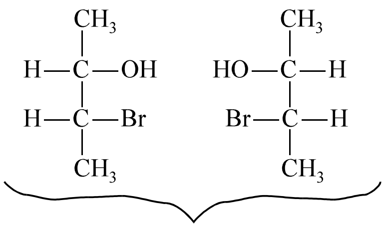


D (–) Erythrose

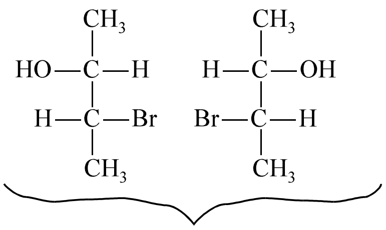


D (–) Threose

Thus any compound having two dissimilar chiral carbon atoms may exist in four isomeric forms. Of these isomers having identical groups on same side are termed as *erythro*-isomer while those having similar group on opposite side are termed as *threo*-isomer. Thus isomers of 3-bromo-2-butanol may be designated as erythro- or threo- as follows:



erythro-isomers



threo-isomers

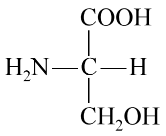
(*i*) **Compounds with one asymmetric carbon atom**

It includes the following:

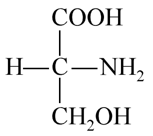
(*a*) *Stereochemistry of lactic acid*: Compounds like lactic acid, malic acid etc., contain one asymetric carbon atom and hence can have two configuration, one of these being dextro and other laevorotatory. These are related to each other as object and mirror image and, therefore, constitute a pair of enantiomorphs. Their configurations have been shown earlier.

Compounds containing one asymmetric carbon also occur in an optically inactive form which in fact is a mixture of equal amounts of '*d*' and '*l*' varieties and is known as *racemic* or *dl* or (±) forms. However this form can be separated into '*d*' and '*l*' forms and such type of optical inactivity is said to be because of *external compensation.*

(*b*) *Stereochemistry of serine*: Serine is an amino acid which contains an asymmetric carbon atom and hence exists in two forms: *dextro* and *laevo*. These are related to each other as object and its mirror image and are thus enantiomorphs. However naturally occurring serine is laevorotatory.



d-Serine

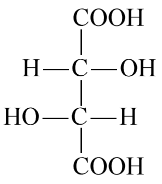


l-Serine

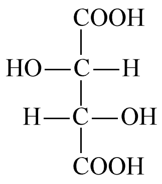
A third form of serine is a mixture of *d*- and *l*-forms which is optically inactive due to external compensation and is called racemic or *dl*-form.

(*ii*) **Compounds with two asymmetric carbon atoms**

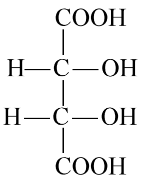
Stereochemistry of tartaric acid: Tartaric acid contains two asymmetric carbon atoms which are similar to each other. Theoretically the number of possible isomers is $2^2 = 4$ and they may be represented as:



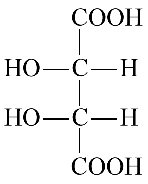
(I)



(II)

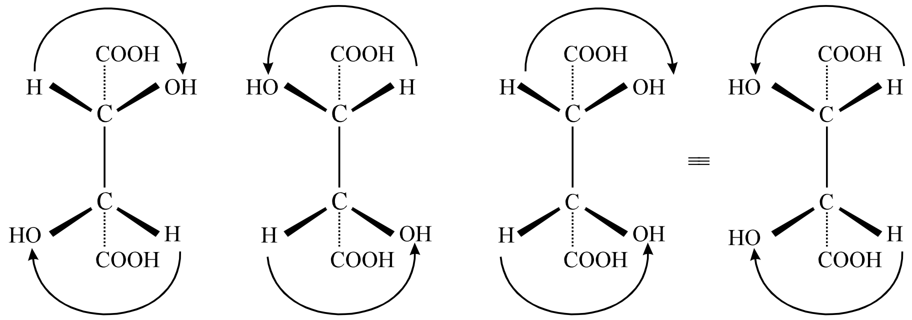


(III)



(IV)

Of these formulae I and II are related to each other as object and mirror image and are thus enantiomorphs. Similarly III and IV are related as object and mirror images but when one of these is rotated through 180° they become identical. Thus for tartaric acid only three different arrangements may be visualised.



[A] [B] [C]

(+) Tartaric acid (M.P. 170°)

(–) Tartaric acid (M.P. 170°)

meso-Tartaric acid (M.P. 140°)

(±) or *dl*-Tartaric acid (M.P. 206°)

Fig. 1.29 *Different Forms of Tartaric Acid*

The formulae A and B are enantiomorphs to each other whereas A and C or B and C are not related to each other as object and mirror image and so constitute pairs of diastereoisomers. The formula C has a plane of symmetry and is thus optically inactive.

If it is considered that the force which rotates the plane of plane polarised light operates from —H to —OH via —COOH groups (see Fig. 6.10), then structure A will rotate it in clockwise directioin and will be *d*-tartaric acid and the structure B will rotate it in anti-clockwise direction and will represent *l*-tartaric acid. However, in case of structure C one asymmetric carbon atom is rotating it in clockwise direction whereas the other equally in an anticlockwise direction and thus the isomer becomes optically inactive.

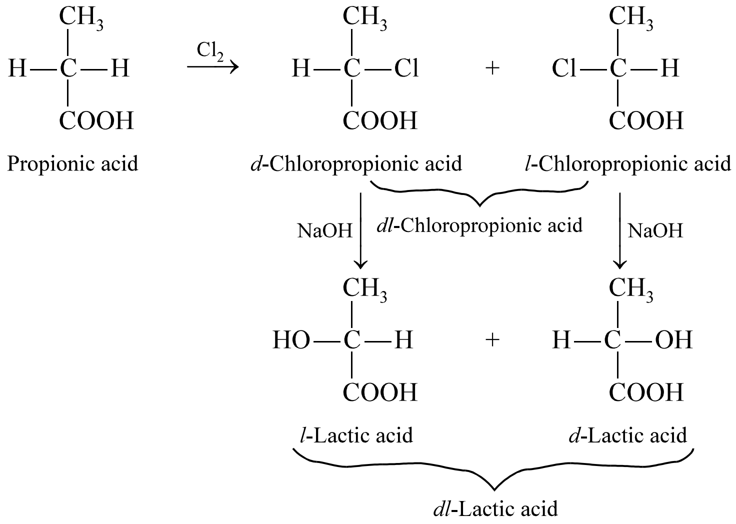
This optical inactivity in the molecule C has arisen because of equal and opposite rotation by two similar asymmetric C-atoms of the same molecule. In other words, we can say that the dextrorotation of one-half of the molecule is compensated by the laevorotation of the other half. Since this compensation comes from within the molecule itself; the molecule is said to be inactive due to **internal compensation**.

Besides these three forms, tartaric acid also occurs in a racemic or *dl* or (±) form which is inactive because of *external compensation*. Melting points and densities of the meso- and racemic forms differ considerably from those of *d*- and *l*- forms.

Resolution

In the laboratory synthesis of compounds containing asymmetric carbon atom the product is almost an equal mixture of two enantiomorphs *d* and *l*. Even when the starting material is racemic mixture or an optically active compound, the product obtained is racemic, hence inactive. On the other hand, asymmetric compounds in nature always occur in optically active form.

Thus if propionic acid is converted to chloropropionic acid in the laboratory, it will result in the formation of *dl* or (±) chloropropionic acid. Similarly if (±) chloropropionic acid is hydrolysed to give lactic acid, the later also is obtained in racemic form. The reason for this is that in the conversion of propionic acid to its chloro derivative a hydrogen is replaced by chlorine and there are two such hydrogens identically placed in the molecule. The replacement of one of these hydrogens gives one enantiomorph. Since the chances of the substitution of the two hydrogens are equal, the product is a racemic mixture, *e.g.*:



If the hydrolysis of chloropropionic acid proceeds by S_N2 mechanism it is accompanied with inversion of configuration and the *d*-form will be converted to *l*-lactic acid whereas the *l*-form will be converted to *d*-lactic acid. Since the two forms of chloropropionic acid are present in equal amounts the product in this case also is a mixture of equal amounts of the two enantiomorphs and therefore racemic.

The separation of a racemic (dl) mixture into the component d- and l-enantiomorphs is termed as resolution. Since most of the chemical and physical properties of enantiomorphs are same they cannot be separated by general methods of separation like fractional distillation, fractional crystallization etc. The methods commonly used for resolution are:

(*a*) **Mechanical Resolution:** Pasteur in 1848 used this method to demonstrate that racemic tartaric acid was actually a mixture of *d*- and *l*-acid. The method is thus of historical importance and can be applied to those solids only which form two types of well defined crystals. These crystals are also related to each other as object and mirror images and can be seen under a magnifying glass and picked mechanically.

However, only a few compounds are known to form such well defined crystals and besides the method is very laborious.

(*b*) **Biochemical Resolution:** Pasteur in 1858 observed that when certain micro-organisms were allowed to grow in the solution of a racemic mixture of certain compounds, they consumed preferentially only one stereoisomer, leaving the other in the solution. The form left over in solution can be isolated by fractional crystallization. For example, *dl*-tartaric acid, when treated with micro-organism P. glaucum is converted to *l*-tartaric acid because *d*-tartaric acid is consumed by the organism.

However, the method has only limited application because it is not easy to find the proper organism which may consume one of the isomer in preference to the other. Another drawback of the method is that one-half of the compound is consumed. The poisonous enantiomers cannot be separated by this method because no micro-organism can consume poisonous compounds.

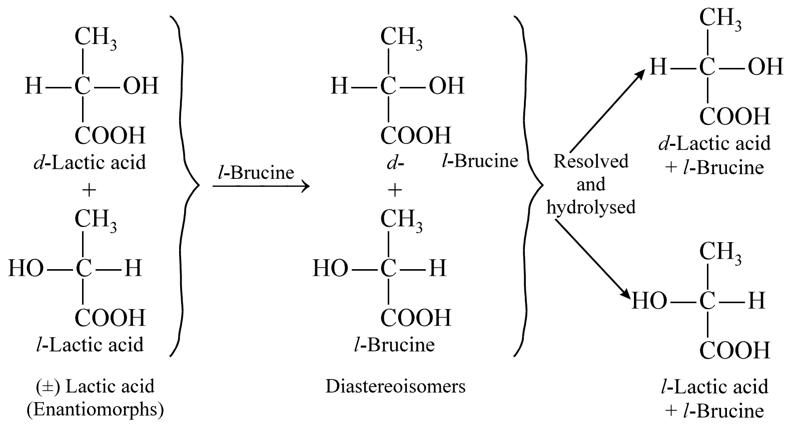
(*c*) **Chemical Method of Conversion to Diastereoisomers:** This method is also due to Pasteur (1858). He noticed that though the enantiomorphs have the same physical properties, diastereoisomers differ significantly in their physical properties. Therefore, racemic mixture may be resolved by converting them to diastereoisomers, by reaction with an asymmetric substrate, and then resolving diastereoisomers by taking advantage of the difference in their physical properties like solubility. The separated diastereoisomers may be converted to optically active compounds. For example (±) lactic acid when treated with *l*-brucine will give two diastereoisomers which may be resolved by taking advantage of differential solubility. Hydrolysis of diastereoisomers yields the optically active product.

The bases used for the resolution of *dl*-acid mixtures are (–) quinine, (+) cinchonine and (–) strychnine etc.

Similarly, for the resolution of bases an optically active acid may be used. The acids used are (+) tartaric acid, (–) malic acid, (–) mandelic acid etc. The following scheme will make the point clear.

$$dl\ \text{Base} \xrightarrow{d\text{-Acid}} \left\{\begin{array}{l}(1)\ \ d\text{-Base-}d\text{-Acid}\\ (2)\ \ l\text{-Base-}d\text{-Acid}\end{array}\right\} \xrightarrow[\text{and hydrolysed}]{\text{Resolved}} \begin{array}{l} d\text{-Base} + d\text{-Acid}\\ l\text{-Base} + d\text{-Acid}\end{array}$$

The method is most commonly used but is applicable mainly to acids and bases. Compounds like alcohol and aldehyde may also be resolved by this method by conversion to diastereoisomeric esters and hydrazones respectively.



(*d*) **Differential Adsorption Method:** When a racemic mixture in the solution form is placed on chromatographic column containing optically active substances like starch, quartz etc., then the enantiomorphs will move down the column at different rates and thus can be separated because of the adsorption selectivity of the adsorbent. The *dl*-mandelic acid has been resolved by adsorption over starch. This method eliminates the necessity of converting the *dl*-mixture to diastereoisomer.

(*e*) **Differential Reactivity or Kinetic Method:** The enantiomorphs react with optically active substances at different rates. Therefore, in some cases it is possible to obtain a separation (usually partial) by stopping the reaction before it acquires equilibrium. However, this method results in only partial resolution and is similar to asymmetric synthesis.

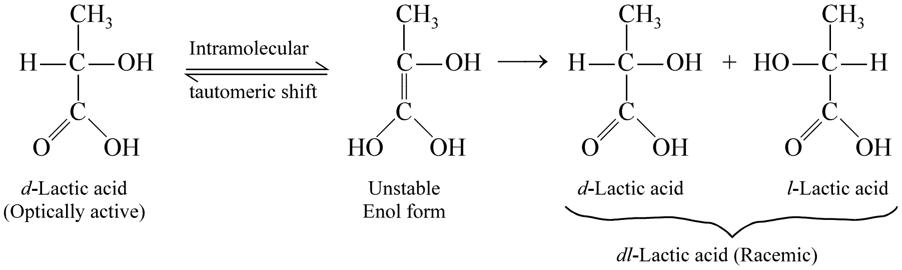
Racemisation

During his researches on stereochemistry Walden observed that many optically active substances when kept for long time tend to become racemic mixtures. Later on it was found that application of heat, light etc., to the optically active compounds, may result in the loss of their optical actrivity. *This conversion of dextro or laevo compounds to their racemic (dl) forms is known as* **Racemisation**.

Racemisation occurs through some intramolecular rearrangement caused by light, heat or catalysts. Because of this rearrangement the optically active compound exists temporarily in equilibrium with this rearranged product. The latter does not have an asymmetric centre so that when it again forms the asymmetric centre, both *d*- and *l*-forms are obtained in equal amounts. For example lactic acid may recemise as follow:

The tartaric acid on heating is converted to racemic as well as meso form.

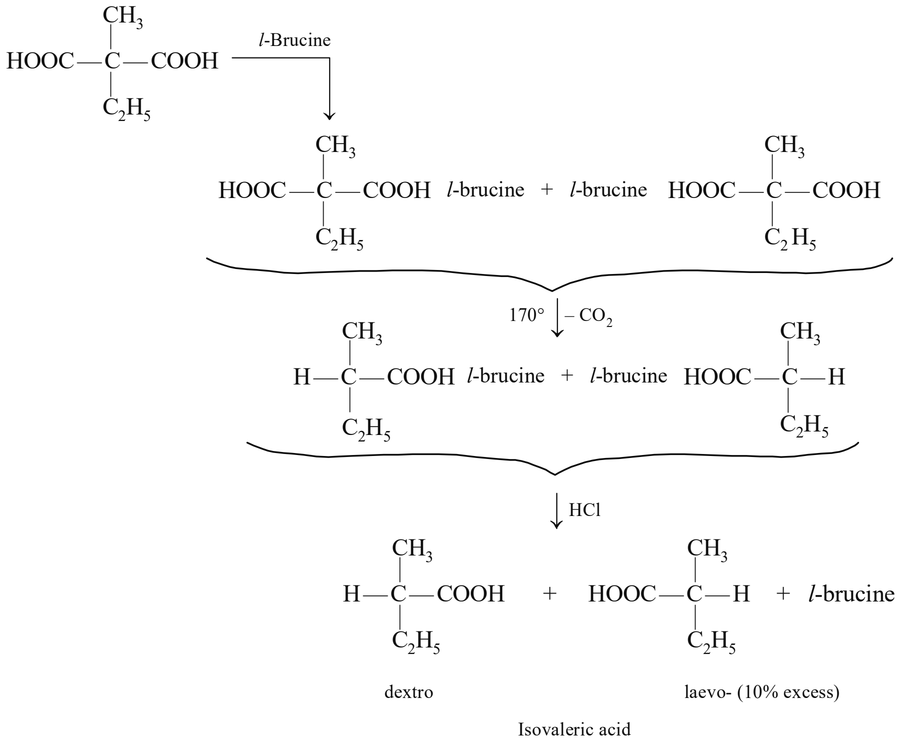
It has been observed that compounds having carbonyl group adjacent to asymmetric carbon atom carrying a hydrogen are most easily racemised. Other substances which cannot enolise easily do not under go racemisation ordinarily.



Asymmetric Synthesis

Whenever an attempt is made to synthesize an optically active compound in the laboratory, the product is always racemic and thus optically inactive. This racemic mixture must be resolved in order to get optically active products.

NOTES



Isovaleric acid

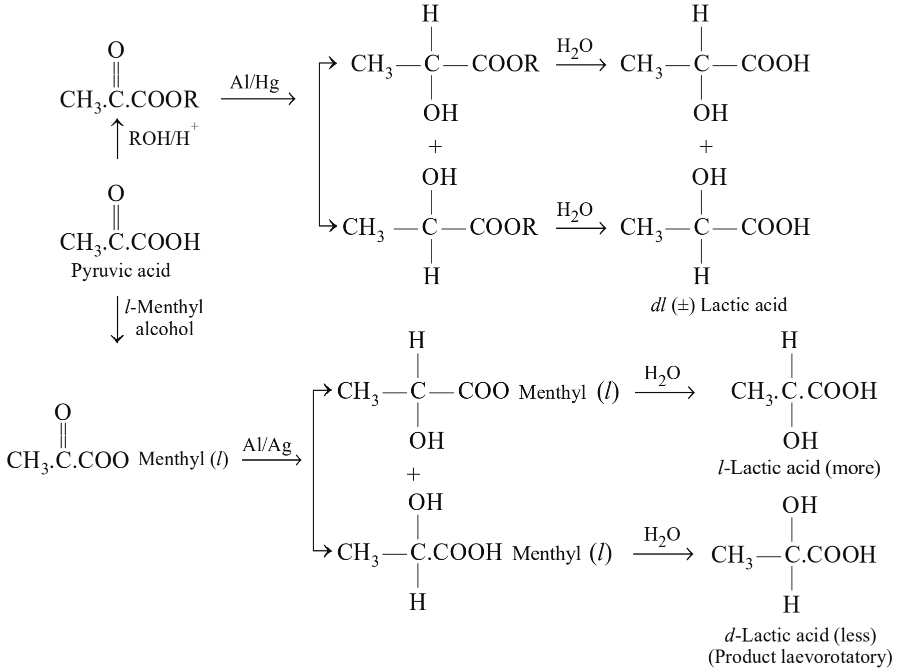
However, if some dissymmetric substance is used in the raction then the two enantiomorphs may not be formed in equal amounts. The product in this case will be optically active because of unequal amounts of the isomers formed. *Such a synthesis in which optically active (asymmetric) compound is obtained from optically inactive (symmetric) compound without recourse to resolution is termed asymmetric synthesis.*

The methods commonly used for asymmetric synthesis are given below:

1. With Optically Active Reagents, Catalysts or Solvent: The active reagent, catalysts or solvent create an environment of asymmetry and often the rate of formation of one enantiomorph is faster than the rate of formation of other resulting in optically active product.

The first asymmetric synthesis was caried out by Marckwald in 1904 when he prepared *l*-isovaleric acid from ethyl methyl malonic acid using *l*-brucine. The laevo form is obtained in 10% excess over the dextro form.

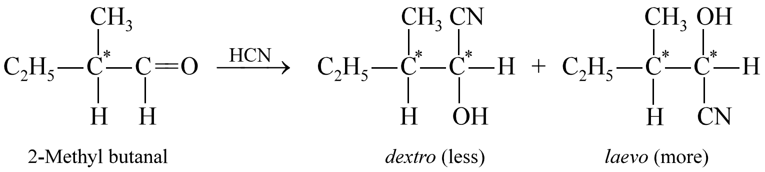
If pyruvic ester is reduced to give lactic ester the latter on hydrolysis yields racemic mixture but if pyruvic acid is first esterified with an optically active alcohol like *l*-menthyl alcohol and then reduced and hydrolysed the product is laevorotatory. Thus:



A few examples are known where active catalyst or solvent has been used for asymmetric synthesis. Thus when mixed ketones are reduced with hydrogen using nickel catalyst treated with optically active amino acids, one enantiomorph of secondary alcohols is formed predominantly.

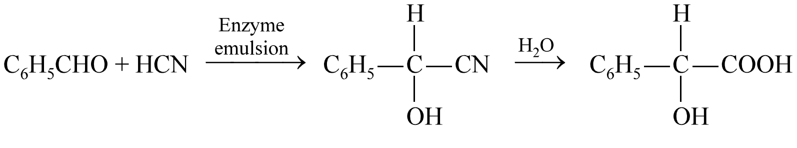
The preparation of alcohols, containing asymmetric carbon atoms from aldehydes, using Grignard reagent, gives optically active product if optically active ether is used as solvent.

2. With Active Substrate: When a new asymmetric centre is created in a molecule which is already having an asymmetric centre, then the two diastereoisomers are formed in unequal amounts—thus giving optically active compound. For example, 2-methylbutanal on additiion of HCN gives optically active cyanohydrin.



Net rotation laevo

3. With Enzymes: In fact enzymes act as active catalyst and the reaction of benzaldehyde with HCN in presence of a enzyme emulsion gives optically active mandelo nitrile which on hydrolysis gives *l*-mandelic acid.

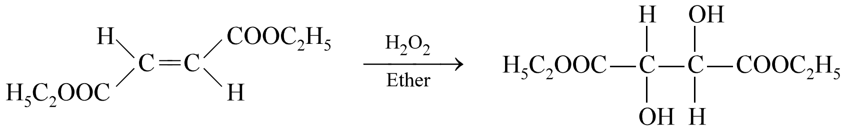


l-Mandelo nitrile *l*-Mandelic acid

4. With Circularly Polarised Light: A wave of plane-polarised light may be considered to be made up of right and left circularly polarised wave. The plane of polarisation of circularly polarised light wave rotates continuously around the axis of propagation of the wave. The electric field of the right circularly polarised light may be considered as right handed screw and that of a left circularly polarised light wave as left handed screw.

W. Kuhn and Knopf showed in 1930 that when optically active compounds are synthesized under the influence of circularly polarised light the resulting product is slightly optically active. When right circularly polarised light is used the product is usually dextrorotatory and when the left circularly polarised light is used the product is laevorotatory. This type of asymmetric synthesis is known as **absolute asymmetric synthesis**.

Davis and coworkers in 1945 found that hydroxylation of ethyl fumarate in a beam of right circularly polarised light gave a dextrorotatory product.



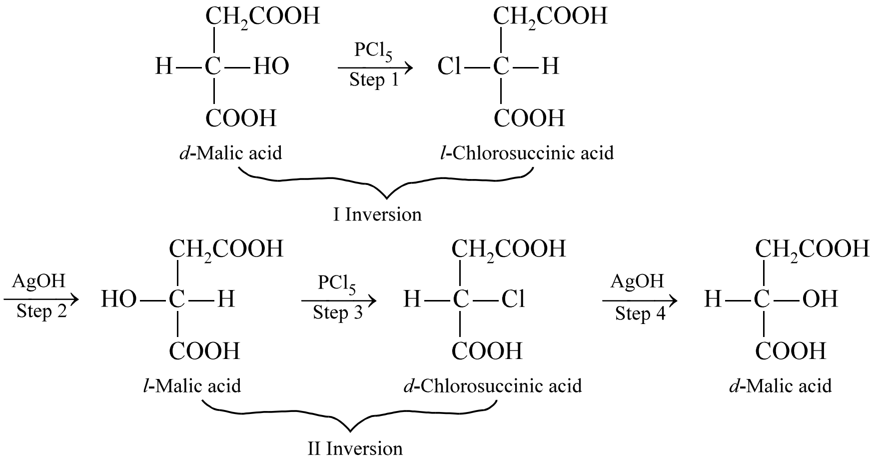
Ethyl fumarate

d-Diethyl tartaric acid

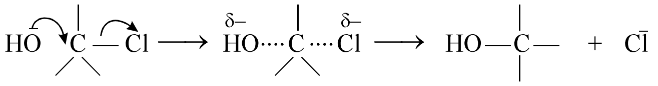
However, the yields and results have been poor, so far.

Walden Inversion

P. Walden observed in 1895 that in many reactions when a group or atom directly attached to asymmetric carbon is replaced by another group or atom, the configruation of the new compound, and usually the sign of rotation also, may be opposite to that of the initial compound. *The term Walden inversion or optical inversion is applied to any step of a reaction in which the inversion of configuraton occurs.* It is important to note that any change in the direction of rotation is purely coincidental and the term Walden inversion refers only to the change in configuration of the molecule. For example, in the conversion of *d*-malic acid to *l*-malic acid and *vice-versa*, steps 1 and 3 involve a change in configuration and are therefore Walden inversions.



In some cases the inversion is almost quantitative whereas in some cases partial inversion occurs. Factors like nature of the compound, reagent and the solvent, etc., play an important role in the Walden inversion. The mechanism of inversion is perhaps a bimolecular substitution (in above case nucleophilic substitution) occurring by the attack of the reagent from the opposite side of the leaving group—resulting in inversion of configuration. However, the mechanism is not very clearly understood. In Walden inversion involving simple bimolecular nucleophilic substitution reaction following mechanism has been proposed by Hughes and Ingold.



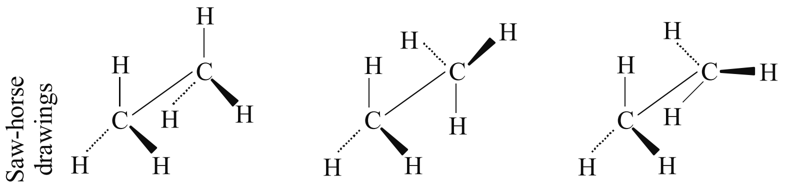
$$HO + C-Cl \longrightarrow \overset{\delta-}{HO}\cdots C\cdots\overset{\delta-}{Cl} \longrightarrow HO-C- \;+\; \bar{Cl}$$

This can be readily understood by considering the molecule to have the shape of an umbrella. The inversion of configuration may be compared to the upside down turning of umbrella (↑ ⟶ ↓) on a particularly windy day.

Conformations of Alkanes

The sigma bond joining the two carbon atoms in ethane is symmetrical about the nuclear axis. This symmetry of the bond permits free rotation of the two carbon atoms with respect to each other, along the bond axis without breaking the bond. Since the two carbon atoms are having tetrahedral arrangement and the valency angles are 109.5°, the free rotation of carbons on their axis gives rise to various arrangements of relative position of the hydrogens attached to these carbon atoms. *All such arrangements of the atoms in a molecular structure, in space, which are possible because of the concept of free rotation around a single σ (sigma) bond are known as* ***Conformations*** *of the molecule. Since conformations are obtained on rotation around a bond, they are sometimes also called rotamers. It can also be said that conformations are different arrangement of atoms that can be converted into one another by rotation about a single bond.* The study of the preferred conformation in a molecule and relating their physical and chemical properties to their preferred conformation is known as **Conformational analysis**.

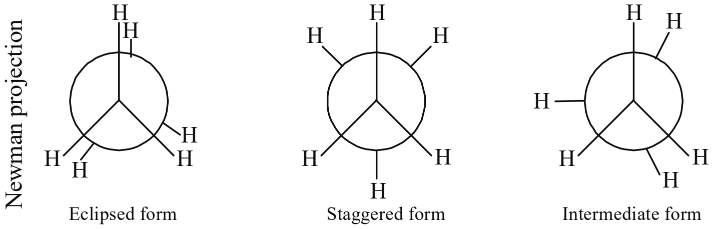
Methane has only one carbon atom and so only one spatial arrangement is possible whereas ethane could be represented as shown in the form of **saw-horse** drawings:



1. Eclipsed form 2. Staggered form 3. Intermediate form

In the above representation the dark-black lines are supposed to be below the plane of paper and the dotted lines to be above the plane of paper.

In the spatial arrangement (1) shown, the hydrogen atoms of one carbon atom lie exactly opposite or parrallel to those of the other and the arrangment is known as *Eclipsed form.* In (2) the hydrogen atoms of one carbon lie exactly in the middle of the position occupied by the hydrogens of the other carbon atom. This arrangement is known as *Staggered form.* Any other arrangement which will be in between these two extreme positions of hydrogens is shown in (3). A better way to represent these forms is to use **Newman projection** formulae, as shown below.



In writing Newman projection formulae the molecule is viewed from the top along the C—C bond. The top carbon atom is shown as a dot and bottom carbon atom as a circle with three hydrogen attached to each one of them.

Obviously, there will be a slight difference in the energy of each of these forms, though they will be having identical chemical and physical properties. In the eclipsed form hydrogen atoms are placed opposite to each other resulting in crowding of the molecule and therefore repulsive forces will be greater. The eclipsed form is of high energy, and thus will be unfavoured. The crowding and repulsive forces will be slightly less in intermediate form hence its energy will be lower than eclipsed form. In staggered form the hydrogen atoms are far apart from each other and the repulsive forces will be minimum. Consequently this form will be the favoured one and of lowest energy. The curve in Fig. 1.30 shows the change in the energy of the molecule as the carbon atoms are rotated on their axis.

Any point in the above curve for ethane refers to some conformation of ethane molecule. The ones at the trough of the curve are of minimum energy known as staggered conformations while those at the crest are of maximum energy called eclipsed conformations. The energy difference between the staggered and eclipsed form in ethane is small, *i.e.*, only 3 kcal/mole and so these forms are easily interconvertible but under normal conditions most of the ethane molecules exist in staggered form, *i.e.*, the form of least interaction amongst hydrogen.

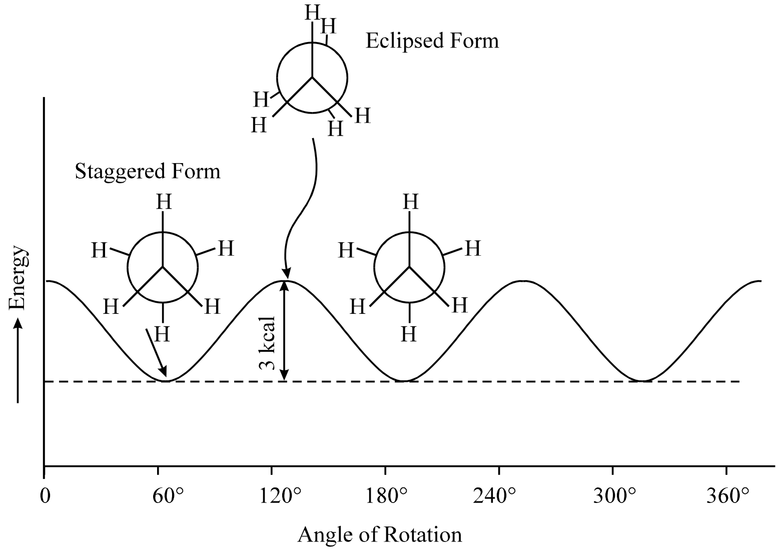
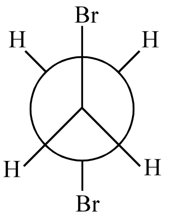
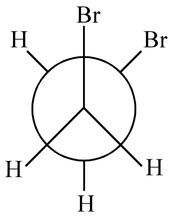


Fig. 1.30 *Energy of Various Conformations of Ethane*

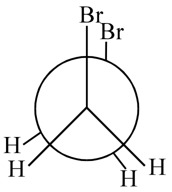
In case of 1,2-dibromoethane the important conformations are:



Staggered or anti-conformation



Gauche or skew conformation

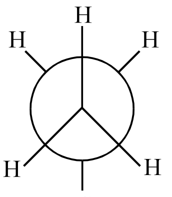


Eclipsed or syn conformation

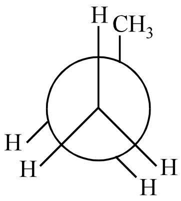
The dipole moment of staggered or anti-form will be zero as the two C-Br bonds are antiparallel to each other while gauche form will have finite dipole moment and the eclipsed or syn form will have maximum dipole moment. Actual dipole moment of 1,2-dibromoethane is 1 Debye under normal conditions indicating that staggered and gauche conformations are in equilibrium and the equilibrium constant changes with temperature as the population of gauche form increases.

Conformations of Propane

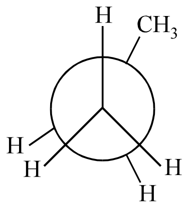
For propane, the important conformations are given below:



Staggered conformation



Eclipsed conformation

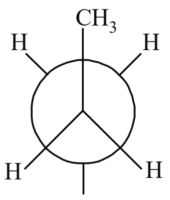


Other intermediate conformation

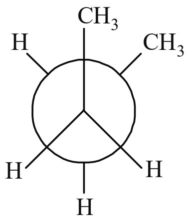
There is only one H—to—CH_3 interaction which raises the energy difference between staggered and eclipsed conformation to about 3.3 kcal/mole. Under normal conditions most of the propane molecules exist in staggered conformation.

Conformations of *n*-Butane

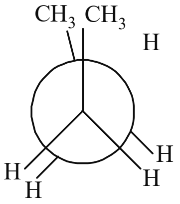
The important conformations for butane are:



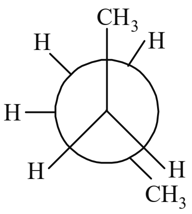
Staggered conformation



Gauche conformation



Eclipsed conformation



Intermediate conformation

Figure 1.31 represents the potential energy as a function of angle of rotation for *n*-butane.

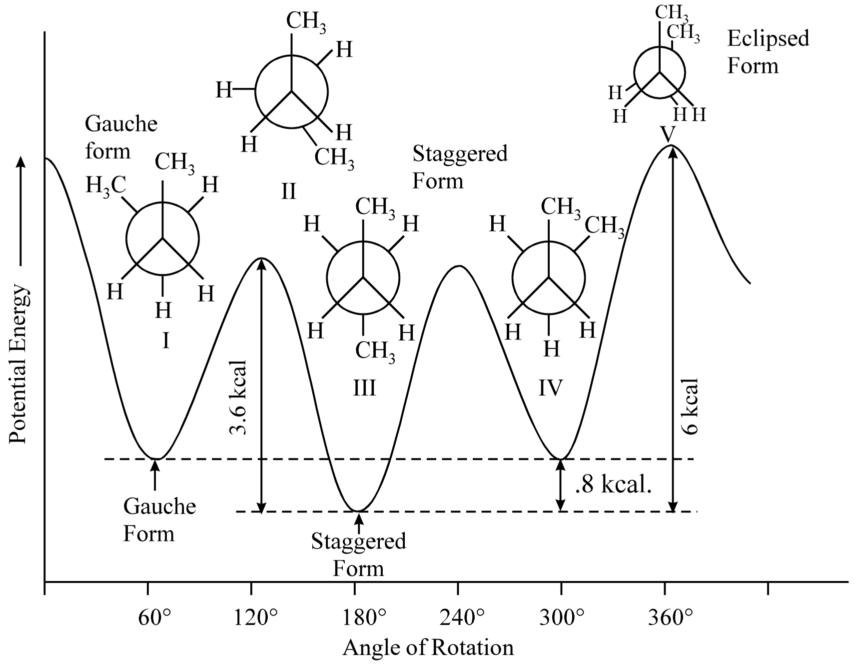


Fig. 1.31 *Energy of Various Conformations of Butane*

Study of the above diagram for the energy of various ecnformations of *n*-butane indicates that eclipsed form V representing the eclipsing of two bulky methyl groups is the conformation of highest energy while the staggered form III in which the methyl groups are maximum distance apart (*i.e.*, 180°) is the conformation of least energy and hence most stable. In addition, another maxima, lower than the one for eclipsed conformation represents the eclipsing of the methyl groups with the hydrogens II.

There is yet another trough, higher in energy than the one for staggered conformation, representing gauche conformation I and IV in which the methyl groups are at 60° to one another.

The energy barrier between the highest crest (corresponding to eclipsed form) and the lowest trough (corresponding to staggered form is approximately 6.0 kcal/mole, while the energy difference between the second crest (representing interaction of two methyl groups with two hydrogen) and the lowest trough is about 3.6 kcal mole.

The gauche form (the trough higher than the one representing staggered form) differs from the staggered form by about 0.8 kcal/mole.

Thus *n*-butane has three stable conformations, two gauche or skew (I and IV in Fig. 1.31) which are mirror images of each other and one staggered conformation (III) which is most stable.

These different conformations corresponding to different energy are called **conformational isomers** or **conformers**. Conformations III and I or III and IV are not mirror images of each other and hence are **conformational diastereoisomers**.

Enantiotopic and Diastereotopic Atoms, Groups or Faces

Homotopic faces, atoms, or groups can never be differentiated in NMR, in any reaction, or in any other way. On their own, enantiotopic faces, atoms, or groups appear identical, yet they respond differently with chiral compounds. Diastereotopic faces, atoms, and groups appear to be different at all times.

Methods of Resolution

A pair of enantiomers can be separated in several ways, but conversion to diastereomers and separation of these by fractional crystallization or chromatographic methods are used most often.

Optical Purity

In an enantiomeric mixture, optical purity is defined as the excess of one enantiomer over the other. Optical purity is measured as a fraction or as a percentage. This is also known as enantiomeric excess, and it's written as 'ee.

1.6.3 Relative Stability of Cycloalkanes and Baeyer's Strain Theory

The properties of cycloalkanes are determined by the size of ring. Thus 3- or 4-membered rings are difficult to prepare while 5- or 6-membered ring compounds are prepared easily. Similarly 3- or 4-membered rings are more reactive and tend to undergo addition reactions rather than substitution reactions.

From an examination of the stability of cycloalkanes it is clear that the stability increases with the size of ring upto cyclopentane and from cyclohexane onwards all cycloalkanes are quite stable. The relative stability of cycloalkanes was explained by Adolf von Baeyer in a theory known as **Baeyer's strain theory**, first postulated in 1885.

According to Le Bel and van't Hoff, the four valencies of carbon atom are directed towards the corners of a regular tetrahedron and hence the angle between any two valencies is 109°28'. Therefore Baeyer argued if *carbon atoms unite to form a closed chain, the valency angles are distorted from their natural directions and a strain is set up in the molecule depending on the extent of distortion of natural valency angles. The greater the strain, the greater is the instability of the ring.* It was also assumed that various ring systems are planar.

On the basis of the above concept of Baeyer's strain theory, a number of phenomenon were explained. For example it explained the relatively greater stability of saturated aliphatic hydrocarbons—as in these compounds there is no distortion from normal valency angle and therefore there is no strain in the molecule. One the other hand unsaturated compounds having double or triple bonds are under considerable strain because of distortion of valency angle[1] (in fact the valency angle is reduced to zero) therefore they are unstable.

Baeyer's strain theory has also been applied to the problem of relative stability of cycloalkanes. In cyclopropane, the carbon atoms lie at the corners of an equilateral triangle. The bonds joining these carbon atoms are, thus, at an angle of 60°; and the distortion of each bond is $1/2\,(109°28' - 60°) = 24°44'$. This distortion sets up strain in the molecule called **Baeyer strain** and therefore cyclopropane is relatively unstable. Similarly the values of distortion of valency angle in different cycloalkanes may be obtained and is given below:

Double bond	Cyclopropane	Cyclobutane	Cyclopentane	Cyclohexane	Cycloheptane
+54°44′	+24°44′	+9°34′	+0°54′	–5°16′	–9°33′

According to strain theory, the strain is proportional to the distortion of normal valency angle. Thus from the values given above it follows that cyclopentane is under least strain and should therefore be most stable. In the other systems the molecules are under strain and therefore tend to open up to relieve the strain by forming saturated compounds. Since the instability is directly proportional to the strain, it is clear from the above data that cyclopentane is more stable than cyclobutane which in turn is more stable than cyclopropane. The compounds having double bonds are the least stable of all. These theoretical deductions have been fully confirmed by experiments.

Additional evidence in favour of Baeyer's strain theory is provided in the formation of lactones from g- and d-hydroxyacids as the resulting rings are 5- and 6-membered with nominal strain. Similarly only g- and d-amino acids form lactams readily, the ring size being 5- and 6- having minimum strain. Another example is the ready formation of 5- and 6-membered ring anhydride when 1,4- and 1,5-dicarboxylic acids are heated.

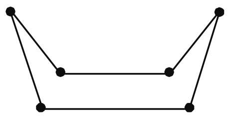
Limitations of Baeyer's Strain Theory

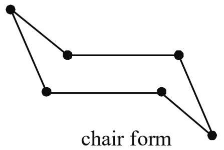
However, Baeyer's theory has failed to explain many known facts. Some of these are given below:

1. On the basis of distortion strain cyclohexane should be somewhat unstable which is against the known facts.
2. Data on the heat of combustion of various cycloalkanes suggests that rings larger than cyclopentane or cyclohexane are stable. In fact, they are equal in stability to the corresponding alkanes, whereas according to this theory higher rings should be considerably strained and therefore unstable.
3. Cycloalkanes with rings of 10, 15, 17 or more carbon atoms have been prepared and found to be stable.
4. It cannot explain the ease with which carbon-carbon double bonds are formed.

Sache-Mohr Theory of Strainless Rings

Baeyer had assumed that the carbon atoms of ring lie in the same plane and his strain theory was able to explain satisfactorily the reactivity or stability of rings containing upto five carbon atoms. In order to explain the anomalous stability of larger rings, Sachse in 1890 suggested that *rings with six or more carbon atoms are not planar but are puckered. Since the carbon atoms lie in different planes the normal valency angle is retained and the rings are known as strainless rings.* According to him cyclohexane exists in two strainless forms—non-rigid 'boat' or trough form and rigid 'chair' form. These are also referred to as different conformations of cyclohexane. The chair form of cyclohexane is more stable than the boat form and under normal conditions most cyclohexane molecules exist in the chair form. It is not possible to isolate these forms because the energy of interconversion of these forms is only 5.6 kcal/mole. Such non-planar strain-free rings (puckered rings) are also possible for higher cycloalkanes.


boat form


chair form

The theory was further elaborated by Mohr in 1918 who emphasized the predominance of chair form and applied the theory of strainless rings to fused ring systems like decalin. The *cis*- and *trans*-forms of decalin were isolated by Huckel in 1925. Mohr assigned boat and chair forms to two cyclohexane rings fused in *cis* and *trans* decalins respectively. However Hassel in 1946 suggested that both in *cis* and *trans* decalins the two rings are in chair form—the only difference being in the mode of combination of the two rings.


(Mohr) (Hassel)

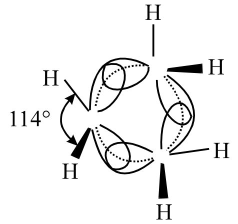
cis-Decalin


(Mohr) (Hassel)

trans-Decalin

Coulson and Moffit's Concept

A covalent bond between two atoms is formed by the overlap of atomic orbitals of the atoms involved. The greater the extent of overlapping the stronger is the bond formed. In cycloalkanes the carbon atoms are in sp^3 hybridised state and the bond angles (C—C—C angle) should be 109.5°. Theoretically the C—C—C bond angle in cyclopropane should be 60° and it cannot be 109.5°. Therefore the carbon atoms in cyclopropane cannot be located as in the case of ordinary carbon-carbon bond but are placed in such a manner that only a partial overlap of sp^3 hybrid orbital occurs—so that the C—C—C valency angle is distorted only slightly (in fact to approx. 105°) and H—C—H angle is increased from normal 109.5° to 114°. In short the sp^3 hybrid orbitals overlap at an angle to form so called '*bent*' or '*banana*' bonds. As the extent of overlapping in appreciably less the carbon-carbon bond in cyclopropane is much weaker than the carbon-carbon bond in aliphatic saturated compounds.



Bent Bond
(Orbital angle 105° but nuclear angle 60°)

Similarly, in cyclobutane the molecule has bent bonds but the decrease in overlapping is much less than in cylopropane. It is therefore more stable than cyclopropane.

Thus according to Coulson and Moffit's concept, the decrease in the stability of a ring compound is due to relatively poor overlapping of atomic orbitals in the formation of carbon-carbon bonds in cyclopropane and cyclobutane.

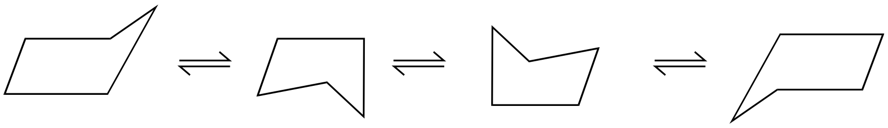
1.6.4 Conformational Analysis of Alicylic Compounds

Study of the preferred conformation of a compound and correlating it with the physical and chemical properties of the preferred conformation of the compounds is known as **Conformational Analysis**. In simple alicyclic compounds, due to distortion of valency angle (Baeyer's strain), the molecule tends to take up non-planar configuration forming **strainless rings**. Apart from Baeyer's strain there exist other types of strain in the molecule. Thus in cyclopropane every hydrogen atom is almost in contact with the neighbouring hydrogen atoms thus producing strain due to mutual repulsion of three pairs of hydrogen atoms. This strain associated with partial or complete eclipsing of neighbouring atoms is called **eclipsing strain**.

In cyclobutane apart from Baeyer's angle strain and eclipsing strain due to mutual repulsion of four pairs of eclipsing hydrogen atoms, there is an additional strain due to *non-bonded interactions* (bond-opposition strain) between first and fourth carbon atoms which are only 2.2 Å away from each other. The theoretical value of all these strains together is much greater than the experimental value of strains determined thermodynamically. Therefore it is suggested that one of the carbon atoms of cyclobutane is twisted out of plane to reduce the actual strain in the molecule. This strain which twists one or more atoms of the ring out of plane is termed as **torsional strain** or **Pitzer strain**.

Similarly in cyclopentane, though the Baeyer's angle strain is very small yet the molecule acquires strainless '*envelope*' type conformation which is flexible. This is due to the large Pitzer torsional strain because of mutual repulsion of five pairs of eclipsing hydrogen and bond-opposition strain for non-bonded carbon atoms.It is obvious that by acquiring puckered state more stability is achieved due to staggering of hydrogen atoms than is lost through increasing angle strain.

The individual carbon atoms of the ring move up and down to the average plane of the ring in a manner which results in continuous change in the out of plane carbon giving it a wave like appearance.



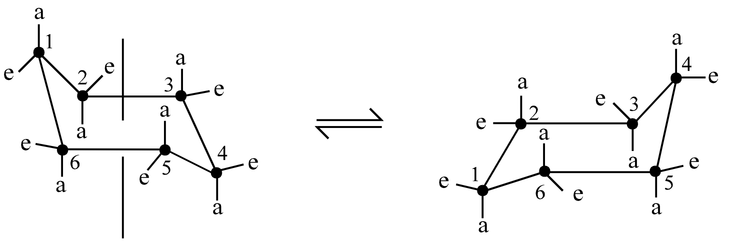
Conformation of Cyclohexane

Sachse in 1890 suggested that cyclohexane ring exists in two nonplanar forms *i.e.* boat and chair conformations. The energy difference between the two forms was found to be only 5.6 kcal/mole by Pitzer. This energy barrier is too small to prevent their interconversion. Therefore it is not possible to resolve them.

NOTES

By electron diffraction studies Hassel in 1943 demonstrated that at room temperature most of the molecules of cyclohexane exist in chair conformation. This was to be expected as the boat form has greater energy content. In the chair form all the C—H bonds on adjacent carbon atoms are in *skew* position while in the boat form only four of them are in skew position and two in *eclipsed* position. These eclipsed interactions are responsible for higher energy of the boat form. Bowspirit-flagpole interactions (*f-f*) and eclipsed interactions (*x-x*) (*y-y*) are shown here in boat form:

However, in the chair conformation all the twelve hydrogens are not equivalent. If a line is drawn through the centre of the cyclohexane chair then it will be found that six C—H bonds are parallel to this line and six C—H bonds are directed outwards away from this line, as shown in the figure below. The former are known as *axial* (*a*) bonds while latter are known as *equatorial* (*e*) bonds. It should be noted that all bond angles are 109.5° and the axial bonds on adjacent atoms, though parallel to the line drawn through centre, are directed in opposite direction, *i.e.*, upwards and downwards. The chair conformation is sufficiently flexible to turn itself upside down so that all bonds which were axial orginally become equatorial and *vice versa*.



Interconversion of the two chair forms of cyclohexane
(a = axial bond; e = equatorial bond)

The potential energy curve of cyclohexane as a function of conformations of cyclohexane is shown in Fig. 1.32.

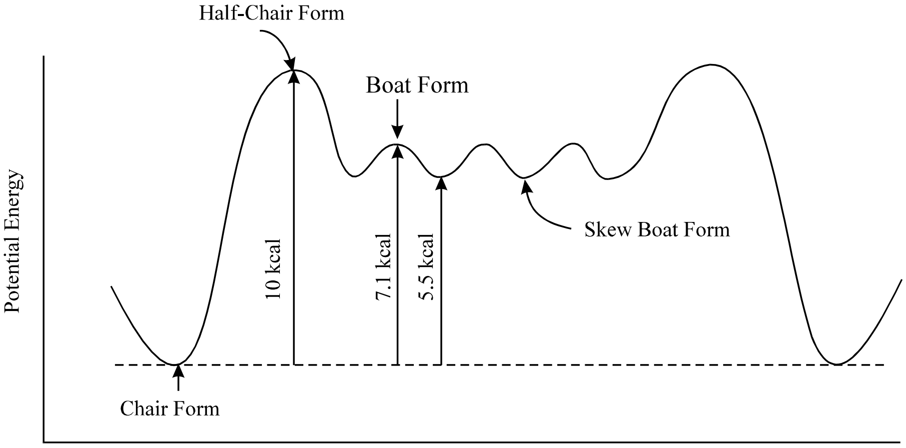
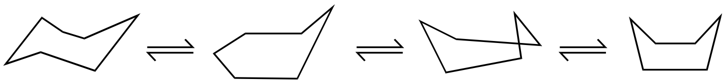


***Fig. 1.32** Interconversion of Conformations of Cyclohexane*

As can be seen the chair form is the most stable one. It is due to the fact that there is neither the angle strain nor the bond opposition or eclipsing strain. If the chair form is to be converted to boat form, some angular distortion is required because several bonds have to be rotated and the molecule passes through the highest energy state corresponding to half-chair form (*i.e.*, an energy barrier of approximately 10 kcal/mole), then through skew boat form and finally acquires the boat form.

The energy difference between the chair and boat form is high enough so that these conformations are capable of existing but not high enough to prevent their interconversion at room temperature. Hence they are not separable.

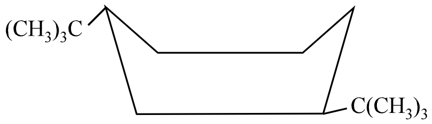
In the boat form also there is no angle strain but there is bond opposition or eclipsing strain of four pairs of hydrogen of bottom carbon atoms and also strain due to interaction of pairs of hydrogen at the top carbon atoms known as **bowspirit flagpole** interaction.



Chair form Half-chair form Skew boat form Boat form

As a result almost 99.9% of cyclohexane molecules exist in chair conformation under normal conditions. However, there are some molecules in which cyclohexane ring exists in boat form. For example, [2.2.2] Bicyclooctane must exist in boat form due to structural requirement.

Similarly, *trans*-1,3-*di*-*t*-butylcyclo-hexane exists in boat form because if this molecule takes up chair conformation there would be very high interaction between axial *t*-butyl group and axial hydrogen atoms.

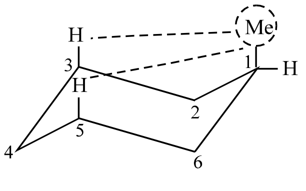


trans-1, 3-*di*-*t*-Butylcyclohexane

Monosubstituted Cyclohexanes

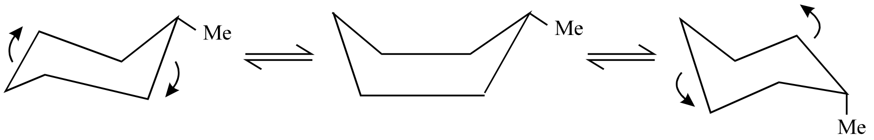
As pointed out earlier most molecules in cyclohexane exist in chair conformtion. In the chair conformation of cyclohexane each and every carbon has two kinds of bonds, those parallel to an axis drawn through the ring pointing in upward and downward direction on alternate carbon atoms known as 'axial' or 'a' bonds and those pointing sideways (one on each carbon) known as equatorial or '*e*' bond (Barton, Hassel and Pitzer (1953) nomenclature).

It has been found that any group other than hydrogen in axial position interacts with other axial hydrogen atoms (non-bonded repulsions) on the third carbon atom as shown here (axial-axial interaction).



The interactions are minimum when the substituent group is in equatorial position. Thus the energy of the conformation having a substituent in equatorial position is much lower than the conformation having the same group in axial position.

If we consider methylcyclohexane, theoretically two isomeric chair forms are possible—one in which the methyl substituent is in equatorial position and the other in which the methyl substituent is in axial position. The situation is further complicated because of the fact that equatorially substituted chair conformation can readily converts itself into a flexible form and then to another chair conformation in which the same substituent now becomes axial.



Interconversion of chair conformation of methylcyclohexane via flexible boat form

The axial conformer has two interactions (axial-axial) with non-bonded hydrogen (as in gauche form of butane). No such interactions are there in equatorial conformer and the energy difference between the two forms is around 1.8 kcal/mole. Hence about 95% of the molecules in methylcyclohexane exist in equatorial conformation at room temperature but can be frozen out as distinct separate entities at –78°C.

If there are more than one substituents then that chair conformation is the preferred form which has maximum number of equatorial substituents. These stability trends of substituted cyclohexanes can actually be verified by the study of acidities of the alicyclic dicarboxylic acids.

Transannular Strain

The higher heats of combustion of medium size (8 to 13 membered) alicyclic compounds and the difficulties in their formation is attributed to a non-classical *transannular strain.* In these alicyclic compounds hydrogens situated on the opposite sides of the ring are very close and their mutual repulsion leads to transannular interaction strain. This strain may lead to change in the bond angles and may also result in a number of unusual reactions where a positive carbocation centre (formed during the reaction) may migrate to another carbon atom which may be remote along the carbon chain but close in space to it.

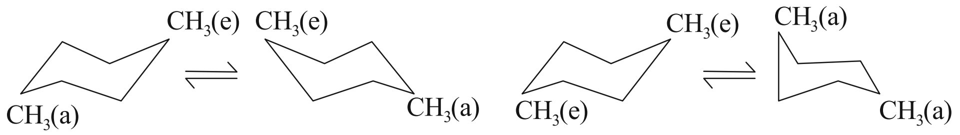
Disubstituted Cyclohexanes

In the chair form of cyclohexane the substituents prefer to occupy the less sterically hindered equatorial position. In di- or poly- substituted cyclohexanes all the substituents may or may not occupy equatorial position in every isomer but that isomer is usually more stable in which all or most substituents occupy equatorial positions.

NOTES

1, 4-Dimethyl cyclohexane exists in two stereoisomeric forms *cis*- and *trans*- each of which can have two conformations:

cis-isomer *trans-isomer*

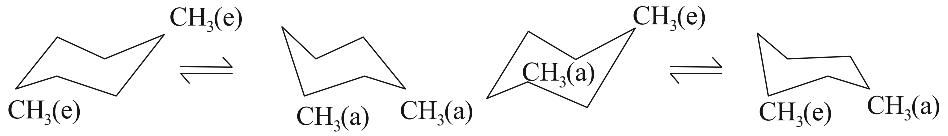


	cis- (e,a)	*cis*- (a,e)	*trans*- (e,e)	*trans*- (a,a)
Strain Energy	1.8 kcal	1.8 kcal	0 kcal	3.6 kcal

The order of their stability is: *trans*- (e,e) > *cis*- (e,a) ° *cis*- (a,e) > *trans*- (a,a)

1, 3-Dimethylcyclohexane. Its stereoisomers and conformations are:

cis-isomer *trans-isomer*

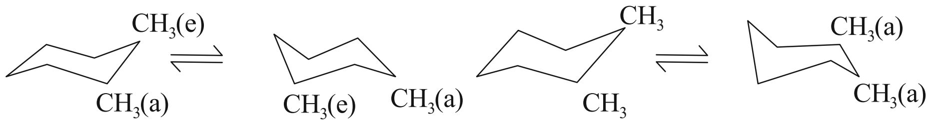


	cis- (e,e)	*cis*- (a,a)	*trans*- (e,a)	*trans*- (a,e)
Strain Energy	0 kcal	> 3.6 kcal	1.8 kcal	1.8 kcal

The order of their stability is: *cis*- (e,e) > *trans*- (e,a) ° *trans*- (a,e) > *cis*- (a,a)

1, 2-Dimethylcyclohexane. Stereoisomers and conformations are:

cis-isomer *trans-isomer*



	cis- (e,a)	*cis*- (a,e)	*trans*- (e,e)	*trans*- (a,a)
Strain Energy	1.8 kcal	1.8 kcal	0 kcal	3.6 kcal

The order of their stability is: *trans*- (e,e) > *cis*- (e,a) ° *cis*- (a,e) > *trans*- (a,a)

The conformational energy (or strain energy) of a conformation is the energy difference between molecules with a substituent in axial and equatorial positions.

In case the two substituents are different, then the conformation in which the group with higher conformational energy occupies the equatorial position is generally more stable. It may be noted that conformational energy is not dependent simply on the size but effective volume and presence of charge also play an important role in deciding it.

Configuration and Conformation

The term "Configuration" refers to the arrangement of groups or atoms in space around dissymmetric (or asymmetric) part of the molecule. Thus compounds with one asymmetric carbon atom *e.g.* lactic acid have two different configurations which are distinguished by difference in specific rotation. Configuration therefore refers to spatial molecular structure and is represented by a three-dimensional or projection formula. Even the geometrical isomers differ in configuration or arrangement of groups in space around the double bond or ring.

On the other hand term 'Conformation' or 'Conformer' is used to indicate the momentary arrangements of atoms or groups in space which result from the rotation about single bond whether these conformers are capable of independent existence or not. The energy difference between the conformation of simple componds is not large enough to allow them to exist independently.

Two or more isomers of an optically active compund or geometrical isomerism, exhibiting compound have differences in the arrangement of atoms or groups (known as configuration of each isomer) which cannot be interconverted into each other without breaking one or several bonds. Thus configurations cannot be converted into each other without breaking bonds. *d*-Lactic acid cannot be converted to *l*-lactic acid by rotating the molecule around or as a result of free rotation around single bond. Similarly *cis*-butene cannot be converted to *trans*-butene simply by rotation without breaking the bond.

On the other hand conformations are formed as a result of rotation around single bond. As there is some hindrance to rotation due to generally present non-bonded interaction, each of these momentary arrangement (conformation) has its own property differing in dipole moment, potential energy and other thermodynamic properties.

1.6.5 Conformation of Sugars

Sugar is the generic name for sweet-tasting soluble carbohydrates used in food. Simple sugars, also called monosaccharides, include glucose, fructose, and galactose. Compound sugars, also called disaccharides or double sugars, are molecules made of two monosaccharides joined by a glycosidic bond.

Carbohydrate conformation defines the overall three-dimensional structure adopted by a carbohydrate (saccharide) molecule formed as a result of the through-bond and through-space physical forces which it experiences occurring from its molecular structure. The physical forces that determine the three-dimensional shapes of the molecules of all monosaccharide molecules, oligosaccharide molecules and polysaccharide molecules are also defined using the terms 'Steric Interactions' and 'Stereoelectronic Effects'.

Saccharide and other chemical conformations can be represented using two-dimensional structure representations that follow set conventions and rules. Characteristically, conformation can be defined by means of description of a molecule's angles, for example sets of three sequential atoms (bond angles) and four sequential atoms (torsion angles, dihedral angles), where the locations and angular directions of nonbonding electrons, the 'Lone Pair Electrons' are also considered.

Conformations adopted by saccharide molecules in response to the physical forces arising from their bonding and nonbonding electrons, modified by the molecule's interactions with its aqueous or other solvent environment, strongly influence their reactivity with and recognition by other molecules. Chemical transformations and biological signalling mediated by conformation dependent molecular recognition between molecules trigger all essential processes in living organisms.

Monosaccharide Conformation

Pyranose and furanose forms can exist in different conformers and the different conformations can be interconverted if an energy requirement is fulfilled. For the furanose system there are two possible conformers, namely Twist (T) and Envelope (E). In the pyranose system, five conformers are possible, namely Chair (C), Boat (B), Skew (S), Half-Chair (H) or Envelope (E). In all conditions, there are four or more atoms that make up a plane. To define which atoms should be above and below the plane, the molecule must be oriented so that the atoms are numbered clockwise while observing from the top. Atoms above the plane are prefixed as a superscript and atoms below the plane are suffixed as a subscript. If the ring oxygen is above or below the plane, then it must be prefixed or suffixed appropriately.

Conformational Analysis

The chair conformation of six-membered rings has a dihedral angle of 60° between the adjacent substituents, therefore, typically making it the most stable conformer. Since there are two possible chair conformations, namely the steric effect and the stereoelectronic effect, such as the anomeric effect, 1,3-diaxial interactions, dipoles and intramolecular hydrogen bonding must be taken into consideration while considering the relative energies. Conformations with 1,3-diaxial interactions are normally not favoured because of steric congestion and can shift equilibrium to the other chair form, for example ${}^{1}C_{4}$ to ${}^{4}C_{1}$. The size of the substituents significantly affects this equilibrium. However, intramolecular hydrogen bonding can be an example of a stabilizing 1,3-diaxial interaction. Dipoles also play a role in conformer stability, aligned dipoles lead to an increase in energy while opposed dipoles lead to a lowering of energy hence a stabilizing effect, this can be complicated by solvent effects. Polar solvents tend to stabilize aligned dipoles. All interaction must be considered while determining a preferred conformation.

Conformations of five-membered rings are limited to two types, namely Envelope (E) and Twist (T). The Envelope (E) conformation has four atoms in a plane while the twist form only has three. In the Envelope (E) form, two different scenarios can be noticed, one where the ring oxygen is in the four atom plane and the other where it is puckered above or below the plane. When the ring oxygen is not in the plane the substituents eclipse and when it is in the plane torsional strain is relieved. Conformational analysis for the twist form is similar thus leading to the two forms being very close in energy.

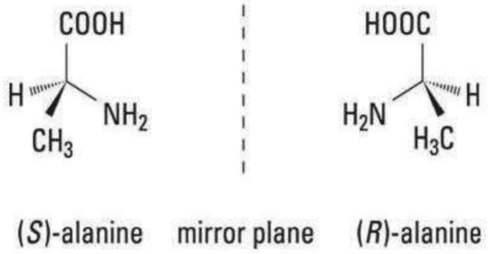
Steric strain

It is an increase in a molecule's potential energy induced by van der Waals repulsions that cannot be lessened by rotating around a single bond. Steric strain is common in alkenes and ring systems.

1.6.6 Stereochemistry of the Compounds Containing Nitrogen, Sulphur and Phosphorus

Chirality is a geometric property of some molecules and ions. A chiral molecule/ ion is non-superposable on its mirror image. The presence of an asymmetric carbon center is one of several structural features that induce chirality in organic and inorganic molecules. The term chirality is derived from the Ancient Greek word for hand.

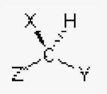
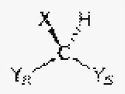
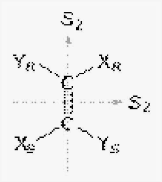
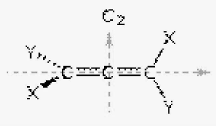
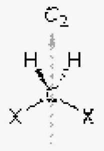
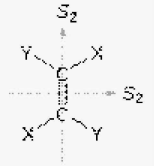
The mirror images of a chiral molecule or ion are called enantiomers or optical isomers. Individual enantiomers are often designated as either right-handed or left-handed. Chirality is an essential consideration when discussing the stereochemistry in organic and inorganic chemistry. The concept is of great practical importance because most biomolecules and pharmaceuticals are chiral. Chiral molecules and ions are described by various ways of designating their absolute configuration, which codify either the entity's geometry or its ability to rotate plane-polarized light. Following example illustrates chirality of (*S*)-Alanine (left) and (*R*)-Alanine (right).



Chirality is based on molecular symmetry elements. Specifically, a chiral compound can contain no improper axis of rotation (S_n), which includes planes of symmetry and inversion center. Chiral molecules are always dissymmetric (lacking S_n) but not always asymmetric (lacking all symmetry elements except the trivial identity). Asymmetric molecules are always chiral.

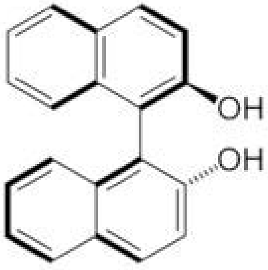
Following Table 1.4 illustrates the molecular symmetry and chirality.

Table 1.4 *Molecular Symmetry and Chirality*

Rotational Axis (C_n)	**Improper Rotational Elements (S_n)**		
	Chiral No S_n	**Achiral** Mirror Plane $S_1 = \sigma$	**Achiral** Inversion Centre $S_2 = i$
C_1			
C_2			

Stereogenic Centers

In general, chiral molecules have **point chirality** at a single *stereogenic* atom, which has four different substituents. The two enantiomers of such compounds are said to have different **absolute configurations** at this center. This center is thus stereogenic, i.e., a grouping within a molecular entity that may be considered a focus of stereoisomerism. The stereogenic atom, also known as the *stereocenter*, is usually carbon. However a stereocenter can coincide with any atom, including metals, as in many chiral coordination compounds, phosphorus or sulfur. The low barrier of nitrogen inversion make most *N*-chiral amines (NRR2 R3) impossible to resolve, but *P*-chiral phosphines (PRR2 R3) as well as S-chiral sulfoxides (OSRR2) are optically stable. Following is the example of 1,12 -Bi-2-Naphthol of a molecule lacking point chirality.



The presence of a stereogenic atom describes the chiral molecules, though many variations and exceptions exist. For example, it is not necessary for the chiral substance to have a stereogenic atom, such as 1-bromo-3-chloro-5-fluoroadamantane, methylethylphenyltetrahedrane, certain calixarenes and fullerenes, which have inherent chirality. The C_2-symmetric species 1,12 -bi-2-naphthol (BINOL), 1,3-dichloroallene have axial chirality. (*E*)-cyclooctene and many ferrocenes have planar chirality.

When the optical rotation for an enantiomer is too low for practical measurement, the species is said to exhibit cryptochirality.

Even isotopic differences must be considered when examining chirality. The derivative of benzyl alcohol PhCHDOH is chiral.

The *S* enantiomer has $[a]_D = +0.715°$.

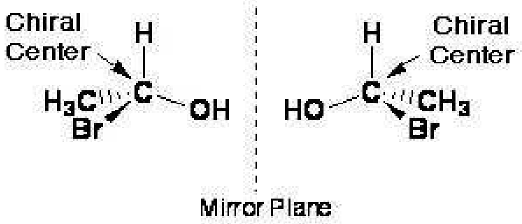
Chirality is a symmetry property, not a characteristic of any part of the periodic table. Thus many inorganic materials, molecules, and ions are chiral. In the coordination chemistry and organometallic chemistry, chirality is pervasive and of practical importance. The example is tris(bipyridine)ruthenium(II) complex in which the three bipyridine ligands adopt a chiral propeller-like arrangement. The two enantiomers of complexes, such as $[Ru\ (2,22\ \text{-bipyridine})_3]^{2+}$ may be designated as Ë (capital lambda, the Greek version of 'L') for a left-handed twist of the propeller described by the ligands, and Ä (capital delta, Greek 'D') for a right-handed twist. Also referred as dextro- and levo- (laevo-).

The term, optical activity, is derived from the interaction of chiral materials with polarized light. In a solution, the (") form, or levorotatory form, of an optical isomer rotates the plane of a beam of linearly polarized light counter-clockwise. The (+) form, or dextrorotatory form, of an optical isomer does the opposite. The rotation of light is measured using a polarimeter and is expressed as the optical rotation.

Chiral Centre

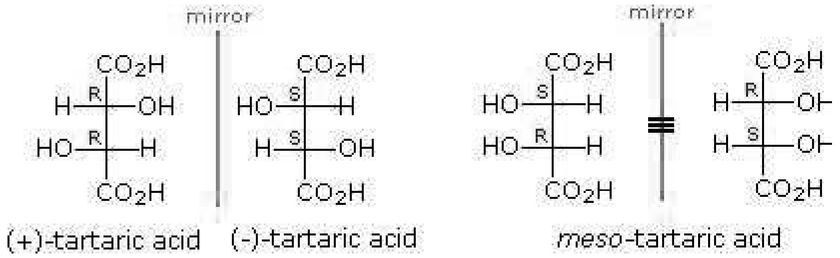
A **chiral centre** is an atom that has four different groups bonded to it in such a manner that it has a non-superimposable mirror image. The term 'Chiral Centre' is also sometimes expressed by the term **chirality centre**.

In the molecule shown below, the carbon atom is a chiral centre or chirality centre. It has four different groups attached, and the two structures are non-superimposable mirror images of each other.



Molecules with a single chirality centre or with more than one chirality centre are termed as 'chiral'. The exceptions are *meso* compounds. For example, tartaric acid has two chirality centres, so it is expected to have $2^2 = 4$ stereoisomers.

NOTES

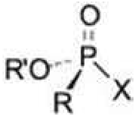


But there are only three isomers. The (S, R) and (R, S) isomers are a single *meso* compound because they are superimposable on each other. They are achiral because they have an internal plane of symmetry. The most common chirality centres in organic molecules are sp^3 hybridized carbon atoms, because they can form four bonds.

Following are some more types of chirality centre:

Quaternary N Atoms

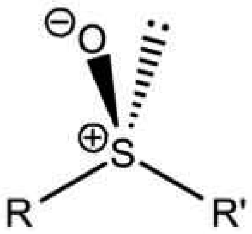
Tetravalent P Atoms



The above chiral tetravalent P atom displays the absolute configuration of the most active nerve agent stereoisomers for AChE inhibition. Many nerve gases contain chiral P atoms.

Sulfoxides

In sulfoxides, the fourth group is a lone pair. Unlike in amines, the energy required to invert this stereocentre is high, so sulfoxides are optically stable.



Principally, the following Cahn-Ingold-Prelog sequence rules assign priorities to the groups that are attached to each chiral centre:

- The atom with higher atomic number receives higher priority.
- If there is a tie, we go one bond further out until we come to the earliest difference.
- If there is still a tie, we keep going further out until we find a difference.

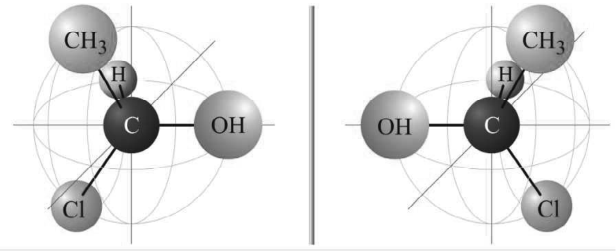
- Double and triple bonds are treated as if they were separate single bonds to the same atom.

Finding Chirality Centers

Chirality means a molecule that is mirrored and would not be superimposable. Typically, a chiral molecule can usually be found if there is no plane of symmetry. The most simple and common example is our hands. They are mirror images but one cannot be put onto the other such that they would appear the same. Same is applicable to molecules. First determine a specific atom whether it be a carbon or other, where there are four different substituents bonded to the atom.

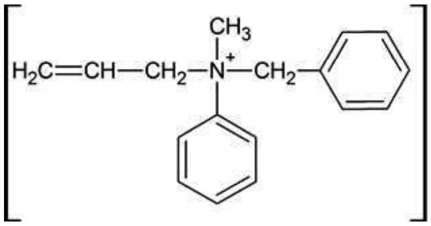
Chiral molecule is, therefore, a molecule which cannot be superimposed on its mirror image. A common example is an organic molecule containing a carbon atom to which four different atoms or groups are attached. Such molecules exhibit optical activity, i.e., they rotate the plane of a polarised light beam.

Following image illustrates four different substituents that are bonded to a chirality center.

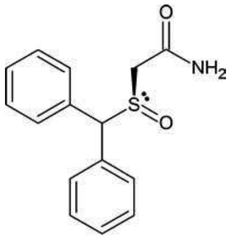


A carbon with four different groups results in a chiral molecule and is referred to as a chiral or asymmetric or stereogenic center.

The example given below shows a resolvable compound containing a chiral nitrogen atom. It was resolved by William Pope and Stanley Peachey in 1899. It had the structure shown below.



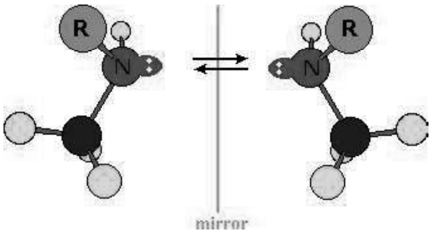
Chiral sulfoxides are used in certain drugs, such as esomeprazole and armodafinil, which exhibit the feature of a stereogenic sulfur center, as shown below.



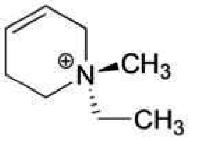
armodafinil

Stereogenic Nitrogen

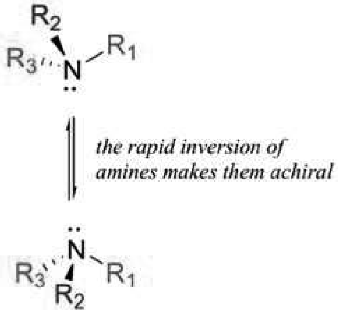
Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram, in which the remainder of the molecule is represented by R. If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. It rapidly inverts its configuration, as represented through equilibrium arrows, by passing through a planar, sp^2-hybridized transition state, leading to a mixture of interconverting R and S configurations. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of R and S configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. Hence, the nitrogen does not contribute to isolable stereoisomers.



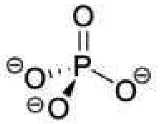
Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



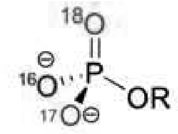
a chiral quaternary ammonium



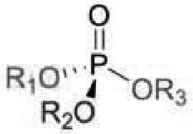
The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter, as shown below.



phosphate (achiral)



labeled phosphate ester (chiral)

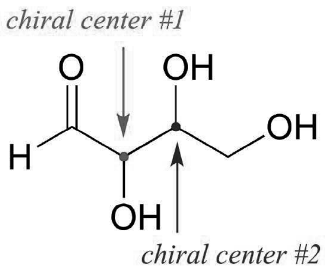


a chiral phosphate triester

In the stereochemistry of reactions at the phosphate center, the incorporated sulfur and/or ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

1.6.7 Compounds with Multiple Chiral Centers

We have discussed about compounds with a single chiral center. Now let us understand about those compounds which have multiple chiral centers. Following is the stereoisomeric four-carbon sugars with two chiral centers.

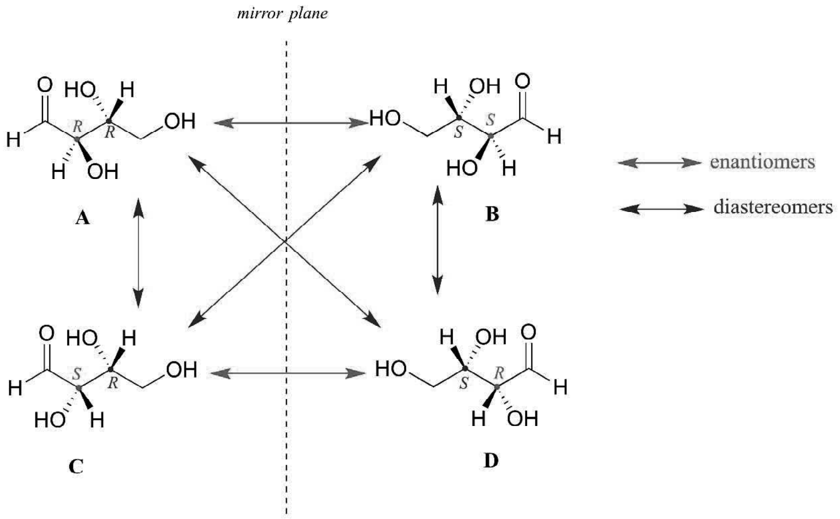


In the following example, in Compound A both chiral centers have the *R* configuration. The mirror image of Compound A is Compound B, which has the *S* configuration at both chiral centers. If we flip the Compound A and put it next to Compound B then it shows that they are not superimposable. Both the Compounds A and B are non-superimposable mirror images, i.e., enantiomers.

In the Compound C, the configuration is 'S' at chiral center 1 and 'R' at chiral center 2. Compounds A and C are stereoisomers since they have the same molecular formula and the same bond connectivity, but a different arrangement of atoms in space, as per the definition of the stereoisomer. Because they are not mirror images of each other and hence they are not enantiomers. By definition, they are diastereomers of each other.

Both the Compounds C and B also have a diastereomeric relationship, according to the same definition.

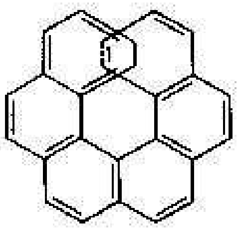
Therefore, the Compounds A and B are a pair of enantiomers, and Compound C is a diastereomer of both of them. Additionally the Compound D is the mirror image of Compound C, and the two are not superimposable. Therefore, C and D are a pair of enantiomers. Compound D is also a diastereomer of Compounds A and B.



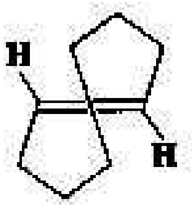
1.6.8 Chirality Due to Helical Shape

A **chiral** molecule is one that is not superimposable on its mirror image. Molecules that are **helices** can be right-handed or left-handed and are therefore non-superimposable on their mirror image. The molecule does not have a complete turn of the helix to be chiral.

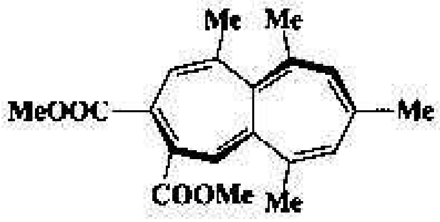
Hexahelicene is chiral because one side of the molecule must lie above the other owing to crowding of the rings. The hexahelicene, a spiral molecule is shown below.



In trans-cyclooctene the carbon chain must lie above the double bond on one side and below it on the other, this leading to chirality. The trans-cyclooctene is shown below.



Heptalene has two fused 7-membered rings and is not flat. Its twisted structure makes it chiral, but heptalene itself cannot be resolved because the two forms rapidly interconvert. Huge substituents slow this process, however, in the case of the molecule shown below the two enantiomers have been isolated, i.e., a resolvable heptalene derivative.



Check Your Progress

6. What is stereomesrism?
7. Write the properties of geometrical isomers.
8. Define the term 'waldon inversion'.
9. On what is chirality based ?
10. Define chiral centre.

1.7 ANSWERS TO 'CHECK YOUR PROGRESS'

1. If the single and double bonds are present alternately in a molecule, it is said to contain double bonds in conjugation and the molecule is called a conjugated molecule**.**
2. Cross conjugation is a special type of conjugation in a molecule. Here out of a set of three π bonds only two interact with each other by conjugation while the third one is excluded from interaction. A cross conjugated system has a double bonded unit single bonded to one of the middle atoms of another conjugated chain.
3. Fulvene is one of several hydrocarbons with the same formula as benzene, C_6H_6. The fulvenes are the class of molecules based on this simple hydrocarbon frame, the parent chemical, fulvene itself, is rarely encountered.
4. Fullerenes are a family of carbon compounds having at least 60 carbon atoms forming carbon spheres, where carbon atoms are arranged in semi-regular polyhedra distributed over the sphere.
5. Tautomers are isomers of a compound, which diffes only in the position of the protons and electron. The carbon skeleton of the compound is unchanged but tunctional groups are different. A reaction which involves simple proton transfer in an intra molecular fashion is called a tautomerism keto-enol. tautomerism is very common.
6. Compounds having the same atoms or groups with a different spatial arrangement are called stereoisomers. This type of isomerism is called stereoisomerism and is of two kinds: (A) Geometrical Isomerism and (B) Optical Isomerism.
7. Properties of geometrical isomers. The geometrical isomers are generally two different compounds having appreciable difference in their physical and chemical properties—though the differences in the latter are few. Thus *cis*-isomer, in general have lower m.p. and higher values for density, refractive index, dipole moment, etc., as compared to *trans*-isomers.
8. The term Walden inversion or optical inversion is applied to any step of a reaction in which the inversion of configuraton occurs.
9. Chirality is based on molecular symmetry elements.
10. A chiral centre is an atom that has four different groups bonded to it in such a manner that it has a non-superimposable mirror image. The term 'Chiral Centre' is also sometimes expressed by the term chirality centre.

1.8 SUMMARY

- Concepts like resonance, hybridization of atomic orbitals, orbital box diagrams for electronic configurations are a consequence of the valence bond theory.
- When the centres of electron density are on the axis common to the nuclei or the overlapping is coaxial the orbital is known as s (sigma).

- The M.O. formed by sideways overlapping, having only one nodal plane along the nuclear axis, is known as p (pi) orbital.
- 2*s* and 2*p* orbitals of carbon in the excited state undergo a process of mixing up and redistribution to form new orbitals of equivalent energy. This concept is known as Hybridization and the resultant new orbitals are called Hybridized orbitals.
- When bonds are formed energy is reduced, consequently the energy required to break a bond into its constituents is referred to as Bond energy and is a measure of Bond strength. The greater the energy required to break a bond, the greater will be its strength.
- The bond energy for sigma bond is more than that of a pi bond.
- The measure of the tendency of chemically bonded atom to attract electrons is known as electronegativity.
- Induction of polarity or dipole, in an otherwise non-polar bond, and consequent electron shift along a chain of atoms is known as inductive effect.
- Inductomeric effect is a temporary effect and brought into play only in the presence of charged attacking reagent. However this does not have an important role in organic reactions except in assisting the displacement of electrons in inductive effect.
- The effect involving the complete transfer of a shared pair of electrons to one of the atoms joined by a double or triple bond at the requirement of attacking reagent, is known as electromeric effect.
- If the single and double bonds are present alternately in a molecule, it is said to contain double bonds in conjugation and the molecule is called a conjugated molecule.
- Erythro and threo system of specifying configuration originated from tetraldoses erythrose and threose which are diastereoisomers.
- Fulvene is one of several hydrocarbons with the same formula as benzene, C_6H_6. The fulvenes are the class of molecules based on this simple hydrocarbon frame, the parent chemical, fulvene itself, is rarely encountered.

1.9 KEY TERMS

- **Resonance:** Resonance or mesomerism is a way of describing delocalized electrons within certain molecules or polyatomic ions where the bonding cannot be expressed by one single Lewis structure**.**
- **Hydrogen bond:** It is a weak bond between two molecules resulting from an electrostatic attraction between a proton in one molecule and an electronegative atom in the other.
- **Hybridization:** Orbital hybridization is the concept of mixing atomic orbitals into new hybrid orbitals suitable for the pairing of electrons to form chemical bonds in valence bond theory.

- **Aromaticity:** The term aromaticity is used to describe a cyclic, planar molecule with a ring of resonance bonds that exhibits more stability than other geometric or connective arrangements with the same set of atoms.
- **Benzenoid:** To refers to a class having the six-membered ring structure or aromatic properties of benzene.
- **Non-benzenoid:** Non-benzenoid aromatic compound are chemical compounds with conjugated pi-electron system with ring of 5 to 7 carbon atoms. They exhibit aromaticity due to alternate pi-bonds in the molecule.
- **Alternant hydrocarbons:** A member of a class of conjugated molecules whose carbon atoms can be divided into two sets so that members of one set are formally bonded only to members of the other set.
- **Stereochemistry:** Stereochemistry is defined as a sub-discipline of chemistry which involves the study of the relative spatial arrangement of atoms that together forms the structure of molecules and their manipulation.
- **Isomerism:** The compounds having same molecular formula but different physical characteristics or chemical properties are known as isomers and this phenomenon is known as isomerism.
- **Torsional strain:** The stains which twists one or more atoms of the ring out of plane is termed as torsional strain.
- **Configuration:** The term configuration refers to the arrangement of groups or atoms in space around dis-symmetric part of molecule.
- **Functional isomerism:** Isomerism exhibited by compounds differing in functional groups is known as functional isomerism.
- **Configurational isomers:** To convert one configurational isomer to another, a bond must be broken and reformed.

1.10 SELF ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. Write the conditions and rules for resonance.
2. What is the effect of resonance on electron displacement?
3. What are the types of fullerenes?
4. Draw the orbital picture of hyperconjugation.
5. Write a short note on static stain theory.
6. What do you understand by conformational analysis of cycloalkanes?
7. Mention compounds with one asymmetric carbon atom.

Long-Answer Questions

1. Analyze aromaticity in benzenoid and non-benzenoid compounds.
2. Describe energy level of π-molecular orbitals with diagrams.

3. Explain the PMO approach for aromaticity.
4. Discuss Hukels, rule.
5. Discuss stereochemistry, isomerism and its types in detail.
6. Explain structural isomerism and its types in detail.

1.11 FURTHER READING

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UNIT 2 REACTION MECHANISM: STRUCTURE AND REACTIVITY

NOTES

Structure

2.0 INTRODUCTION

The basic organic chemistry reaction types are addition reactions, elimination reactions, substitution reactions, pericyclic reactions, rearrangement reactions, photochemical reactions and redox reactions. In organic synthesis, organic reactions are used in the construction of new organic molecules. The production of many man-made chemicals such as drugs, plastics, food additives, fabrics depend on organic reactions.

Chemical kinetics, also known as reaction kinetics, is the study of rates of chemical processes. Chemical kinetics includes investigations of how different experimental conditions can influence the speed of a chemical reaction and yield information about the reaction's mechanism and transition states, as well as the construction of mathematical models that can describe the characteristics of a chemical reaction.

Radical, also called Free Radical, in chemistry, molecule that contains at least one unpaired electron. Most molecules contain even numbers of electrons, and the covalent chemical bonds holding the atoms together within a molecule normally consist of pairs of electrons jointly shared by the atoms linked by the bond. Most radicals may be considered to have arisen by cleavage of normal electron-pair bonds, every cleavage having produced two separate entities, each of which contains a single, unpaired electron from the broken bond (in addition to all the rest of the normal, paired electrons of the atoms).

Radicals are important in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes. A large fraction of natural products is generated by radical-generating enzymes. In living organisms, the radicals superoxide and nitric oxide and their reaction products regulate many processes, such as control of vascular tone and thus blood pressure. They also play a key role in the intermediary metabolism of various biological compounds. Such radicals can even be messengers in a process dubbed redox signaling. A radical may be trapped within a solvent cage or be otherwise bound. Radical chain reactions play an important part in organic chemistry both as radical substitution and radical addition reactions. Radical addition chain reactions, for instance, may be found in radical polymerization.

In this unit, you will study about reaction mechanism, structure and reactivity, types of mechanisms, types of reactions, thermodynamic and kinetic requirements, Hammond's postulate, Curtin-Hammett principle, potential energy diagrams, carbocations, carbanions, free radicals, carbenes and nitrenes, resonance and field effects, steric effect, quantitative treatment, Hammett equation and linear free energy relationship, substituent and reaction constants, Taft equation, free radical reactions, neighbouring group assistance, reactivity for aliphatic and aromatic substrates at a bridgehead, allylic halogenation (NBS), oxidation of aldehydes to carboxylic acids, auto-oxidation, coupling of alkyenes and arylation of aromatic compounds by diazonimum salts, Sandmeyer reaction,free redical rearrangement and Hunsdiecker reaction.

2.1 OBJECTIVES

After going through this unit, you will be able to:

- Explain types of mechanisms, and types of reactions
- Understand thermodynamic and kinetic requirements
- Describe generation, structure, stability and reactivity of carbocations, carbanions, free radicals, carbenes and nitrenes
- Discuss the effect of structure on reactivity
- Explain free radical reactions, and rearrangement

- Understand the reactivity for aliphatic and aromatic substrates at a bridgehead
- Discuss allylic halogenation (NBS) and oxidation of aldehydes to carboxylic acids

2.2 TYPES OF REACTIONS

All the organic reactions can be broadly classified into the following five types:

1. Substitution Reactions
2. Addition Reactions
3. Elimination Reactions
4. Molecular Reamangement Reaction
5. Molecular Reaction

Let us study them in detail.

1. **Substitution Reactions:** A substitution reaction is that which involves the direct replacement or displacement or substitution of an atom or a group of atoms in an organic molecule by another atom or group of atoms without any change in the remaining part of the molecule.

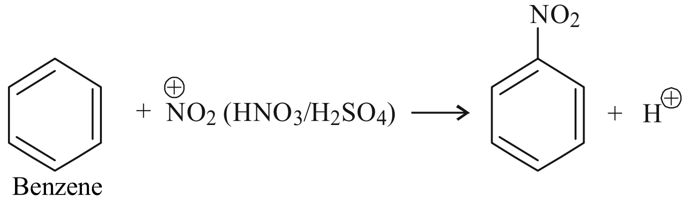
   Example:

   $C_2H_5Br + KOH_{(Aac)} \rightarrow C_2H_5OH + KBr$

   Depending upon the nature of the substituents the substitution reactions are of three types:

   (i) Nucleophilic substitution reaction: Substitution reactions brought about by nucleophiles are called nucleophilic substitution reactions. For example alkyl halide have C – X bond Due to high electronegativity of helogen atom the bond is polarised as $\overset{\delta+}{C}-\overset{-\delta}{C}$ and carbon atom acquires partial positive change. The nucleophile (negative ion) attack this carbon and brings about the substitution reaction.

   (ii) Electrophilic substitution reactions: Substitution reactions brought about by electrophiles are called electrophilic substitution reactions. These are characterisitc reactions of benzene and other aromatic compounds due to electron richness of the benzene ling.



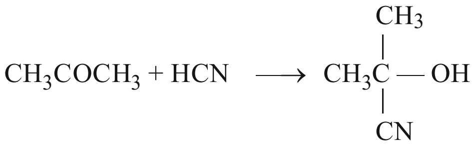
   (iii) Free-radical substitution reactions: Substitution reactions brought about by free radicals are called free radical substitution reactions. Free radical substitution reactions are given by alkanes for example, chlorine react with methane in the presence of diffused sunlight.

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \xrightarrow[\text{homolytic fussuin}]{h\nu} 2\,\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: \quad \text{(Chlorine free radicals)}$$

NOTES

$$CH_4 + 2:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} \longrightarrow \underset{\text{methyl chloride}}{CH_3Cl + HCl}$$

2. **Addition Reactions:** An addition reaction is that which involves the combination between the reaction and substrate molecules leading to the formation of a single compounds. Depending upon the nature of the reagent addition reactions are also of the following three types:
   (i) **Nucleophilic Addition Reactions:** Addition reaction brought about by nucleophiles are called nucleophilic addition reaction. Addition of hydrogen cyanide to acetone is a nucleophic addition reaction.



$$CH_3COCH_3 + HCN \longrightarrow CH_3\overset{\overset{\large CH_3}{|}}{\underset{\underset{\large CN}{|}}{C}} - OH$$

   (ii) **Electrophilic Addition Reactions:** Addition reaction brought about by electrophiles are called electrophilic addition reactions. Addition of HCl to ethylene is an electrophilic addition reaction.

$$CH_2 = CH_2 + HCl \rightarrow \underset{\text{Ethyl Chloride}}{CH_3\,CH_2\,Cl}$$

   (iii) **Free Radical Addition Reactions:** Addition reactions brought about the free radicals are called free radical addition reactions.

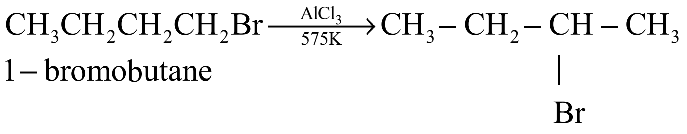
   Addition of hydrogen bromide to alkene in the presence of peroxide.

$$CH_2 = CH_2 + HBr \rightarrow CH_3 - CH_2\,Br + Br$$

3. **Elimination Reactions:** These are totally opposite to addition reactions. An elimination reaction may be defined as the one which involves the loss of two atoms or group of atoms from the same or adjacent atoms of a substrate leading to the formation of a double or triple bond.

$$CH_3CH_2CH_2\,Br + KOH_{alc} \rightarrow CH_3\,CH = CH_2 + KBr + H_2O$$

4. **Molecular Rearrangement Reaction:** Reactions involving the emigration of an atom or a group from one atom to another in the same molecule are called rearrangement reactions.



$$\underset{1-\text{bromobutane}}{CH_3CH_2CH_2CH_2Br} \xrightarrow[575K]{AlCl_3} CH_3 - CH_2 - \underset{\underset{\large Br}{|}}{CH} - CH_3$$

2-bromobutane

5. **Molecular Reaction:** Reactions which occur through the reorganization of pi-electrons through a transition state without intervention of ionic or radical intermediates are called molecular reaction usually acids or bases have no effect or such reactions.

2.2.1 Types of Reactions, and Thermodynamic and Kinetic Requirements

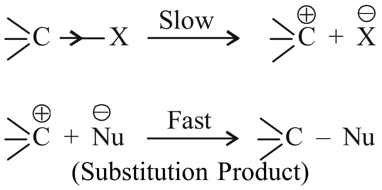
The types of reactions are as follows:

Let us study the types of mechanism in detail.

(1) Substitution Reactions

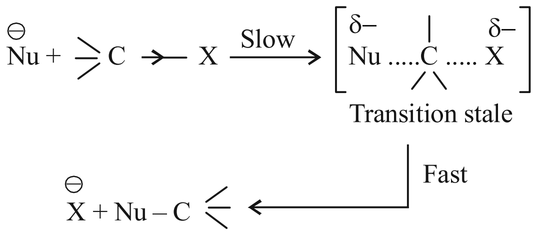
(i) **Nucleophilic Substitution Reaction Mechanism:** Substitution reactions brought about by nucleophilic substitution reaction are called the nucleophilic substitution reaction. The reaction takes place by the following two mechanisms:

(a) **Unimolecular Substitution Reaction** ($S_N{}^1$) **→:** When only one molecule participates in the rate determining step, the reaction is called unimolecular reaction. The unimolecular $S_N{}^1$ takes place in two steps.



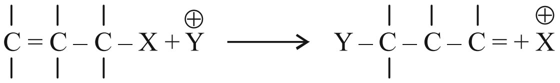
Rate of the (Propotional sign) $[>C — X]$

(b) **Bimolecular Substitution Reaction** ($S_N{}^2$) **→:** When two molecules participates in the rate determining step, it is called bimolecular reaction.



Rate of the reaction α $[\overset{\ominus}{Nu}]\,[>C \rightarrow X]$

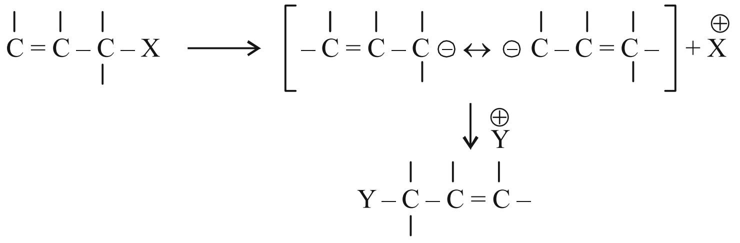
(ii) **Electrophilic substitution Reaction:** Allylic substrates indugo electrophilic substitution with rearranged product formation.



$$C=C-C-X+\overset{\oplus}{Y} \longrightarrow Y-C-C-C=+\overset{\oplus}{X}$$

The above mechanism follows two paths:

(a) **Unimolecular Substitution Reaction:** ($S_N{}^1$) **→:** When only one molecule participates in the late determining step, the reaction is called unimolecular reaction. The unimolecular $S_N{}^1$ takes place in two steps.

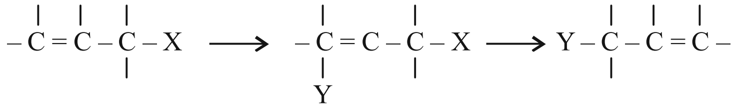


$$\mathrm{C=C-C-X} \longrightarrow \left[-\mathrm{C=C-C}\ominus \leftrightarrow \ominus\,\mathrm{C-C=C-}\right] + \overset{\oplus}{\mathrm{X}}$$

$$\downarrow \overset{\oplus}{\mathrm{Y}}$$

$$\mathrm{Y-C-C=C-}$$

(b) **Bimolecular Substitution Reaction:** ($S_N{}^2$) →**:** When two molecules participates in the rate determing step, it is called bimolecular reaction.

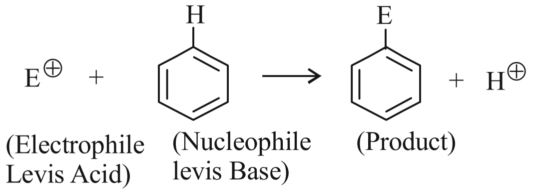


$$-\mathrm{C=C-C-X} \longrightarrow -\underset{\mathrm{Y}}{\mathrm{C}}\mathrm{=C-C-X} \longrightarrow \mathrm{Y-C-C=C-}$$

Most electrophilic allylic rearangements invilves hydrogen as the teaching group but there are examples in which metallic atom such as learning group.

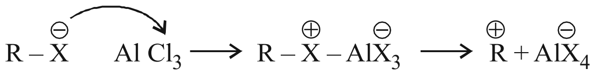
Electrophilic aromatic substitution proceeds in large, by just one mechanism 'arenium ion mechanism'. Arenium ion mechanism is multistep process of consists of mainly the following three steps:

I. Generation of electrophile:



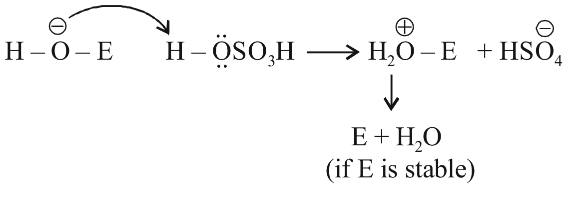
Generation of electrophile follow one of the path ways depending upon whether a Bronsted acid or lewis acid is present.

Lewis acid - base chemistry



$$\mathrm{R-\overset{\ominus}{X}}\quad \mathrm{Al\,Cl_3} \longrightarrow \mathrm{R-\overset{\oplus}{X}-\overset{\ominus}{Al}X_3} \longrightarrow \overset{\oplus}{\mathrm{R}} + \mathrm{Al}\overset{\ominus}{\mathrm{X}}_4$$

Bronsted acid - base chemistry



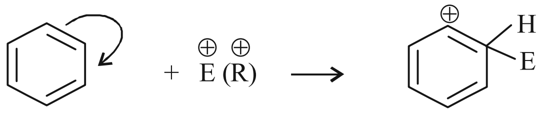
$$\mathrm{H-\overset{\ominus}{O}-E}\quad \mathrm{H-\ddot{O}SO_3H} \longrightarrow \mathrm{H_2\overset{\oplus}{O}-E} + \mathrm{HS\overset{\ominus}{O}_4}$$

$$\downarrow$$

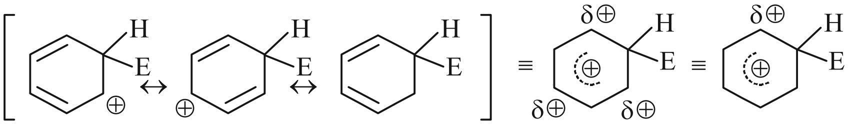
$$\mathrm{E + H_2O}$$

(if E is stable)

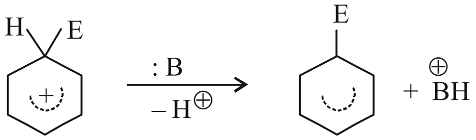
II. Attack of electrophile on π-electron sysem of the benzene ring and formation of acenium ion complex:



The product of this attack is a resonance stabilized non aromatic σ complex or benzenenonium ion or arenium or wheland intermediate.



III. The arenium ion in a fast step losses a proton in presence of a base. The stability enhancing aromatic sextel is them restered and hence this step is exothenic.



The aromatic electrophilia substitution reaction follow the second order late law.

Rate α [Nenzyne] [E]

Free radical substitution reaction mechanism

Free radiacal substitution reactions generally follow the chain reaction mechanism.

Chlorination of methane takes place in three steps:

(i) **Initiation:** In this step free radical is formed.

$$Cl:Cl \xrightarrow{ho} \dot{C}l + \dot{C}l$$

(ii) **Chain propagation**

(a) $\dot{C}l + H:CH_3 \longrightarrow \dot{C}H_3 + HCl$

(b) $Cl:Cl + \dot{C}H_3 \longrightarrow CH_3 + \dot{C}L$

(iii) **Chain termination**

$$\dot{C}l + \dot{C}l \longrightarrow Cl_2$$

$$\dot{C}H_3 + \dot{C}l \longrightarrow CH_3Cl$$

$$\dot{C}H_3 + CH_3 \longrightarrow C_2H_6$$

2. Addition Reaction

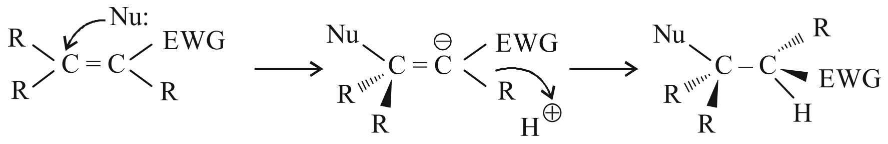
Nucleophilic addition reaction initiated by the nucleophilic species. The electron with drawing groups (WSG) will act by pulling electrons act of the double bond either inductively or measomerically. The important point here is that the EWG has to withdraw π-electron density from the double bond-usually by resonance into π-orbital. It is in step reaction.

(a) Formation of carbonion:

The electron with drawing group present in the substrate pulls the electron along the π-bond towards itself- learning the far that end away with least electron density, forming carbanion intermediate.

(b) Addition of electrophile:

Some soft of electrophiles must be present (after H^+) to react with carbanion and form the second - bond.



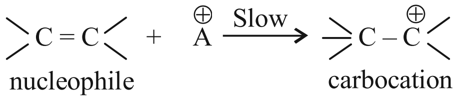
(Some EWG - CHO, COR, CN, NO_2, SOR etc.)

(ii) Electrophilic addition reaction

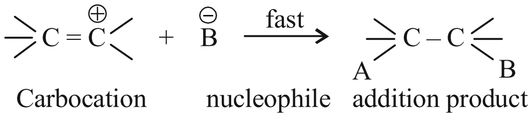
General mechanism for an electrophile addition to $>C=C<$ or $-C\equiv C-$ may be represented as:

(a) **Generation of electrophile:** The driving force of this reaction is formation of electrophile.

(b) **Formation of intermediate carbocation:** Since the π electrons of alkenes are polarised and are not stevically shielded, they are readily attacked by the electrophile.



(c) **Addition of nucleophile to the carbocation and formation of product:** The carbocation formed in the second step, is casily attacked by the seagent that acts as nucleophile, when the nucleophile attacks the carbocations it denotes its lone pair of electrons to form a σ bond between itself and carbon.

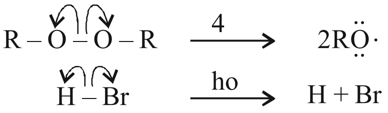


(iii) Free Radical Addition Reaction

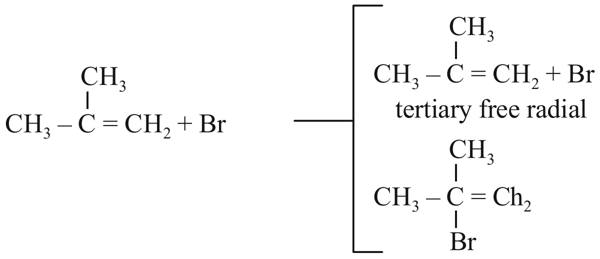
The addition of hydrobronic acid to alkene in the presence of peroxides/UV light follows free radical mechanism.

Peroxide promoted HBr addition to the alkens is a free radical chain reaction inrolves following mechanism.

(a) Initiation: Alkyl peroxides contain a weak – O – O – single step bond that is readily broken homolytically.



(b) Propagation:

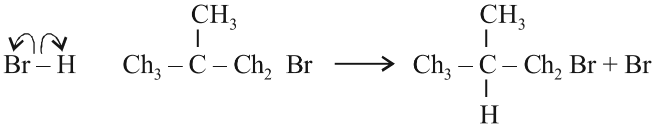


$$CH_3-\underset{}{\overset{CH_3}{C}}=CH_2+Br \longrightarrow \begin{cases} CH_3-\overset{CH_3}{C}=CH_2+Br \\ \text{tertiary free radial} \\ CH_3-\underset{Br}{\overset{CH_3}{C}}=Ch_2 \end{cases}$$

Primary free radical

(I) Due to stability of tertiary free radical and reactivity of Br toward the branched carbon is less, the formation of tertiary free radical is faster.

(II) The second propagation step is abstracting step in which a tertiary free radical abstracts a hydrogen atom from another molecule of H Br and forms addition product.

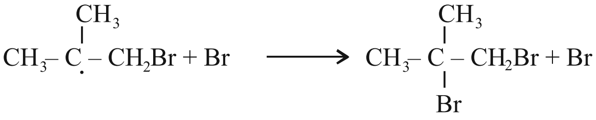


$$Br-H \quad Ch_3-\overset{CH_3}{C}-Ch_2\ Br \longrightarrow Ch_3-\underset{H}{\overset{CH_3}{C}}-Ch_2\ Br+Br$$

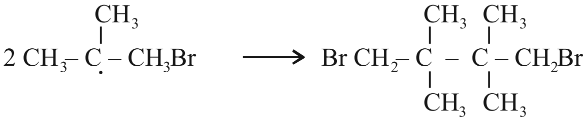
The Br then repeates the first propagation step and so on.

(c) Termination: In the termination step of free radical chain reaction, free radicals are destroyed by radical recombination reactions.

$$Br^{\cdot}+Br^{\cdot} \longrightarrow Br_2$$



$$CH_3-\underset{\cdot}{\overset{CH_3}{C}}-CH_2Br+Br \longrightarrow CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_2Br+Br$$

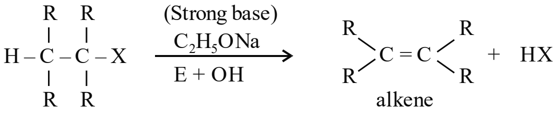


$$2\,CH_3-\underset{\cdot}{\overset{CH_3}{C}}-CH_3Br \longrightarrow Br\,CH_2-\underset{CH_3}{\overset{CH_3}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-CH_2Br$$

3. Elimination Reactions

Auanding the departing fragments from the same skeleton atom, from adjacent carbon atom or at 1, 3 or more widely separated elimination reaction are known as respectively α- elimination, β-elimination and γ-elimination reaction.

Elimination Reactions in Solution: Consider the most popular reaction for alkene formation.



$$H-\underset{R}{\overset{R}{C}}-\underset{R}{\overset{R}{C}}-X \xrightarrow[E+OH]{\text{(Strong base)}\ C_2H_5ONa} \underset{\text{alkene}}{R_2C=CR_2} + HX$$

There are three fundamental events in these elimination reactions.

(i) Removal of proton

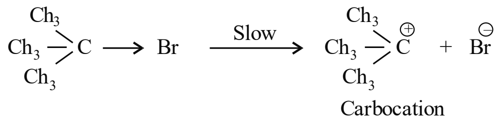
(ii) Formation of carbon-π bond

(iii) Breaking of the bond to the leaving group

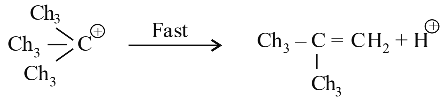
Depending upon the relative timing of these events, different mechanisms are possible.

I- E_1 reaction mechanism (Unimolecular)

(i) Loss of leaving group (LG) and formation of carbocation

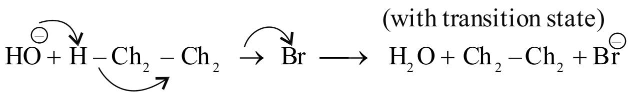


(ii) Removal of H+ and formation of C = C bond

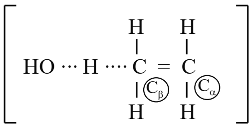


II- E_2 reaction mechanism (Bimolecular)

Simultaneous H+ removal, C = C bond formation and loss of leaving group.



The activated complex or transition state has a partially formed O–H bond, partially broken H-C_β bond and a partially formed $C_\alpha - C_\beta$ π bond and a partially broken C_α – Br bond.



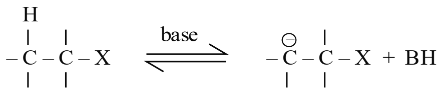
The reaction exhibits second order kinetics.

Rate of reaction α [substrate] [Base]

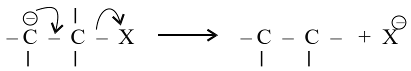
III- E_1 Cb reaction Mechanism

Removal of H^+ and formation of carbonion, loss of leaving group and formation of C = C bond. Mechanism involves two steps:

(i) Carbanion formation



(ii) Loss of leaving group and formation of π bond



Kinetics for E1 Cb mechanism

$$SH + \overset{\ominus}{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{\ominus}{S} + BH$$

$$\overset{\ominus}{S} \longrightarrow \text{alkene}$$

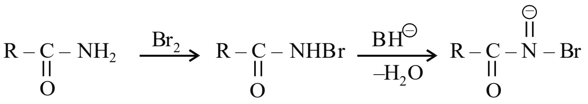
$$\text{Rate} = \frac{k_1 k_2\,[SH][\overset{\ominus}{B}]}{k_{-1}\,[BH] + k_2}$$

4. Rearrangement Reaction

In the various organic reactions, structure changes in the functional group take place and the original carbon skeleton remains unchanged. Exception example of rearrangement reaction is Hofmann's reaction: Conversion of an anide into a primary amine with one carbon atom less, by the action of alkaline hypothalite or bromine and NaOH (in which atoms are changed).

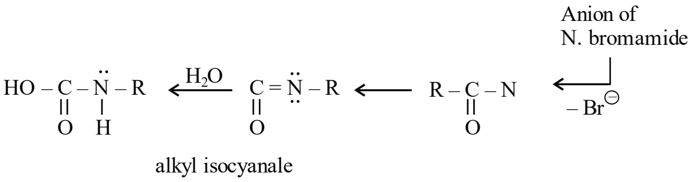
$$RCONH_2 + Br_2 + 4KOH \rightarrow RNH_2 + 2KBr + K_2CO_3 + 2H_2O$$

Mechanism

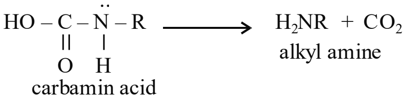


$$R-\underset{\overset{\|}{O}}{C}-NH_2 \xrightarrow{Br_2} R-\underset{\overset{\|}{O}}{C}-NHBr \xrightarrow[-H_2O]{BH^{\ominus}} R-\underset{\overset{\|}{O}}{C}-\overset{\overset{\ominus}{\|}}{N}-Br$$

It is rearrangement.



$$HO-\underset{\overset{\|}{O}}{C}-\underset{\overset{|}{H}}{\ddot{N}}-R \xleftarrow{H_2O} \underset{\overset{\|}{O}}{C}=\ddot{N}-R \longleftarrow R-\underset{\overset{\|}{O}}{C}-N \xleftarrow[-Br^{\ominus}]{} $$



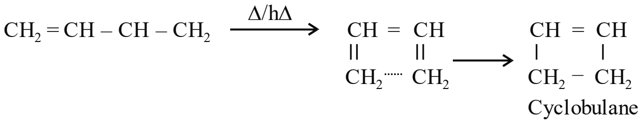
$$HO-\underset{\overset{\|}{O}}{C}-\underset{\overset{|}{H}}{\ddot{N}}-R \longrightarrow H_2NR + CO_2$$

Rearrangement of N-bromanide or its anion into alkyl isocyanate is known as the Hafmann's rearrangement.

5. Molecular Reactions

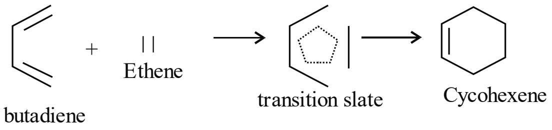
These reactions occur under the influence of heat or light. There are of two types.

(i) **Electrocyclic reaction:** Molecular reaction which occur through the reorganization of π-electrons within the same molecule are called electrolytic reaction, for example, the ring closure of 1, 3 butadiens to cyclobutene.



$$CH_2=CH-CH-CH_2 \xrightarrow{\Delta/h\Delta} \begin{matrix} CH = CH \\ \| \quad\quad \| \\ CH_2 \cdots CH_2 \end{matrix} \longrightarrow \begin{matrix} CH = CH \\ | \quad\quad | \\ CH_2 - CH_2 \end{matrix}$$

(ii) **Cycloaddition reaction:** Molecular reactions which involves the addition of the olefinic substrate to another through the reorganisation of p electrons are called cycloaddition reactions. Diels-Alder reaction.



Thermodynamics and Kinetic Parameter

A reaction is feasible or not and rate of the reaction occur analysed with the help of thermodynamics and chemical kinetics.

NOTES

All chemical reactions may be regarded as an equilibrium process, the point of equilibrium being directed by the relative energies of the reactant are the product. Reaction which do not proceed at all are also equilibrium process for which the value of equilibrium constant is zero or nearly zero.

The energy content of a molecule is usually expresed as its free energy (G), which is a measure of the potential energy of a molecule which is related to enthalpy (H) and entropy (S) as:

$G = H - TS$

Enthalpy relates to bonding, whereas entropy relates to the degree to which a molecular system is disordered. The entropy contribution to free energy depends on temperature because S is multiplied by absolute temperature. As the temperature increases, the term TS become large and can sometimes dominate over H. The free energy change at constant temperature is expressed.

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

For forward reaction = ΔG (–ve) [there is overall release of energy]

For backward reaction = ΔG (+ve)

Enthaply factor which determines the success of a reaction,

ΔH is sufficiently negative, ΔG is negative, reaction is feasible, such reactions are called enthalpy driven reactions.

Equilibrium constant associated with free energy,

$\Delta G = -RT \ln K$ (R = Universal Gas Constant)

The high value of K (equilibrium constant) favours the direction of product, higher value of K is associated with high rate of the reaction.

Kinetic Measure

Although a negative value of ΔG tells us about the reaction to proceed in the forward direction, it does not tell us if the reaction will proceed at a measurable rate.

The reaction rate is depends open the concentration of the various species. Kinetics often used to gain an insight of the reaction mechanism. Most of the organic reactions are ultistep processes in which one of the steps, the slowest step, is the rate determining step. Kinetic studies give us information about this step and helps in identifing the species participating in this step.

Suppose a reaction proceeds as below:

$A + B \rightleftharpoons C$

and it is observed that when the concentration of either A or B is doubled, the rate of reaction is also doubled. This shows that the reaction depends upon the concentration of both A and B.

Rate α [A] [B]

Rate = k [A] [B] (k = Rate Constant)

NOTES

Order of reaction and molecularity: The order of a reaction n is the sum of all the exponents of the concentration of various reactants of the rate law

Rate = k $[A]^x [B]^y$

(Order of reaction) n = (x + y)

The molecularity of a reaction may be defined as the number of species that are undergoing covalency changes in the rate determining step.

2.2.2 Kinetic and Thermodynamic Control

The feasibility of a particular reaction is based on the energetics (energy considerations) for that reaction. Thermodynamics is the study of the energy flow in a system. If thermodynamics predicts that a reaction will not occur under certain conditions—then it is no use trying it, because it would not occur. However if a reaction is predicted by thermodynamics, then though theoretically it may take place but unless its reaction rate is fast enough, it will be of no use. The energetics of a system can be interpreted in terms of heat content of the system termed as **Enthalpy** (H) in thermodynamics.

Usually, all reactions have an equilibrium which is characterized by an equilibrium constant (K). Equilibrium constant for a reaction depends on Gibb's free energy (G) change of the system. To understand the concept of Gibb's free energy, it may be applied to a hypothetical equilibrium.

$$\underset{\text{Reactants}}{\overset{}{A + B}} \rightleftharpoons \underset{\text{Products}}{C + D}$$

Equilibrium constant $K = \frac{[C][D]}{[A][B]}$

The relation of free energy with equilibrium constant is given by the equation:

$$\Delta G \text{ (Change in free energy)} = -2.3\ RT \log K$$

where R is gas constant, T is temperature, in absolute scale.

Thus both A and B possess certain amount of energies and in order that the reactions may proceed some existing bonds in these reactants must be broken. Breaking of bond requires energy. So for the reaction to occur a certain amount of energy must be provided to the reactants. Similarly when C and D are formed new bonds must be created. Formation of bonds releases energy—which may be greater or less depending upon individual bond energies involved. Thus the energy of a chemical reaction is equal to the difference in energy between reactants and products. If in formation of products, the energy is released the reaction is said to be **exothermic** whereas if the energy is absorbed the reaction is known as **endothermic**. In exothermic reactions, the total energy of the system is lowered and it thus becomes more stable after the reaction, i.e., the products are more stable than the reactants. In endothermic reactions, the system goes to a higher energy level and products are less stable than reactants. This difference of energy is also referred to as change in free energy. The idea has been illustrated in Figure. 2.1.

NOTES

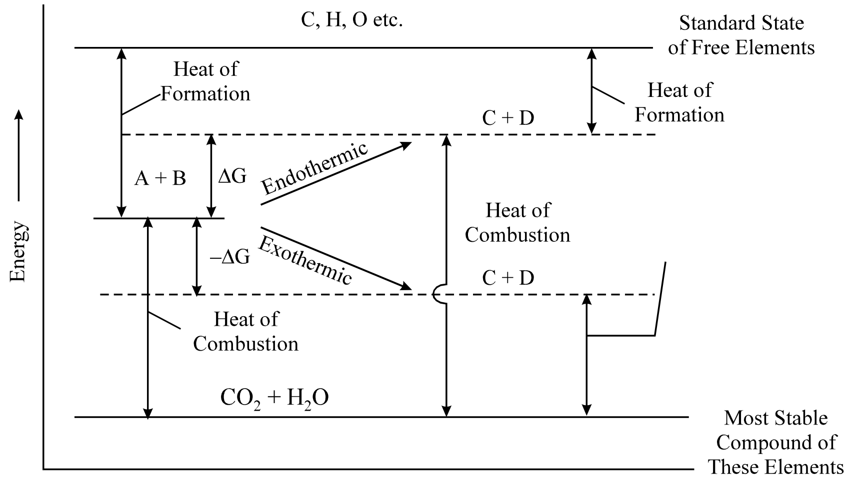


Fig. 2.1 *Energy relations between Elements, Compounds, Reactants and Products*

The change in free energy (ΔG) is related to the change in enthalpy (ΔH) or heat content and change in entropy (ΔS) of the system by the equation.

$\Delta G = \Delta H - T\Delta S$ where T is absolute temperature.

The entropy is a measure of randomness or disorder or probability of a system. The greater the disorder the greater is the entropy. For example, molecules in gaseous state are much more disorderly as compared to the liquid state. Again in the liquid state molecules are more disorderly as compared to solid state. So the entropy of such a system decreases as we go from gaseous to solid state via liquid state. For a reaction of the type A + B → C + D, usually the entropy change is small or negligible because the number of molecules before and after the reaction is same and molecules are distributed with same randomness. Entropy is negative for the reactions of the type A + B → C and positive for the reaction A → C + D. In case entropy changes are negligible the value of ΔG is obtained from change in enthalpy directly. A negative value of ΔG indicates the thermodynamic probability of a reaction.

Kinetic Versus Thermodynamic Control of Reactions

Product distribution in a chemical reaction is generally influenced by two factors:

1. Relative stability of the product (thermodynamic factor)
2. Rate of formation of the product (kinetic factor)

Suppose in a reaction two products 'A' and 'B' are formed, of which 'B' is more stable. It the activation energy for the formation of 'A' is lower than that of formation of 'B' it will be formed faster (kinetic control), otherwise the product 'B' will be formed as it is more stable (thermodynamic control). Thus the kinetic product distribution is derived from the energy difference between the transition states leading to the two products while the thermodynamic product distribution is derived from the free energy difference between the two products. In both cases it is the lower energy species which predominates over the other one.

Consider a case where a starting material (R) gives rise to two different products (A) and (B) via different pathways. Reaction forming (A) via T.S. (A) will be factor since at has a more stable transition state. Hence it is a kinetic product.

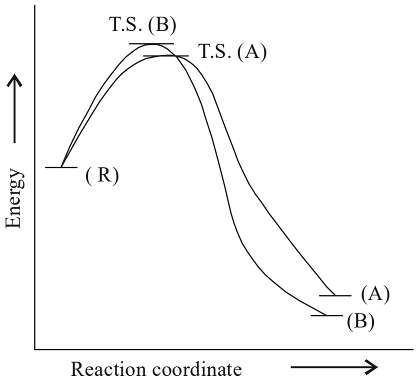


Fig. 2.2 *Transition States*

On the other hand (B) in more stable since it is has a lower energy. Hence it is a thermodynamic product.

The conditions of the reaction, such as temperature, pressure and solvent, decide upon the favoured pathway.

In the above reaction at low temperatures, (A) will be formed predominantly and stop as it has not got the energy to revert to (R), i.e., the reaction is irreversible. Hence the product ratio will depend on the rates of formation of (A) and (B).

On the other hand, at higher temperature the reaction forming (A) becomes reversible and hence though (A) may be formed initially it reverts to (R) and then reacts to give the more stable (B).

At still higher temperatures both the reactions become reversible and the product ratio is decided by the equilibrium constants of the two reactions.

In conclusion, it may be stated that:

(i) At low temperatures the reaction is kinetically controlled and the major product is (A).
(ii) At higher temperatures the reaction is thermodynamically controlled and the major product is more stable (B).
(iii) In every reaction the first product formed is kinetically controlled.
(iv) An essential condition for thermodynamic control is the reversibility of the reactions permitting equilibration of products.
(v) Short reaction times favour kinetic control while longer reaction times favour thermodynamic control.
(vi) If a reaction is under kinetic control, at a given temperature it will always be under kinetic control at any lower temperature.
(vii) If a reaction is under thermodynamic control at a given temperature it will also be under thermodynamic control at any higher temperature.

During addition of HBr to 1, 3-butadiene a mixture of 3-bromo-1-butene and 1-bromo-2-butene is formed. At –80°C, 3-bromo-1-butene is the major product (kinetic control) while at 40°C, 1-bromo-2-butene is the major product (thermodynamic control).

In sulphonation of naphthalene with oleum at 80°C the product is 1-naphthalene sulphonic acid (kinetic control) whereas at 160°C the product is 2-naphthalene sulphonic acid (thermodynamic control).

Kinetics of Reaction and Reaction Rates

Kinetics deals with the rate of reaction and factors affecting the rate. For the type of reaction $A + B \rightarrow C + D$ if the rate is expressed as Rate = $K. [A][B]$, where K is the rate constant. The reaction is dependent on two concentrations, that of A and B and is a second order reaction. Since two molecules are involved in collision and are undergoing valency change it is **bimolecular reaction**.

Alternatively the reaction may occur in two steps such as:

$$(i)\ A \xrightarrow{\text{Slow}} \underset{\text{Intermediate}}{Z} \quad \text{and} \quad (ii)\ Z + B \xrightarrow{\text{Fast}} \underset{\text{Product}}{C + D}$$

In this case Rate = $K[A]$ as only A is involved in rate determining slow step.

For a reaction of the type $A \rightarrow C + D$, the rate = $K[A]$, is dependent on the concentration of A only and is a first order reaction. Since only one molecule is undergoing valency change it is a **unimolecular reaction**.

The above two types of reactions may proceed as,

$$(i)\ \underset{\text{Reactants}}{A + B} \xrightarrow{\text{Slow}} \underset{\text{Intermediates}}{Z} \xrightarrow{\text{Fast}} \underset{\text{Products}}{C + D}; \quad \text{Rate} = K[A][B]$$

$$(ii)\ \underset{\text{Reactants}}{A} \xrightarrow{\text{Slow}} \underset{\text{Intermediates}}{Z} \xrightarrow{\text{Fast}} \underset{\text{Products}}{C + D}; \quad \text{Rate} = K[A]$$

Both are two-step reactions involving formation of intermediate Z. When more than one step is involved in a reaction it is known as multi-step reaction. The rate of such a reaction is equal to the rate of the slowest step known as the **rate determining step** and the kinetics of the reaction is the kinetics of the slowest or the rate determining step.

In contrast to this, in a single step reaction all the molecules are undergoing valency change simultaneously and hence such a reaction is known as synchronous or concerted reaction.

The two general theories commonly used to explain reactions, their rates, order, etc. are as follows:

(i) Curtin – Hammett Principle

According to this principle, if for a chemical reaction there is a pair of reactive intermediates or reactants that interconvert rapidly and each forming different products irreversibly then the product ratio will depend only on the difference in the free energy of the transition state forming each product and not on the equilibrium constant between the intermediates. For example, in a reaction where A and B are in equilibrium and A changes into C and B into D both irreversibly, K is the equilibrium constant between A and B and K_1 and K_2 are rate constants for the formation of C and D respectively. If the rate of interconversion between A and B is much faster than either rate constants than Curtin-Hammett Principle products then the C : D product ratio will not be decided by K but by the relative energies of the transition states.

$$C \xleftarrow{K_1} A \overset{K}{\rightleftharpoons} B \xrightarrow{K_2} D$$

Curin-Hammett Principle is important in explaining the selectivity ratios in stereoselective reactions.

(ii) Hammond's Postulates

Also known as Hammond-Leffler postulate it concerns the transition state of organic chemical reactions. It states that if a transition state and an intermediate occur consecutively in a reaction and have nearly the same energy their interconversion will involve only a small reorganization of the molecular structure.

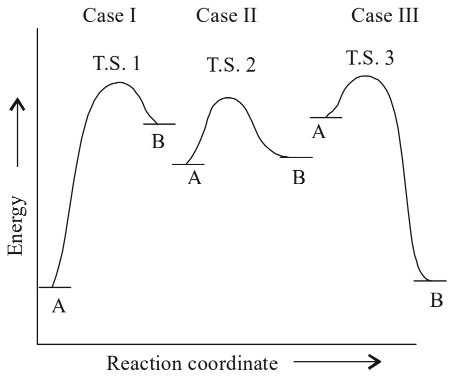


Fig. 2.3 *Hammond-Leffler Postulate*

In essence the postulate states that the structure of a transition state resembles that of the species nearest to it in free energy. Since due to the very nature of transition state it is not possible to observe them and deduce their structure, Hammond's postulate allows us to make assumption about the structure of transition state. Consider the following three cases:

***Case I*:** In such a highly endothermic reaction TS_1 resembles the structure of B being closer to it in energy.

***Case II*:** Here neither A nor B has a structure similar to TS_2.

***Case III*:** In a highly exathermic reaction the structure of TS_3 resembles reactant A is the transition state is much closer to the reactant in energy.

In order to predict the effect of substituents on the energy of the transition state and hence on the rates of reaction, **Polanyi-Hammond postulate** states that *mutual conversion between two species which are adjacent to each other on the reaction coordinate requires only a minor change in the structure provided they have nearly the same energy.*

If an energy-rich intermediate is formed after the transition state on the reaction coordinate, then the structure of the transition state has only a minor difference as compared to that of the reaction intermediate. Thus the effect of substituents on the energy of the transition state can be estimated by noting the effect these substituents have on the energy of the reaction intermediate. Such energy-rich reaction intermediates are often observed in electrophilic aromatic substitution as sigma (σ) complexes or as carbonium ion in addition of hydrogen halide to olefins.

Polanyi-Hammond postulate helps not only in the prediction of the structure of transition state but also in predicting the effect of substituents on the energy of activation and rates of reactions.

2.2.3 Potential Energy Diagrams and Transition States and Intermediates

The energy corresponding to ultraviolet and visible radiations may bring about the following electronic excitations:

(*i*) Sigma bonding electrons to vacant sigma antibonding orbitals $(\sigma \rightarrow \sigma^*)$

(*ii*) Pi bonding electrons to vacant pi antibonding orbitals $(\pi \rightarrow \pi^*)$

(*iii*) Nonbonding electrons to vacant sigma antibonding orbitals $(n \rightarrow \sigma^*)$

(*iv*) Nonbonding electrons to vacant pi antibonding orbitals $(n \rightarrow \pi^*)$

The energy required for these transitions is in the order $\sigma \rightarrow \sigma^* > n \rightarrow \sigma^* > \pi \rightarrow \pi^*$ $> \; n \rightarrow \pi^*$.

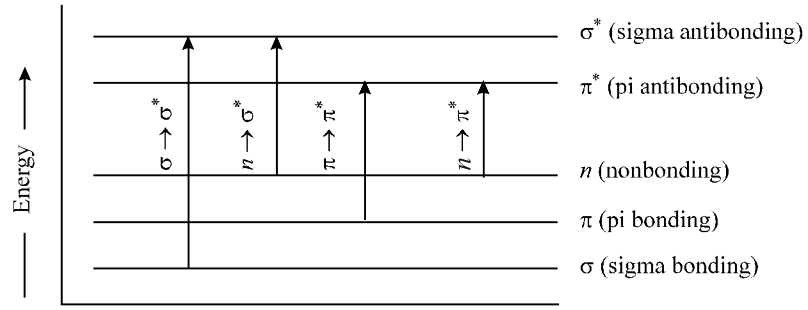


***Fig. 2.4** Energy Levels and Electronic Transitions Possible in a Molecule*

(*i*) $\sigma \rightarrow \sigma^*$ **transitions**: The energy required for these transitions is high and lies in the vacuum ultraviolet region (below 210 nm). Consequently compounds in which all valence shell electrons are involved in single bond formation such as saturated hydrocarbons do not show any absorption in ordinary ultraviolet region (*i.e.*, 200–400 nm). Methane shows an absorption band at 125 nm corresponding to $\sigma \rightarrow \sigma^*$ transition.

(*ii*) $n \rightarrow \sigma^*$ **transitions**: The energy required to promote a nonbonding (unshared) electron to vacant sigma antibonding orbital is much less than that required for $\sigma \rightarrow \sigma^*$. Hence molecules having lone pair or nonbonding electrons tend to absorb higher wavelength as compared to compounds having only sigma electrons.

Thus $n \rightarrow \sigma^*$ transitions in:

$CH_3\ddot{O}H$ occurs at 183 nm

$CH_3\ddot{N}H_2$ occurs at ← 215 nm

$CH_3\ddot{I}$ occurs at ← 258 nm

$(CH_3)_3\ddot{N}$ occurs at ← 227 nm

Polar solvents shift these $n \rightarrow \sigma^*$ transitions towards shorter wavelength (higher energy) because of some interaction of nonbonding electrons with the solvent. The spectrum of tri-methylamine in aqueous acid shows no absorption due to $n \rightarrow \sigma^*$ transition (at 227 nm) because in acid solution tri-methylamine gets protonated and there are no free nonbonding electrons.

(*iii*) $\pi \rightarrow \pi^*$ **transitions**: The excitation of bonding pi electrons to vacant antibonding pi orbitals requires still lesser energy as compared to $n \rightarrow \sigma^*$ excitation. Hence these absorptions generally occur in common ultraviolet region.

$\pi \rightarrow \pi^*$ transitions in some common compounds are given below:

Ethylene $(CH_2{=}CH_2)$	170 nm
Acetone $(CH_3CO.CH_3)$	180 nm
Acetylene $(CH{\equiv}CH)$	← 178 nm

Conjugation of π bonds shifts the wavelength of maximum absorption to longer wavelength. Thus 1,3 butadiene has a λ_{max} at 217 nm.

Polar solvents further shift the wavelength of absorption to longer regions in conjugated systems.

(*iv*) ***n*** $\rightarrow \pi^*$ **transitions**: Such transitions are possible only in compounds having both the nonbonding (*n*) electrons as well as multiple bonds (π electrons) as they involve excitation of nonbonding electron to vacant antibonding pi orbital. These are generally the lowest energy transitions and occur at higher wavelengths.

$n \rightarrow \pi^*$ transitions in some common compounds are given below:

Acetone (CH_3COCH_3)	280 nm
Acetaldehyde (CH_3CHO)	292 nm
Benzaldehyde (C_6H_5CHO)	328 nm
Nitroethane $(C_2H_5NO_2)$	271 nm

Here also the conjugation shifts the absorption to a higher wavelength. Thus $CH_2{=}CH{-}CH{=}O$ absorbs at 320 nm but the polar solvents shift these $n \rightarrow \pi^*$ transitions to lower wavelength due to interaction between nonbonding electrons with polar solvents.

Thus $n \rightarrow \pi^*$ transition of acetone in hexane occurs at 280 nm, in ethanol at 270 nm and in water at 264 nm.

Molecules having σ, π and *n* electrons may undergo all types of possible transitions giving a number of absorption bands. The table below gives some examples.

Table 2.1 Possible Transitions Giving a Number of Absorption Bands

Compound	λ_{max}	ε_{max}
CH_3COCH_3	$n \rightarrow \sigma^*$	
	166 nm	16,000
	$\pi \rightarrow \pi^*$	
	180 nm	10,000
	$n \rightarrow \pi^*$	
	280 nm	20
CH_3CHO	$n \rightarrow \sigma^*$	
	160 nm	20,000
	$\pi \rightarrow \pi^*$	
	194 nm	10,000
	$n \rightarrow \pi^*$	
	292 nm	17
C_6H_5CHO	$\pi \rightarrow \pi^*$	
	244 nm	15,000
	$\pi \rightarrow \pi^*$	
	280 nm	1,500
	$n \rightarrow \pi^*$	
	328 nm	20
$C_2H_5NO_2$	$\pi \rightarrow \pi^*$	
	201 nm	5,000
	$n \rightarrow \pi^*$	
	271 nm	19

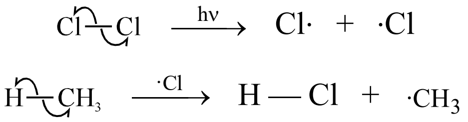
The exact electronic structure of excited state is not well understood but there is some kind of redistribution of electrons—not necessarily in accordance with present valence rules. Absorbed energy is generally re-emitted as light.

The difference between an intermediate and a transition state is that an intermediate has a discontinuous duration (ranging from a few nanoseconds to many days), whereas a transition state only lasts for one bond vibration cycle. Intermediates can be either reactive intermediates (which are unstable molecules) or highly stable compounds.

2.2.4 Methods of Determining-Mechanisms, Isotope Effect

A number of methods besides the study of thermodynamics and kinetics are used to study the course of a reaction. Some of these are:

1. **Identification of products and by-products:** Any proposed mechanism for a reaction must account for the formation of all the products, by-products as well as their ratios. Thus the halogenation of methane in presence of sunlight must account for the formation of ethane as a by-product,



$$Cl-Cl \xrightarrow{h\nu} Cl\cdot + \cdot Cl$$

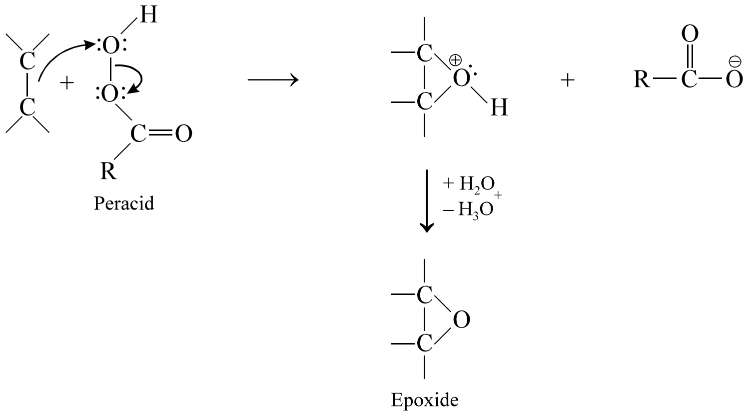
$$H-CH_3 \xrightarrow{\cdot Cl} H-Cl + \cdot CH_3$$

$$Cl-Cl + \cdot CH_3 \longrightarrow CH_3-Cl + \cdot Cl$$

The formation of ethane occurs due to combination of two methyl radicals.

$$\cdot CH_3 + \cdot CH_3 \longrightarrow CH_3-CH_3$$

In epoxidation reaction of alkene with peracids which is an electrophilic attack on the alkene and is of first order with respect to olefin as well as to peracid, the product is stereo- specific suggesting it to have concerted mechanism.



cis-alkene forms *cis*-epoxide while *trans*-alkene forms *trans*-epoxide excluding the possibility of formation of an intermediate carbocation.

2. **Determination of the presence of an Intermediate:** It includes the following:

(*a*) ***Isolation of intermediate:*** An intermediate believed to be formed in a proposed mechanism, may sometimes be isolated by carrying out the reaction under mild conditions.

Thus in Hofmann degradation of an amide using halogen and alkali, an isocyanate intermediate has been isolated supporting the proposed mechanism.

(*b*) ***Detection of intermediate:*** Sometimes an intermediate cannot be isolated but its presence may be indicated by IR, NMR spectra, etc. or some other technique.

In the nitration of benzene which is an electrophilic substitution, involvement of NO_2^+ (nitronium ion) was shown with the help of Raman spectra.

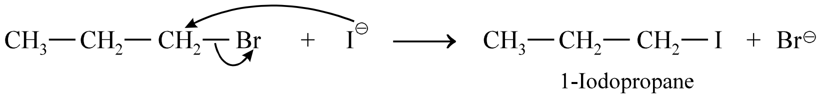
(*c*) ***Trapping of an intermediate:*** The formation of an intermediate may be confirmed by carrying out the reaction in presence of a substance known to react with intermediate and analysing the product for adduct.

Thus benzyne intermediate is known to undergo Diels Alder reaction with dienes. In a reaction where benzyne is suspected to be an intermediate, a little diene is added to the reaction mixture. Formation of adduct with diene (thus trapping it) confirms the involvement of benzyne as intermediate.

(*d*) ***Indirect evidence:*** Indirect evidence also helps in deciding the mechanism of reaction.

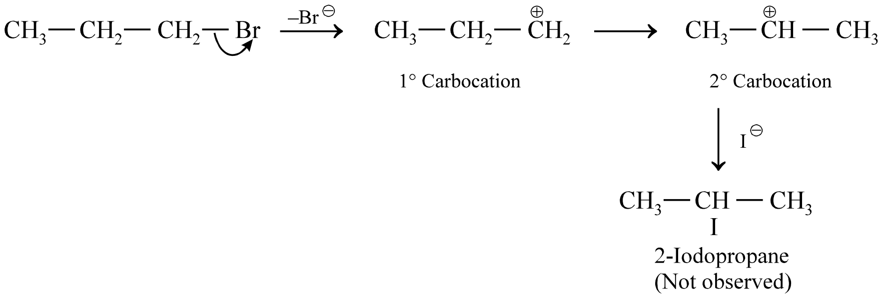
For example, the reaction of 1-bromopropane with sodium iodide forms exclusively 1-iodopropane. Obviously the reaction cannot occur via the formation of a carbocation, because if 1° carbocation is formed, it will rearrange to 2°

carbocation and the product will be 2-iodopropane. Since no 2-iodopropane is formed, reaction must be proceeding through a concerted mechanism.



$$CH_3-CH_2-CH_2-Br + I^{\ominus} \longrightarrow CH_3-CH_2-CH_2-I + Br^{\ominus}$$

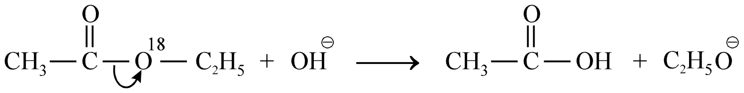
and not as



$$CH_3-CH_2-CH_2-Br \xrightarrow{-Br^{\ominus}} CH_3-CH_2-\overset{\oplus}{C}H_2 \longrightarrow CH_3-\overset{\oplus}{C}H-CH_3 \xrightarrow{I^{\ominus}} CH_3-\underset{I}{CH}-CH_3$$

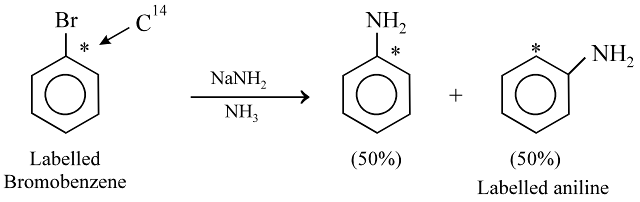
3. **Isotopic labelling:** A lot of information regarding reaction mechanism has been obtained using isotopically labelled molecule and tracing the path of the reaction.

For example, the alkaline hydrolysis of esters labelled with O^{18} helped to prove that the reaction involves bond cleavage between oxygen and acyl group.

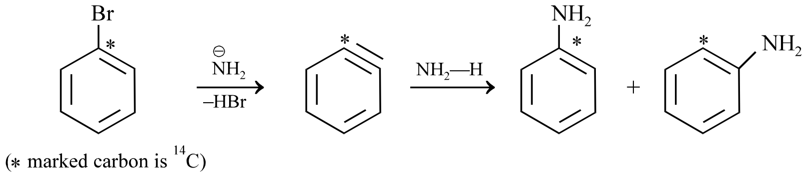


$$CH_3-\overset{O}{\overset{\|}{C}}-\overset{18}{O}-C_2H_5 + OH^{\ominus} \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-OH + C_2H_5O^{\ominus}$$

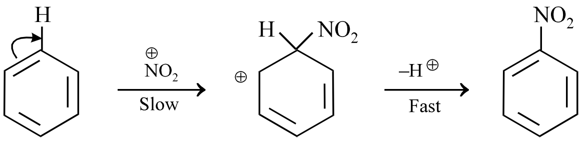
Similarly the benzyne mechanism for nucleophilic aromatic substitution was established by isotopic labelling experiments.



The reaction must proceed via the formation of benzyne intermediate to account for the formation of two products.



Rate of nitration of benzene and deuterobenzene are same suggesting that loss of proton or deutron is not the rate determining step but the fast step.



4. **Kinetic evidence:** The rate of a reaction is the rate of disappearance of a reactant or formation of a product. In some cases change in concentration of a reactant results in no change in the rate of reaction.

NOTES

If the rate is proportional to the change in the concentration of only one reactant, it is first order with respect to that reactant.

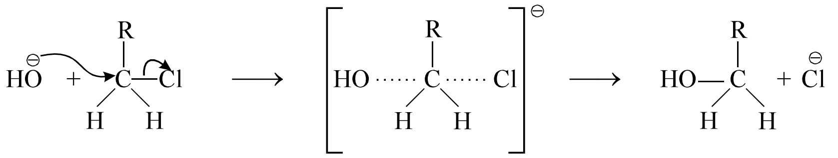
If the rate of reaction is proportional to the change in the concentration of two reactants, it is second order.

The rate law of a reaction is experimentally determined. From this we derive information about the molecularity of the reaction and which reactants are involved in rate determining step. This tells us about reaction mechanism. Thus nucleophilic substitution of alkyl halides may be of two types dpending on kinetic studies.

For primary and secondary alkyl halides the kinetic data tells us that

$$\text{Rate} \propto [\text{Alkyl halide}]\,[\text{Nucleophile}]$$

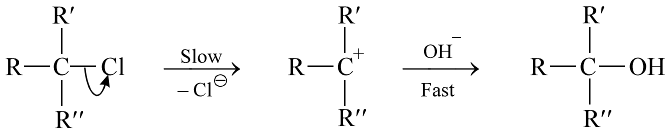
Thus we may write the mechanism as



For tertiary alkyl halides,

$$\text{Rate} \propto [\text{Alkyl halide}]$$

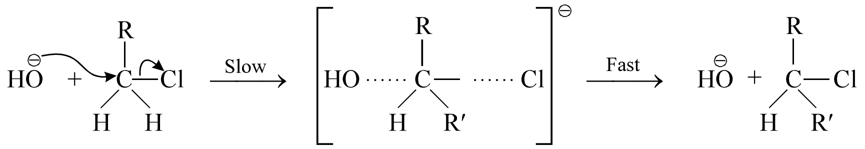
so the mechanism is



5. **Stereochemical evidence:** Information about reaction mechanism can also be obtained by following correlation in the stereochemistry of reactants and products.

Mechanisms of nucleophilic substitution reactions of alkyl halides have been investigated by carrying out experiments with optically active compounds and then checking optical activity of the products.

Thus nucleophilic substitution of optically active secondary alkyl halides lead to formation of optically active products with inversion in configuration. This results in the following mechanism for the reaction:

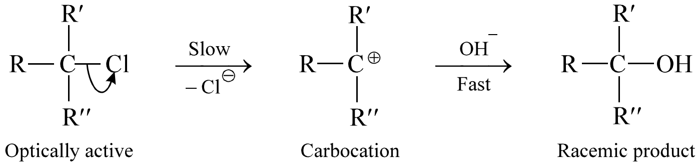


(Attack of nucleophile from side opposite to that occupied by leaving group)

(Inversion in configuration known as Walden inversion)

In case of tertiary alkyl halide the product is always a racemic product starting from an optically active halide visualising formation of a planar carbocation.

NOTES



In rearrangement reaction it is often necessary to find out if the rearrangement is intramolecular or intermolecular. To ascertain this, advantage is taken of stereochemical evidence. The migrating group having an asymmetric centre (and optically active) directly attached to migration origin is allowed to undergo rearrangement.

If the migrating group retains its asymmetric nature (optical activity) in the product then it never got detached completely from the migration origin, suggesting the rearrangement to be intramolecular.

Intramolecular nature of many rearrangements for example, Beckmann, Hofmann, etc. has been established using stereochemical evidence of this kind.

2.2.5 Hard and Soft Acids and Bases

Classical definition of acids and bases is due to Arrhenious who suggested that acids are those substances which give hydrogen ions when dissolved in water whereas bases are substances which give hydroxyl ions. Since then the concept of acid and base has undergone changes from time to time and at present two concepts are in general use regarding acids and bases:

(i) Lowry-BrÖnsted Concept

According to this concept, acids are defined as substances which have a tendency to donate protons and bases as substances having tendency to gain protons. Thus in an acid base reaction transfer of proton from acid to base takes place. When the acid has donated a proton, then the anion has the tendency to gain proton and therefore acts as a base—known as a **conjugate base**. Similarly a base after accepting a proton acquires the characteristics of an acid and is known as a **conjugate acid.** The following examples illustrate the point:

$$\underset{\text{Formic acid}}{\text{H.COOH}} \longrightarrow \overset{+}{\text{H}} + \underset{\text{Conjugate base}}{\text{HCO}\bar{\text{O}}}$$

$$\underset{\text{Hydrochloric acid}}{\text{HCl}} \longrightarrow \overset{+}{\text{H}} + \underset{\text{Conjugate base}}{\bar{\text{Cl}}}$$

$$\underset{\text{Phenol}}{\text{C}_6\text{H}_5\text{OH}} \longrightarrow \overset{+}{\text{H}} + \underset{\text{Conjugate base}}{\text{C}_6\text{H}_5\text{O}^-}$$

$$\underset{\text{Ammonia}}{:\text{NH}_3} + \overset{+}{\text{H}} \longrightarrow \underset{\text{Conjugate acid}}{\overset{+}{\text{NH}_4}}$$

$$\underset{\text{Water}}{\text{H}_2\text{O}} + \overset{+}{\text{H}} \longrightarrow \underset{\text{Conjugate acid}}{\text{H}_3\overset{+}{\text{O}}}$$

$$\underset{\text{Hydroxide ion (base)}}{\bar{\text{O}}\text{H}} + \overset{+}{\text{H}} \longrightarrow \underset{\text{Conjugate acid}}{\text{H}_2\text{O}}$$

Although the definition is similar to the classical concept, it includes a large number of compounds in the category of acids and bases which were not included in classical concept.

$$\underset{\text{Aniline (Base)}}{C_6H_5NH_2} + H^+ \longrightarrow \underset{\text{(Conjugate acid)}}{C_6H_5\overset{+}{N}H_3}$$

$$\underset{\text{Nitromethane (Acid)}}{CH_3NO_2} \longrightarrow H^+ + \underset{\text{(Conjugate base)}}{\overset{-}{C}H_2NO_2}$$

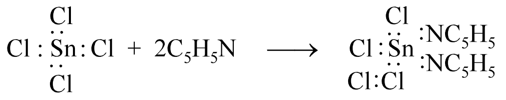
Many substances, like water, can behave both as an acid and a base, and are known as *amphoteric* substances. Strengths of acids may be defined as a measure of the tendency to give protons and strengths of bases as a measure of their tendency to accept protons. Also as a consequence of this concept very strong acids will give very weak conjugate bases and very strong bases will give very weak conjugate acids. Usually the strength is dependent on the type of acid and base taking part in the reaction, their structural features and the solvent. Thus a fairly strong acid when reacting with a stronger acid will behave as a base.

(ii) Lewis concept

The essence of Lowry-Brönsted concept is that an acid donates a proton which may be accepted by a base. A base can only accept a proton or electron deficient species if it is rich in electrons (*viz*. nucleophile). To extend the concept of acids and bases to similar substances in non-hydroxylic solvents Lewis suggested that in such solvents a base may not be required to accept a proton and therefore it is sufficient to define *a base as a substance which has an available pair of electrons.* It may be recalled that this definition of bases coincides with the definition of nucleophiles. Conversely *acids are defined as those substances which are electron deficient* having a vacant orbital and can use it to form a covalent bond with the electron pair of the base. This definition of acids coincides with the definition of electrophiles. Here instead of proton donor, proton itself is considered as acid. Thus Brönsted acids according to Lewis become acid donors. When Lewis concept is used to define the acids and the bases the substances are referred to as *Lewis acids* and *Lewis bases.* Some examples of these are given below:

Lewis Acids	H^+, Li^+, $AlCl_3$, $SnCl_4$, $FeCl_3$, BF_3
Lewis Bases	OH^-, $H_2O:$, $:NH_3$, Cl^-, $C_5H_5N:$(Pyridine)

All the Lewis bases are having unshared pair of electrons. Lewis acids like $AlCl_3$, BF_3, etc., have only six electrons in outermost orbit and are thus deficient in electrons but substances like $SnCl_4$ act as Lewis acids by expanding the octet of central atom.



$$Cl:\overset{Cl}{\underset{Cl}{\ddot{\underset{..}{Sn}}}}:Cl + \underset{\text{Pyridine}}{2C_5H_5N} \longrightarrow \underset{\text{Product}}{Cl:\overset{Cl}{\underset{Cl:Cl}{\ddot{\underset{..}{Sn}}}}\begin{matrix}:NC_5H_5\\:NC_5H_5\end{matrix}}$$

Lewis acids are important as catalysts for many organic reactions.

Check Your Progress

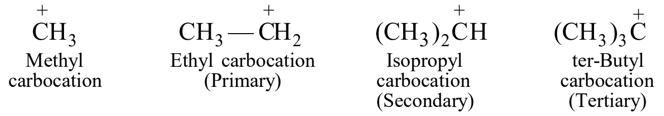
1. What is the classification of organic reactions?
2. Write the three fundamental events in elimination reactions in solutions.
3. What does the Hammod postulate state?
4. What are the classical definitions of acids and bases?

2.3 GENERATION, STRUCTURE, STABILITY AND REACTIVITY

Let us study the different molecules and ions in this section in detail.

2.3.1 Carbocations

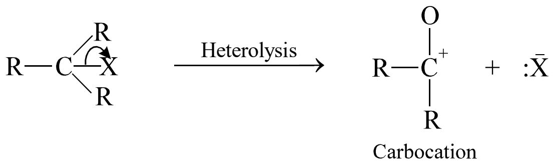
If a covalent bond, in which carbon is attached to a more electronegative atom or group, breaks up by heterolytic fission, the more electronegative atom will take away the electron pair and become negatively charged while the carbon will lose its electron and thus acquire a positive charge. Such cationic species carrying a positive charge on carbon are known as carbocations. These carbocations are called primary, secondary and tertiary depending upon the nature of the carbon atom bearing the charge.



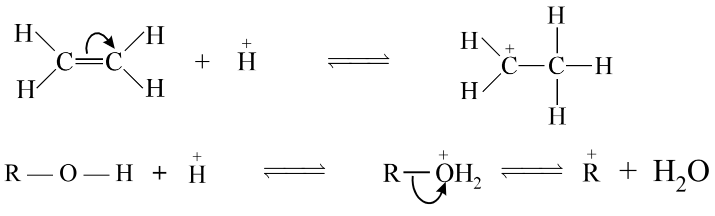
$\overset{+}{C}H_3$ Methyl carbocation; $CH_3-\overset{+}{C}H_2$ Ethyl carbocation (Primary); $(CH_3)_2\overset{+}{C}H$ Isopropyl carbocation (Secondary); $(CH_3)_3\overset{+}{C}$ ter-Butyl carbocation (Tertiary)

Carbocations may be obtained by heterolysis, protonation of olefins or by decomposition of compounds like the diazo.

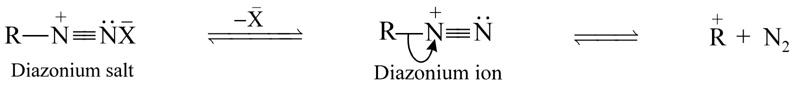
(*i*) **Heterolysis**



(*ii*) **Protonation**



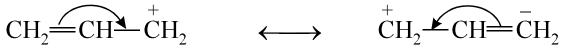
(*iii*) **Decomposition**



Stability

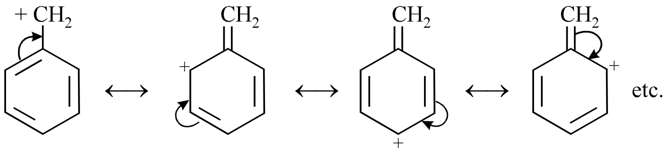
The carbocations like cycloheptatrienyl cation (tropylium cation) are so stable that they can be isolated and studied whereas methyl or ethyl cabocations are so unstable that it is normally not possible to detect them in a chemical reaction. Usually they are very reactive and combine readily with any molecule that can give a pair of electrons for sharing with them which accounts for their instability in general. *If the groups having electron repelling (+I) effect like* $-CH_3$ *are attached to the carbon carrying the positive charge then some of this positive charge or electron deficiency is compensated by this push of the electrons towards the positive carbon and this stabilises the carbocation somewhat.*

An alkyl group is electron releasing (hyperconjugation effect) and larger the number of alkyl groups attached to carbon bearing the positive charge the greater will be the stability of the carbocation. Thus a tertiary carbocation will be more stable than a secondary carbocation which in turn will be more stable than a primary carbocation. *In contrast the groups with electron withdrawing (–I) effect like* $-NO_2$ *will decrease the stability of the carbocation. If the positive charge can be delocalized over adjacent atoms then it results in greater stability of the carbocation. Thus carbocations showing resonance are far more stable than those in which the resonance is not playing any part.* For example allyl and benzyl cabocations are more stable than propyl carbocation.

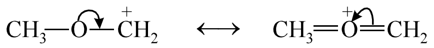


$$CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}\overset{-}{C}H_2$$

(Allyl carbocation)



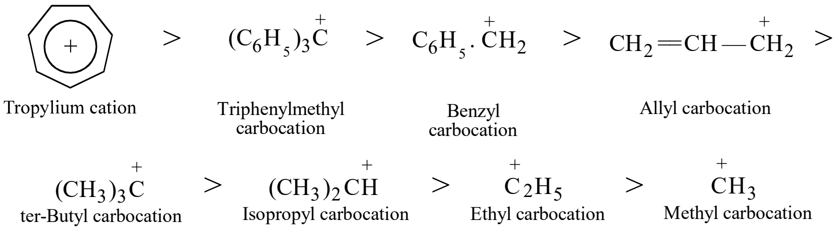
(Benzyl carbocation)



$$CH_3{-}O{-}\overset{+}{C}H_2 \longleftrightarrow CH_3{=}\overset{+}{O}{=}CH_2$$

(Methoxymethyl carbocation)

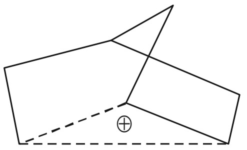
Some of the carbocations in their order of stability are given below:



$$\text{Tropylium cation} > (C_6H_5)_3\overset{+}{C} > C_6H_5\cdot\overset{+}{C}H_2 > CH_2{=}CH{-}\overset{+}{C}H_2 >$$

$$(CH_3)_3\overset{+}{C} > (CH_3)_2\overset{+}{C}H > \overset{+}{C_2H_5} > \overset{+}{CH_3}$$

Some carbocations like norbornyl cation exhibit a symmetrical bridged two electron three centre bonding which has been termed as a **nonclassical carbocation** (J.D. Roberts, 1951). The existence of such ions as reaction intermediates was demonstrated conclusively by G.A. Olah (1964).



In these cations the carbocation centre is always surrounded by eight electrons but is overall electron deficient due to sharing of two electrons between three or more atoms.

According to Brown and Schleyer (1977) a nonclassical carbocation in a positively charged species which cannot be represented by a single Lewis structure because it contains one or more carbon or hydrogen bridges joining the two electron defficient centres. The bridging atoms have coordination numbers higher than usual which may be five or more for carbon and two or more for hydrogen. Thus they have two-electron, three (or multiple) centre bonds including a carbon or hydrogen bridge.

The carbocations are *sp*^{2} hybridised and therefore planar in configuration. In the formation of carbocation intermediate from saturated compounds a tetrahedral carbon atom collapses to a planar arrangement. Thus if an asymmetric carbon atom (*cf.* Isomerism and optical activity) is converted to a carbocation during the course of reaction then, because of the planarity of the latter, the optical activity of the asymmetric carbon atoms will be lost and the resulting product will be optically inactive.

Carbocations undergo three types of reactions:

1. **Combination with a nucleophile or base:** This results in the formation of a neutral molecule. Thus:

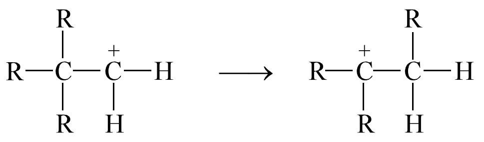
$$\underset{\text{Ethyl cation}}{\overset{+}{C_2H_5}} + \underset{\text{Halide ion}}{:X^-} \longrightarrow \underset{\text{Ethyl halide}}{C_2H_5X}$$

$$\underset{\text{Isopropyl cation}}{(CH_3)_2\overset{+}{CH}} + \underset{\text{Water}}{H_2O:} \longrightarrow (CH_3)_2CH\overset{+}{O}H_2 \xrightleftharpoons{-H^+} \underset{\text{Isopropyl alcohol}}{(CH_3)_2CHOH}$$

2. **Elimination of a proton:** This results in the formation of an olefin, for example,

$$\underset{\text{Ethyl cation}}{CH_3—\overset{+}{C}H_2} \xrightarrow{-\overset{+}{H}} \underset{\text{Ethylene}}{CH_2{=}CH_2}$$

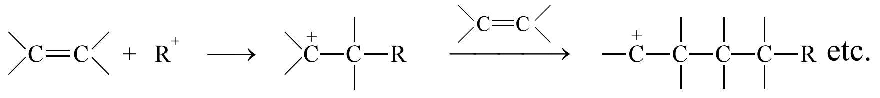
3. **Rearrangement:** In this reaction, another carbocation, usually of greater stability, is formed. Thus a primary carbocation will tend to rearrange so as to form a secondary or tertiary carbocation even if it involves the cleavage of C—H or C—C bonds. Thus:



$$R—\underset{R}{\overset{R}{C}}—\underset{H}{\overset{+}{C}}—H \longrightarrow R—\underset{R}{\overset{+}{C}}—\underset{H}{\overset{R}{C}}—H$$

(A schematic rearrangement reaction)

The carbocations may also combine with olefins to propagate cationic polymerisation.



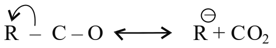
2.3.2 Carbanion

Let us study them in detail.

(i) **Ionization:** The polarity of C – H bond is very small, neterolytic fission of such type of bond is affected y presence of electron attracting substituents (–CN, –NO_2, etc.)

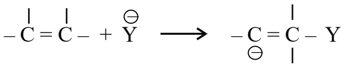
$R-H \longrightarrow R^{\ominus} + H^{\oplus}$

When the leaving group is proton, reaction is simple acid base reaction and acquires a base to remove the proton.



$R-C-O \longleftrightarrow \overset{\ominus}{R} + CO_2$

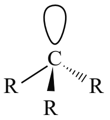
(ii) **Addition of nucleophile:** When a negation ion adds to C = C or C ≡ C, carbanion is generated.



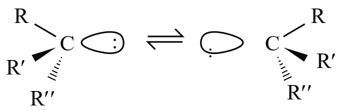
$-\overset{|}{C}=\overset{|}{C}- + \overset{\ominus}{Y} \longrightarrow -\underset{\ominus}{C}=\overset{|}{\underset{|}{C}}-Y$

Structure of Carbanion

It is a trivalent species with formal negative change. The negatively charged carbon is electron rich with octate of electrons in sp^3 hybrid orbits for bonding. The structure of simple un-substituted carbanion is not known with certainty as they could not be isolated but it seems likely that central carbon is sp^3 hybridized and have pyramidal structure similar to those of amines.



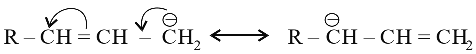
From this structure if appear that if the three R groups are different then carbanion would be chiral and the reaction in which it is intermediate shoudl give retention of configuration practically it could not be demonstrated.



Stability of Carbanions

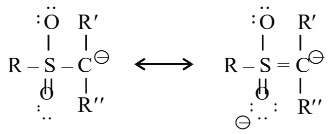
The order of stability of simple carbanion is methyl > primary > secondary > tertiary. The structural features responsible for above order of stability are:

1. **σ-Electron delocalization:** Field effect stabilizes the carbanion by spreading the negative charge on carbon but it is very difficult to separate this effect from resonance effect in case of simple carbanions.
2. **π-Electron delocalization:** When negative charge is conjugated with double or triple bond, the ion is stabilized by resonance in which unshared pair overlaps the π electrons of unsaturated system.



$R-CH=CH-\overset{\ominus}{C}H_2 \longleftrightarrow R-\overset{\ominus}{C}H-CH=CH_2$

3. **pπ – dπ bonding:** Attachment of sulphur or phosphorus atoms to the carbanionic carbon increases the stability of carbanion. One of the possible explanation is, it is due to overlap of unshared pair with an empty d orbitatl (p-d bonding).



4. **S-character of carbanionic carbon:** An increase in amount of S-character at the carbanionic carbon, increases the stability. Thus the order of stability is:

$RC \equiv C^{\ominus} > R_2C = CH^{\ominus} > R_3C - CH_3^{\ominus}$

	$HC \equiv CH$	$CH_2 = CH_2$	$CH_3 - CH_3$
	sp	sp^2	sp^3
S-character	50%	33%	25%

Increased S-character means electrons are closer to nucleus and hence lower energy.

5. **Stabilization by a non-adjacent π bond:** Such stabilization in case of carbanion is less than carbocation.

Reaction of Carbanion

Some of the reactions are as follows:

1. **Reaction with electrophile:** The most common reaction of carbanion is combination with a position species usually a proton.

$\overset{\ominus}{R} + Y^{\oplus} \longrightarrow RY$

2. **Nucleophilic substitution:** Carbanion may act as nucleophile and push out one of the four groups on a saturated carbon atom (S_N^2).
3. **Addition reaction:** Carbanion frequently add to the carbonyl group.
4. **Rearrangement:** Usually carbanions do not undergo rearrangements.

$Ph_3C - \overset{\ominus}{C}H_2 \longrightarrow \overset{\ominus}{P}H_2C\ Ch_2\ PH$

2.3.3 Free Radicals

In chemistry, a radical is an atom, molecule, or ion that has an unpaired valence electron. With some exceptions, these unpaired electrons make radicals highly chemically reactive. Many radicals spontaneously dimerize. Most organic radicals have short lifetimes. A notable example of a radical is the hydroxyl radical (HO.), a molecule that has one unpaired electron on the oxygen atom. Two other examples are triplet oxygen and triplet carbene ($:CH_2$) which have two unpaired electrons.

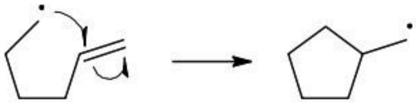
Radicals may be generated in a number of ways, but typical methods involve redox reactions. Ionizing radiation, heat, electrical discharges, and electrolysis are known to produce radicals. Radicals are intermediates in many chemical reactions, more so than is apparent from the balanced equations. Radicals are important in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes. A large fraction of natural products is generated by radical-generating enzymes. In living organisms, the radicals superoxide and nitric oxide and their reaction products regulate many processes, such as control of vascular tone and thus blood pressure. They also play a key role in the intermediary metabolism of various biological compounds. Such radicals can even be messengers in a process dubbed redox signaling. A radical may be trapped within a solvent cage or be otherwise bound.

Depiction in Chemical Reactions

In chemical equations, radicals are frequently denoted by a dot placed immediately to the right of the atomic symbol or molecular formula as follows:

$$Cl_2 \xrightarrow{UV} 2Cl\cdot$$

Radical reaction mechanisms use single-headed arrows to depict the movement of single electrons:



The homolytic cleavage of the breaking bond is drawn with a ‘fish-hook’ arrow to distinguish from the usual movement of two electrons depicted by a standard curly arrow. The second electron of the breaking bond also moves to pair up with the attacking radical electron; this is not explicitly indicated in this case. Radicals also take part in radical addition and radical substitution as reactive intermediates. Chain reactions involving radicals can usually be divided into three distinct processes. These are initiation, propagation, and termination.

- **Initiation** reactions are those that result in a net increase in the number of radicals. They may involve the formation of radicals from stable species as in Reaction 1 above or they may involve reactions of radicals with stable species to form more radicals.
- **Propagation** reactions are those reactions involving radicals in which the total number of radicals remains the same.
- **Termination** reactions are those reactions resulting in a net decrease in the number of radicals. Typically two radicals combine to form a more stable species, for example: $2Cl. \rightarrow Cl_2$

Formation of Radicals

Radicals can be formed by the following methods:

(i) Homolysis

Radicals can form by breaking of covalent bonds by homolysis. The homolytic bond dissociation energies, usually abbreviated as “ΔH°” are a measure of bond strength. Splitting H_2 into 2H., for example, requires a ΔH° of +435 kJ.mol^{-1}, while splitting Cl_2 into 2Cl. requires a ΔH° of +243 kJ.mol^{-1}. For weak bonds, homolysis can be induced thermally. Strong bonds require high energy photons or even flames to induce homolysis.

(ii) From other radicals

Radicals or charged species add to non-radicals to give new radicals. This process is the basis of the radical chain reaction. Being prevalent and a diradical, O_2 reacts with many organic compounds to generate radicals together with the hydroperoxide radical. This process is related to rancidification of unsaturated fats.

(iii) One electron redox

Radicals may also be formed by single-electron oxidation or reduction of an atom or molecule. These redox reactions occur in electrochemical cells and in ionization chambers of mass spectrometers.

Persistence and Stability

Although radicals are generally short-lived due to their reactivity, there are long-lived radicals. These are categorized as follows:

(i) Stable radicals

The prime example of a stable radical is molecular dioxygen (O_2). Another common example is nitric oxide (NO). Organic radicals can be long lived if they occur in a conjugated π system, such as the radical derived from α-tocopherol (vitamin E). There are also hundreds of examples of thiazyl radicals, which show low reactivity and remarkable thermodynamic stability with only a very limited extent of π resonance stabilization.

(ii) Persistent radicals

Persistent radical compounds are those whose longevity is due to steric crowding around the radical center, which makes it physically difficult for the radical to react with another molecule. Examples of these include Gomberg's triphenylmethyl radical, Fremy's salt (Potassium nitrosodisulfonate, $(KSO_3)_2NO.$), aminoxyls, (general formula $R_2NO.$) such as TEMPO, TEMPOL, nitronyl nitroxides, and azephenylenyls and radicals derived from PTM (perchlorophenylmethyl radical) and TTM (tris(2,4,6-trichlorophenyl)methyl radical). Persistent radicals are generated in great quantity during combustion, and may be responsible for the oxidative stress resulting in cardiopulmonary disease and probably cancer that has been attributed to exposure to airborne fine particles.

Gomberg's free radical can be generated by following reaction in lab -

$$(Ph)_3C\text{-}Cl + Ag === (Ph)_3C. + AgCl$$

The reason for persistivity of free radicals is either the delocalisation of unpaired electron (e.g., triphenylmethyl radical) or the unavailability of unpaired electron to other species due to the screening of neighbouring atoms/groups (for example, tri-tert-butylphenoxyl radical).

(iii) Diradicals

Diradicals are molecules containing two radical centers. Multiple radical centers can exist in a molecule. Atmospheric oxygen naturally exists as a diradical in its ground state as triplet oxygen. The low reactivity of atmospheric oxygen is due to its diradical state. Non-radical states of dioxygen are actually less stable than the diradical. The relative stability of the oxygen diradical is primarily due to the spin-forbidden nature of the triplet-singlet transition required for it to grab electrons, i.e., "oxidize". The diradical state of oxygen also results in its paramagnetic character, which is demonstrated by its attraction to an external magnet. Diradicals can also occur in metal-oxo complexes, lending themselves for studies of spin forbidden reactions in transition metal chemistry. Carbenes in their triplet state can be viewed as diradicals centred on the same atom, while these are usually highly reactive persistent carbenes are known, with N-heterocyclic carbenes being the most common example.

Reactivity

Radical alkyl intermediates are stabilized by similar physical processes to carbocations: as a general rule, the more substituted the radical center is, the more stable it is. This directs their reactions. Thus, formation of a tertiary radical ($R_3C\bullet$) is favored over secondary ($R_2HC\bullet$), which is favored over primary ($RH_2C\bullet$). Likewise, radicals next to functional groups such as carbonyl, nitrile, and ether are more stable than tertiary alkyl radicals. Radicals attack double bonds. However, unlike similar ions, such radical reactions are not as much directed by electrostatic interactions. For example, the reactivity of nucleophilic ions with α,β-unsaturated compounds (C=C–C=O) is directed by the electron-withdrawing effect of the oxygen, resulting in a partial positive charge on the carbonyl carbon. There are two reactions that are observed in the ionic case: the carbonyl is attacked in a direct addition to carbonyl, or the vinyl is attacked in conjugate addition, and in either case, the charge on the nucleophile is taken by the oxygen. Radicals add rapidly to the double bond, and the resulting ±-radical carbonyl is relatively stable; it can couple with another molecule or be oxidized. Nonetheless, the electrophilic/neutrophilic character of radicals has been shown in a variety of instances. One example is the alternating tendency of the copolymerization of maleic anhydride (electrophilic) and styrene (slightly nucleophilic).

In intramolecular reactions, precise control can be achieved despite the extreme reactivity of radicals. In general, radicals attack the closest reactive site the most readily. Therefore, when there is a choice, a preference for five-membered rings is observed: four-membered rings are too strained, and collisions with carbons six or more atoms away in the chain are infrequent.

Triplet carbenes and nitrenes, which are diradicals, have distinctive chemistry.

2.3.4 Carbenes

In chemistry, a carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. The general formula is **R-(C:)-R' or R=C:** where the R represents substituents or hydrogen atoms.

The term 'carbene' may also refer to the specific compound **H_2C:**, also called methylene, the parent hydride from which all other carbene compounds are formally derived. Carbenes are classified as either singlets or triplets, depending upon their electronic structure. Most carbenes are very short lived, although

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persistent carbenes are known. One well-studied carbene is dichlorocarbene **Cl_2C:**, which can be generated in situ from chloroform and a strong base.

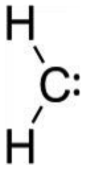


Fig. 2.5 Methylene, the Simplest Carbene

Structures and Bondings

The two classes of carbenes are singlet and triplet carbenes. Singlet carbenes are spin-paired. In the language of valence bond theory, the molecule adopts an sp^2 hybrid structure. Triplet carbenes have two unpaired electrons. Most carbenes have a nonlinear triplet ground state, except for those with nitrogen, oxygen, or sulfur atoms, and halides directly bonded to the divalent carbon.

Carbenes are called singlet or triplet depending on the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they persist long enough. The total spin of singlet carbenes is zero while that of triplet carbenes is one. Bond angles are 125°–140° for triplet methylene and 102° for singlet methylene (as determined by EPR). Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

For simple hydrocarbons, triplet carbenes usually have energies 8 kcal/mol (33 kJ/mol) lower than singlet carbenes, thus, in general, triplet is the more stable state (the ground state) and singlet is the excited state species. Substituents that can donate electron pairs may stabilize the singlet state by delocalizing the pair into an empty p orbital. If the energy of the singlet state is sufficiently reduced it will actually become the ground state. No viable strategies exist for triplet stabilization. The carbene called 9-fluorenylidene has been shown to be a rapidly equilibrating mixture of singlet and triplet states with an approximately 1.1 kcal/mol (4.6 kJ/mol) energy difference. It is, however, debatable whether diaryl carbenes such as the fluorene carbene are true carbenes because the electrons can delocalize to such an extent that they become in fact biradicals. In silico experiments suggest that triplet carbenes can be thermodynamically stabilized with electropositive heteroatoms such as in silyl and silyloxy carbenes, especially trifluorosilyl carbenes.

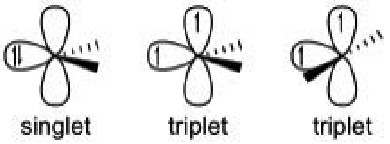


Fig. 2.6 Singlet and Triplet Carbenes

Reactivity

Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.

Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with cis-2-butene or with trans-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product: *cis* from *cis* and *trans* from *trans*, which proves that the methylene is a singlet. If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.

Reactivity of a particular carbene depends on the substituent groups. Their reactivity can be affected by metals. Some of the reactions carbenes can do are insertions into C-H bonds, skeletal rearrangements, and additions to double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.

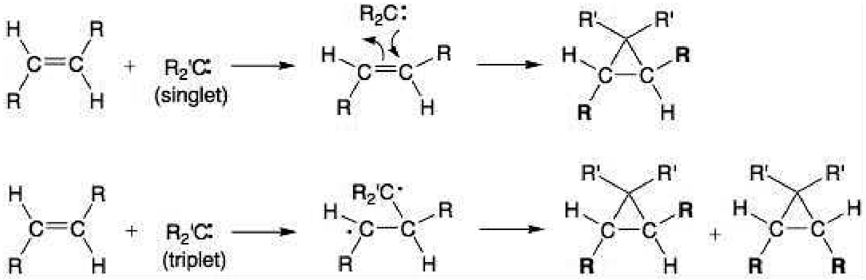


Fig. 2.7 *Carbene Addition to Alkenes*

Cyclopropanation

Carbenes add to double bonds to form cyclopropanes. A concerted mechanism is available for singlet carbenes. Triplet carbenes do not retain stereochemistry in the product molecule. Addition reactions are commonly very fast and exothermic. The slow step in most instances is generation of carbene. A well-known reagent employed for alkene-to-cyclopropane reactions is Simmons-Smith reagent. This reagent is a system of copper, zinc, and iodine, where the active reagent is believed to be iodomethylzinc iodide. Reagent is complexed by hydroxy groups such that addition commonly happens syn to such group.

Fig. 2.8 *Carbene Cyclopropanation*

C—H insertion

Insertions are another common type of carbene reactions. The carbene basically interposes itself into an existing bond. The order of preference is commonly:

1. X–H bonds where X is not carbon 2. C–H bond 3. C–C bond. Insertions may or may not occur in single step.

Intramolecular insertion reactions present new synthetic solutions. Generally, rigid structures favor such insertions to happen. When an intramolecular insertion is possible, no intermolecular insertions are seen. In flexible structures, five-membered ring formation is preferred to six-membered ring formation. Both inter- and intramolecular insertions are amendable to asymmetric induction by choosing chiral ligands on metal centers.

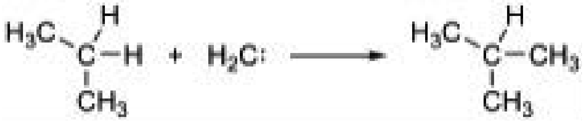


Fig. 2.9 Carbene Insertion

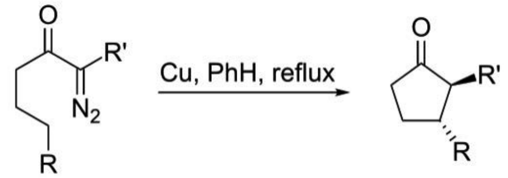


Fig. 2.10 Carbene Intramolecular Reaction

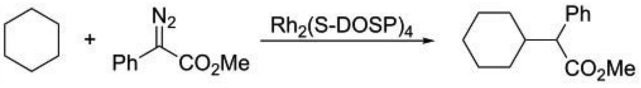


Fig. 2.11 Carbene Intermolecular Reaction

Alkylidene carbenes are alluring in that they offer formation of cyclopentene moieties. To generate an alkylidene carbene, a ketone can be exposed to trimethylsilyl diazomethane.

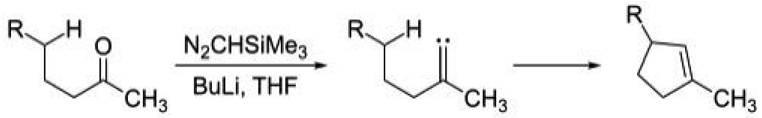


Fig. 2.12 Alkylidene Carbene

Generation of Carbenes

Carbenes can be generated by the following methods:

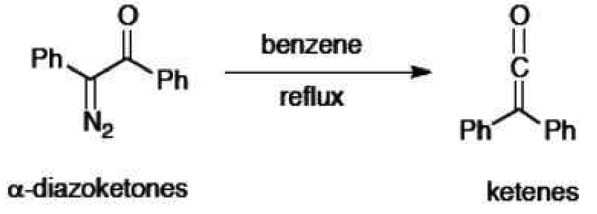
- A method that is broadly applicable to organic synthesis is induced elimination of halides from gem-dihalides employing organolithium reagents. It remains uncertain if under these conditions free carbenes are formed or metal-carbene complex. Nevertheless, these metallocarbenes (or carbenoids) give the expected organic products.

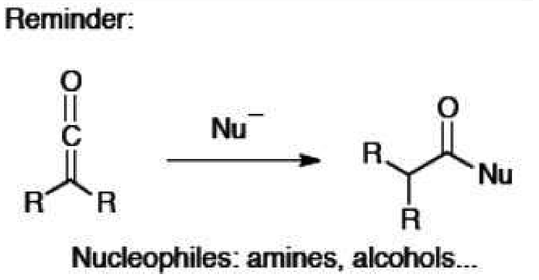
  $R_2CBr_2 + BuLi \rightarrow R_2CLi(Br) + BuBr$

  $R_2CLi(Br) \rightarrow R_2C + LiBr$

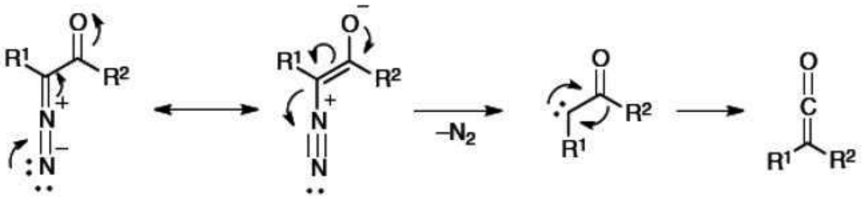
- For cyclopropanations, zinc is employed in the Simmons–Smith reaction. In a specialized but instructive case, alpha-halomercury compounds can be isolated and separately thermolyzed. For example, the 'Seyferth reagent' releases CCl_2 upon heating.

  $C_6H_5HgCCl_3 \rightarrow CCl_2 + C_6H_5HgCl$
- Most commonly, carbenes are generated from diazoalkanes, via photolytic, thermal, or transition metal-catalyzed routes. Catalysts typically feature rhodium and copper. The Bamford-Stevens reaction gives carbenes in aprotic solvents and carbenium ions in protic solvents.
- Base-induced elimination HX from haloforms (CHX_3) under phase-transfer conditions.
- Photolysis of diazirines and epoxides can also be employed. Diazirines are cyclic forms of diazoalkanes. The strain of the small ring makes photoexcitation easy. Photolysis of epoxides gives carbonyl compounds as side products. With asymmetric epoxides, two different carbonyl compounds can potentially form. The nature of substituents usually favors formation of one over the other. One of the C-O bonds will have a greater double bond character and thus will be stronger and less likely to break. Resonance structures can be drawn to determine which part will contribute more to the formation of carbonyl. When one substituent is alkyl and another aryl, the aryl-substituted carbon is usually released as a carbene fragment.
- Carbenes are intermediates in the Wolff rearrangement, as shown below:





Mechanism



2.3.5 Nitrenes

In chemistry, a nitrene (R–N:) is the nitrogen analogue of a carbene. The nitrogen atom has only 6 valence electrons and is therefore considered an electrophile. A nitrene is a reactive intermediate and is involved in many chemical reactions. The simplest nitrene, HN, is also called imidogen.

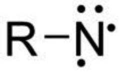


Fig. 2.13 Generic Structure of a Nitrene Group

Electron Configuration

In the most simple nitrene, the linear imidogen (:N–H), two of the 6 available electrons form a covalent bond with hydrogen, two others create a free electron pair and the two remaining electrons occupy two degenerate p orbitals. Consistent with Hund's rule the low energy form of imidogen is a triplet with one electron in each of the p orbitals and the high energy form is the singlet state with an electron pair filling one p orbital and the other one vacant.

As with carbenes, a strong correlation exists between the spin density on the nitrogen atom which can be calculated in silico and the zero-field splitting parameter D which can be derived experimentally from electron spin resonance. Small nitrenes such as NH or CF_3N have D values around 1.8 cm^{-1} with spin densities close to a maximum value of 2. At the lower end of the scale are molecules with low D (< 0.4) values and spin density of 1.2 to 1.4 such as 9-anthrylnitrene and 9-phenanthrylnitrene.

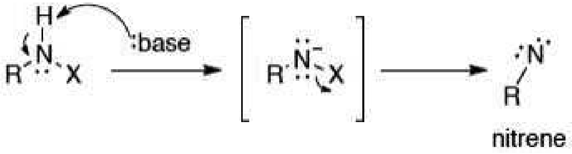
Structure and Hybridization

Nitrenes are nitrogen analogous of carbenes. The nitrogen atom possess only six valence electrons; in nitrenes the triplet state is lower in energy than the single state. Because nitrenes are so reactive, they are not isolated. Instead, they are formed as reactive intermediates during a reaction. There are two common ways to generate nitrenes:

- From azides by thermolysis or photolysis, with expulsion of nitrogen gas. This method is analogous to the formation of carbenes from diazo compounds.
- From isocyanates, with expulsion of carbon monoxide. This method is analogous to the formation of carbenes from ketenes.

Generation

(i) From 1, 1 elimination:

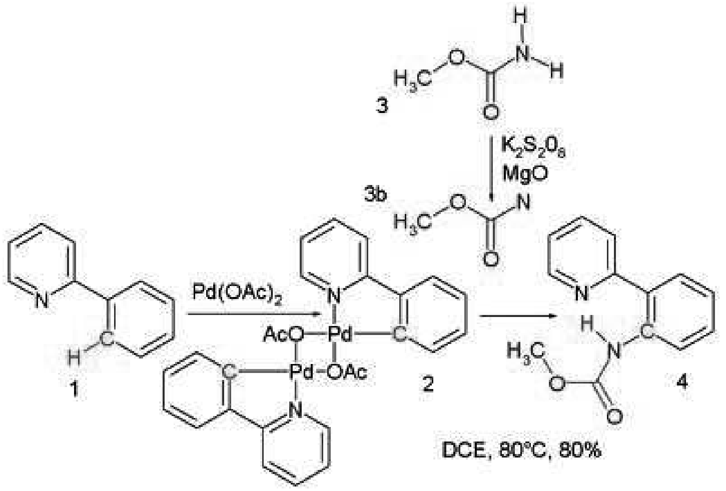


(ii) From azides:

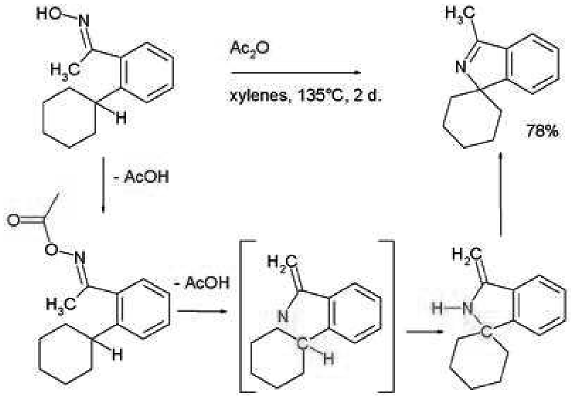
Reactions

Nitrene reactions include:

- **Nitrene C–H Insertion:** A nitrene can easily insert into a carbon to hydrogen covalent bond yielding an amine or amide. A singlet nitrene reacts with retention of configuration. In one study a nitrene, formed by oxidation of a carbamate with potassium persulfate, gives an insertion reaction into the palladium to nitrogen bond of the reaction product of palladium(II) acetate with 2-phenylpyridine to methyl N-(2-pyridylphenyl)carbamate in a cascade reaction:



A nitrene intermediate is suspected in this C–H insertion involving an oxime, acetic anhydride leading to an isoindole:



- **Nitrene Cycloaddition:** With alkenes, nitrenes react to form aziridines, very often with nitrenoid precursors such as nosyl- or tosyl-substituted [N-(phenylsulfonyl)imino]phenyliodinane (PhI=NNs or PhI=NTs respectively))

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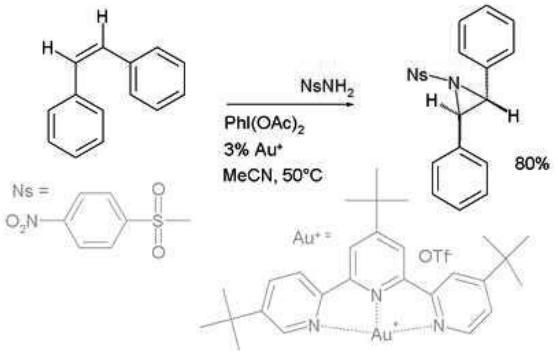
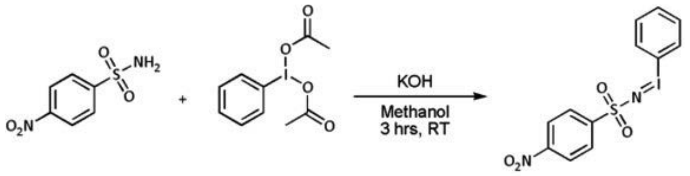
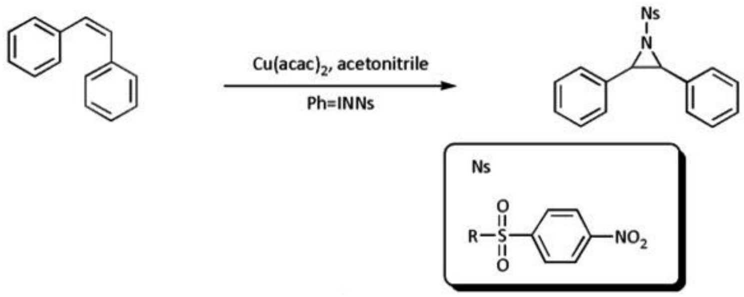
but the reaction is known to work directly with the sulfonamide in presence of a transition metal based catalyst such as copper, palladium, or gold:



In most cases, however, [N-(p-nitrophenylsulfonyl)imino]phenyliodinane (PhI=NNs) is prepared separately as follows:



Nitrene transfer takes place next:



In this particular reaction both the cis-stilbene illustrated and the *trans* form (not depicted) result in the same *trans*-aziridine product, suggesting a two-step reaction mechanism. The energy difference between triplet and singlet nitrenes can be very small in some cases, allowing interconversion at room temperature. Triplet nitrenes are thermodynamically more stable but react stepwise allowing free rotation and thus producing a mixture of stereochemistry.

Check Your Progress

5. Define cabanions.
6. What are diradicals?
7. State the electron configuration of simple nitrene.

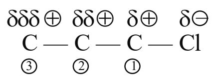
2.4 EFFECT OF STRUCTURE ON REACTIVITY

In organic molecules, the reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it to proceed in a different path. In case of two compounds with same functional group and undergoing same reaction the rates and/or the position of equilibrium are usually different, sometimes slightly, sometimes greatly depending upon the structure of the molecule.

The effect of structure on reactivity of organic molecule may be classified into three major type field, resonance and steric. Resonance and field effect are collectively called as electrical effects.

2.4.1 Field and Resonance effect

A covalent bond between two similar electronegative elements has no polarity. Howevber, when the bond is between two dissimilar electro negative elements it acquires polarity. Now consider a carbon chain in which the terminal carbon is linked to chlorine atom.

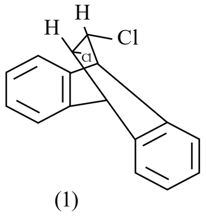


$$\underset{③}{\overset{\delta\delta\delta\oplus}{C}} — \underset{②}{\overset{\delta\delta\oplus}{C}} — \underset{①}{\overset{\delta\oplus}{C}} — \overset{\delta\ominus}{Cl}$$

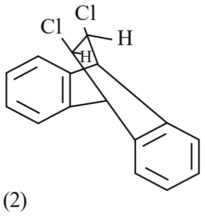
In the above chain, chlorine atom acquires partial negative change due to displacement of covalent electron pair towards chlorine atom.

At the same time due to displacement C_1 is deprived of electrons and acquires partial positive charge. This is compensated by drawing the $C_1 - C_2$ bond electrons closer to itself, resulting to develop partial positive charge on the C_2 atom (less than that of C_1). Thus polarisation of one bond causing polarisation of other bond due to displacement of electrons is called as inductive effect. It is a permanent effect.

For example consider 1 and 2 isomer the acidity of both the isomers will not be affected by inductive effect of chlorine atom as similar types of bonds intervene between chlorine atom and carboxyl group but the field effect will be different in each case. In (1) chlorine atom is closer in space to carboxylic group hence more effective field effect results in lowering of acidity.



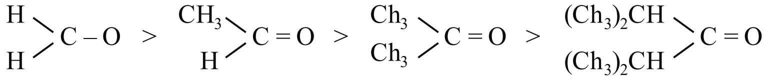
(1)
$PK_a = 6.07$



(2)

2.4.2 Steric effect

Reactivity of the molecule due to presence of the bulky alkyl group hinders approach of the nucleophile to the carbon atom of the reacting molecule, this is called the steric factor (effect) obviously as number and size of alkyl group increase, attack of the nucleophile on the carbon atom becomes more difficult due to the steric hindrance. Reactivity order of the following compounds due to hindrence is as follows:



$$\mathrm{H_2C{-}O} > \mathrm{(CH_3)(H)C{=}O} > \mathrm{(Ch_3)_2C{=}O} > \mathrm{((Ch_3)_2CH)_2C{=}O}$$

Formaldehyde Acetaldehyde Acetone Diisporopyl ketone

2.4.3 Quantitative Treatment

Treatment of the effect of structure on reactivity i.e., how the resonance effect, field effect, and steric effect impact the reaction rate in measurable numbers.

- **The Hammette Equation**

Consider an organic reaction is carried out on a substrate which can be denoted as XRY. X is a variable and Y is the reaction spot and R represents the basic structure. In this type of case, replacing X = H and X = CH_3, result in an increment in the rate of reaction op ten times. However, it is still a mystery what part of the rate enhancement comes from resonance effect, field effect or steric effect. To do so, it is reasonable to use compounds where one or two effects are so small that they simply can be neglected. Although it is the oversimplification of the problem, quantitative result can still be obtained. The Hammette equation is the first attempt to give numerical value for the quantitative treatment of structure on reactivity.

Hammett, proposed the equation for the cases of m and p - X C_6 H_4Y as given below:

$$\log \frac{k}{K_0} = \sigma p$$

where k and K_0 are the constant for the group X ≠ H and X = H, ρ and σ are the constant for reaction conditions and substituent X, respectively.

Derivation of Hammett equation

Hydrolysis of benzoic acid as given:

$$XC_6H_4COOH + H_2O \xrightleftharpoons{Ka} XC_6H_4COO^- + H_3O^+$$

where X is a substituent at the m or p-position and Ka is the dissociation constant. As expected, the dissociation constant was found to be different for differently substituted substrate.

Since an electron withdrawing group will better stabilize the conjugate base (X C_6 H_4 COO^-), resulting in larger magnitude of Ka (Lower pKa). On the other hand, an electron donating group will destabilize the conjugate base (i.e., XC_6 H_4 COO^-), resulting in a smaller magnitude of Ka (higher pKa). Therefore we can say that the electronic effect of a substituent can be represented as the difference between the pKa values of its benzoic acid derivative and the pKa value of benzoic acid itself, mathematically, we can say

$$\sigma_X = \log(Ka) - \log(Ka)_0$$
$$= -\rho(Ka) - r\,(Ka)_0$$

Where the parameter σ_X (or σ) is called as substituent constant, and was found for several different group just substracting its benzoic acid derivative's pKa value from pKa value of benzoic acid.

Table 2.2 *pKa Values and Substituent Constant for XC_6H_6COOH using Benzoic Acids p(Ka)0 = 4.21*

Substituent	**P_m(Ka)**	**P_p(Ka)**	**$\sigma_m = P(Ka)_0 - P_m(Ka)$**	**$\sigma_p = p(Ka)_0 - P_p(Ka)$**
NO_2	3.50	3.43	0.71	0.78
CH_3	4.28	4.38	–0.07	–0.17
OCH_3	4.09	4.48	0.12	–0.27
F	3.87	4.15	0.34	0.06
Br	3.82	3.98	0.39	0.23
Cl	3.84	3.98	0.37	0.23
$CoCH_3$	3.83	3.71	0.38	0.50

Using log m – log n = log m/n

$$\log \frac{Ka}{(Ka)_0} = \sigma$$

Now if we plot a curve between log $Ka/(Ka)_0$ vs σ, we will definitely get a straight line with a slope = 1.

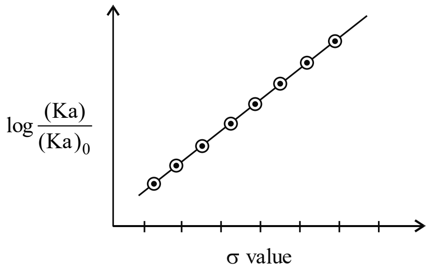


Fig. 2.14 *Variation of log $Ka/(Ka)_0$ vs σ for Substituted Benzoic Acids*

For electron withdrawing groups such as m-Cl, p-Cl the ratio k/k0 > 1 i.e., positive σ value. On the other hand for electron donating groups the value is < 1 i.e., negative value of σ.

Ortho substituents are not usually treated with the contct of the Hammett equation because steric effects can interfere with the purely electronic effects and variable from reaction to reaction.

- **Taft Equation**

The Taft equation is a linear free energy relationship used in physical organic chemistry in the study of reaction mechanism and in the development of quantitative structures activity relationships for organic compound. It was developed by Robert W. Taft in 1952 as a modification to the Hammett equation. Taft equation also describe the steric effects of a substituent.

$$\log \frac{ks}{K_{CH_3}} = \rho^*\sigma^* + \delta Es$$

where

$\log \frac{ks}{K_{CH_3}}$ = ratio of the rate of the substituted reaction compared to the reference reaction

ρ^* = senstivity factor for the reaction to polar effects
σ^* = polar substituent constant that describes the field and the inductive effects of the substituents
δ = senstivity factor for the reaction to steric facxtor for the reaction to steric effect.
Es = steric substituent constant

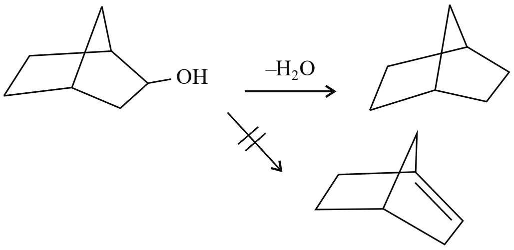
Table 2.3 *Constant Used in the Taft Equation*

Substituent	Es	σ^*
–H	1.24	0.49
$-CH_3$	0	0
$-CH_2CH_3$	–0.07	–0.1
$-CH(CH_3)_2$	–0.47	–0.19
$-C(CH_3)_3$	–1.54	–0.3
$-CH_2Ph$	–0.38	0.22
–Ph	–2.55	0.6

- **Bridgehead System**

Bridgehead alkene represent a subclass of strained organic molecule that have been of intense interest to chemist for over fifty years.

According to Bredt's rule, in small bridging system double bond cannot be placed at the bdigehead of a bridged ring system because it is equivalent to having a trans double bond on a ring, which causes ring strain, and angle strain in small rings. The p orbitals of the bridgehead atom and adjacent atoms are orthogonal to each other and are not properly dligned for the formation of π-bond. It shows tendency of double bond to form away from the bridgehead position.



The bridgehead structure present substitution occuring by the S_N^2 mechanism and inhibits reaction by the S_N^1 mechanism. All the bridgehead ring system are so unreactive towards nucleophlic subsitution.

Check Your Progress

8. How are the effects of structure on reactivity of molecule classified?
9. Define steric effect.
10. Write the Hammett equation.
11. What is the use of the Taft equation?

2.5 FREE RADICAL REACTIONS

Let us study the types of free radical reactions in detail.

2.5.1 Polymerisation Reactions

The combination of simple molecules repeatedly two or more times in some regular manner so that they combine to form a larger or long chain molecule is known as polymerisation. The simple molecules which combine together are called, monomers and the products are known as **dimer** (only two monomer units), **trimer** (only three monomer units), or **polymer** (many monomer units). **Carothers in 1931 defined polymerization as intermolecular combinations that are functionally capable of proceeding indefinitely**. Starting from a monomer M formation of the polymer may be shown as:

$$nM \xrightarrow{\text{Polymerisation}} M_n$$

$$\underset{\text{Monomer}}{M} \xrightarrow{+M} \underset{\text{Dimer}}{M—M} \xrightarrow{+M} \underset{\text{Trimer}}{M—M—M} \xrightarrow{+nM} \underset{\text{Polymer}}{M—(M)_{n+1}—M}$$

Similarly starting from two different monomers M and M^1 the polymerisation may be shown as:

$$\underset{\text{Co-monomers}}{M + M^1} \longrightarrow M—M^1 \xrightarrow{+M} M—M^1—M \xrightarrow{+M^1} \underset{\text{Dimer}}{M—M^1—M—M^1}$$

$$\xrightarrow{n(M + M^1)} \underset{\text{Polymer}}{M—(M^1—M)_{n+1}—M^1}$$

In these cases dimer is the compound having two repetitive monomer units, trimer having three, and polymer having many such repetitive units. *A polymer which is formed from more than one monomer is often referred to as a copolymer of these co-monomers.*

A vast majority of natural products like proteins, starch, rubber cellulose etc., are all polymers and are called natural polymers. The attempts to imitate these natural polymers have resulted in an exhaustive and systematic study of the process of polymerisation and a large number of new synthetic polymers like plastics, nylons, terylene have been developed by purely synthetic methods. The monomers for these synthetic polymers are mostly obtained from petroleum and are called petrochemicals.

Polymerisation reactions are divided into two groups:

1. *Condensation polymerisation* 2. *Addition polymerisation.*

In condensation polymerisation the basic monomer units combine through a condensation reaction by elimination of simple molecules (water, ammonia etc.) to give a product, generally of high molecular weight. Nylon and terylene are condensation polymers. Nylon is a polyamide formed by condensation of adipic acid with hexamethylene diamine accompanied with the elimination of water molecules.

$$\underset{\text{Adipic acid}}{HOOC.(CH_2)_4.COOH} + \underset{\text{Hexamethylene diamine}}{H_2N(CH_2)_6NH_2} \xrightarrow[\text{(Formation of amide linkages)}]{-H_2O}$$

$$\underset{\text{Nylon (Polyamide)}}{HOOC(CH_2)_4—CO[NH—(CH_2)_6.NHCO—(CH_2)_4—CO]_n—NH(CH_2)_6—NH_2}$$

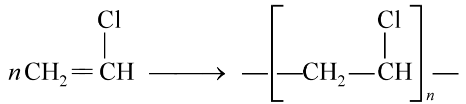
Terylene is a polyester formed by the condensation of terephthalic acid with ethylene glycol accompanied with the elimination of water molecules.

$$\underset{\text{Ethylene glycol}}{n\,HO.CH_2.CH_2.OH} + \underset{\text{Terephthalic acid}}{nHOOC.C_6H_4.COOH} \xrightarrow[\text{(Formation of ester linkages)}]{-H_2O}$$

$$\underset{\text{Terylene (Polyester)}}{HO.CH_2.CH_2—O—[OC.C_6H_4.CO.O.CH_2CH_2.O]_n—OC.C_6H_4.COOH}$$

In addition polymerization, the monomer units combine together to give a new product having the same empirical formula but a higher molecular weight. There is no liberation of simple small molecules like water during addition polymerisation. The monomers for addition polymerisation are mainly unsaturated compounds. For example ethylene polymerises to give polyethylene or polythene—a plastic; and vinyl chloride polymerises to give polyvinyl chloride or P.V.C.

$$\underset{\text{Ethylene}}{n\,CH_2{=}CH_2} \longrightarrow —[CH_2—CH_2]_n— \qquad \textit{(Polyethylene)}$$



$$\underset{\text{Vinyl chloride}}{n\,CH_2{=}\overset{\overset{Cl}{|}}{C}H} \longrightarrow —\left[—CH_2—\overset{\overset{Cl}{|}}{C}H\right]_n— \qquad \textit{(Polyvinyl chloride)}$$

Vinyl chloride

(Polyvinyl chloride)

The addition polymerisation may be initiated by anionic, cationic or free radical reagents. Such a reagent is known as initiator and this determines the type and course of polymerisation reaction. The three different types of mechanisms for addition polymerisation are given below:

Free radical mechanism

1. *Initiation*

$$I \ \textit{(Initiator)} \longrightarrow I. \qquad \textit{(Free radical)}$$

$$I^{\cdot} + CH_2{=}CH_2 \longrightarrow I—CH_2—\dot{C}H_2 \qquad \textit{(New free radical)}$$

2. *Propagation*

$$I—CH_2—\dot{C}H_2 + CH_2{=}CH_2 \longrightarrow I—CH_2—CH_2—CH_2—\dot{C}H_2 \text{ and so on}$$

3. *Termination*

$$2\ I—[—CH_2—CH_2—]_n—\dot{C}H_2 \longrightarrow I—[—CH_2—CH_2]_{2n+1}—I$$

$$\xrightarrow{I^{\cdot}} \underset{\text{Polymer}}{I—[—CH_2—CH_2—]_n—CH_2I} \text{ etc.}$$

Anionic mechanism

1. *Initiation*

$$I \longrightarrow X^- \qquad \text{(Anion)}$$

$$X^- + CH_2{=}CH_2 \longrightarrow X{-}CH_2{-}\overset{-}{C}H_2 \qquad \text{(A new anion)}$$

2. *Propagation*

$$X{-}CH_2{-}\overset{-}{C}H_2 + CH_2{=}CH_2 \longrightarrow X{-}CH_2{-}CH_2{-}CH_2{-}\overset{-}{C}H_2$$

and so on.

3. *Termination*

$$X{-}[{-}CH_2{-}CH_2{-}]_n{-}\overset{-}{C}H_2 \xrightarrow{H^+\text{or a cation}} \underset{\text{Polymer}}{X{-}[{-}CH_2{-}CH_2{-}]_n{-}CH_3}$$

Cationic mechanism

1. *Initiation*

$$I \longrightarrow E^+ \qquad \text{(Cation)}$$

$$E^+ + CH_2{=}CH_2 \longrightarrow E{-}CH_2{-}\overset{+}{C}H_2 \qquad \text{(A new cation)}$$

2. *Propagation*

$$E{-}CH_2{-}\overset{+}{C}H_2 + CH_2{=}CH_2 \longrightarrow E{-}CH_2{-}CH_2{-}CH_2{-}\overset{+}{C}H_2$$

and so on.

3. *Termination*

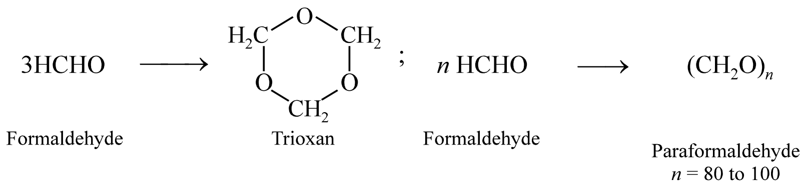
$$E{-}[{-}CH_2{-}CH_2{-}]_n{-}\overset{+}{C}H_2 \xrightarrow{X^-\text{(an anion)}} \underset{\text{Polymer}}{E{-}[{-}CH_2{-}CH_2{-}]_n{-}CH_2X}$$

Distinction Between Condensation and Polymerisation

Some of the points that can distinguish condensation and polymerisation are as follows:

1. Most common feature of the polymerisation reactions is that these are reversible reactions. Thus polymers by simple chemical operations may be converted back to monomers. Condensation reactions may or may not be reversible.
2. The polymers generally have very high molecular weights (except simple dimer, trimer etc.) whereas condensation products have comparatively lower molecular weights.
3. The condensation reaction may takes place between same or different molecules or different types of groups whereas polymerisation occurs between similar monomers except in case of condensation polymerisation.
4. The molecular weight of polymers is a simple multiple of monomer molecular weight except in condensation polymerisation. The condensation products are formed by elimination of simple molecules and thus their molecular weights do not bear any multiple relationship with starting material.
5. Condensation reactions generally proceed through the formation of new carbon to carbon bonds between the condensing molecules whereas it is not necessary in polymerisation reactions. Thus simple polymers of many

compounds like aldehydes involve only formation of bonds between carbon and oxygen. Thus formaldehyde gives:



6. Generally condensation refers to those reactions in which the resultant product is made up of a smaller number of reacting molecules but if the number of reacting molecules is large it is called condensation polymerisation.

2.5.2 Substitution Reaction—Free Radical Substitution

Substitution reactions initiated by free radicals are known as free radical substitution reactions. A mechanism for such a general reaction $A - B + C - D \rightarrow A - C + B - D$ may be written as:

(*i*) Initiation ← $A—B \rightarrow A\cdot + \cdot B$ (Homolysis)
(*ii*) Reaction ← $C—D + A\cdot \rightarrow C—A + \cdot D$ (Propagation)
(*iii*) Termination $\cdot B + \cdot D \rightarrow B—D$
or $\cdot D + \cdot D \rightarrow D—D$

The initiation step is generally induced by heat or light depending on the molecule to be broken homolytically. Peroxides, peracids, azo compounds etc., are the most common source of free radicals. The halogen molecules and ketones give free radicals by absorbing energy from light. In the second step, the step of actual reaction, a free radical on reacting with a molecule C—D generates a new radical ·D. This step is also referred to as propagation step. Finally all free radical reactions terminate by combination of free radicals or by disproportionation. Actually there may be a very large number of propagation steps in between initiation and termination of free radical reactions.

Free radical reactions are characterized by the three important features (*i*) *They are unaffected by the polar substances like acids, bases or polar solvents,* (*ii*) *They are initiated and accelerated by a free radical source, and* (*iii*) *They are inhibited by substances that scavenge free radicals e.g.* O_2, *benzoquinone etc.*

The important free radical substitutions illustrated here are halogenation of alkanes; and arylation of aromatic compounds by diazonium salts (Gomberg reaction).

Reactivity and structure

The reactivity of a substrate to free radical substitution has been studied with hydrogen as a departing group and the chlorine radical as attacking or abstracting reagent. *Normally for different types of hydrogen the rate of substitution increases in the order primary < secondary < tertiary.*

The preferred position of substitution in alkyl radicals attached to aromatic ring is the α-hydrogen because the resulting radical, after removal of hydrogen, can acquire stability by delocalizing this electron over the entire ring. The positions next to electron withdrawing groups like —COOH, —CN etc. are generally not attacked by free radicals. This may appear rather strange because radical reactions are not influenced by electron density distribution in substrate but since the combination of free radical with an electron of the molecule requires sufficient electron density at the centre, hence the effect. Solvents usually have no effect on such reactions. If the reaction takes place with optically active reactants the products are racemic because of planar configuration of free radical.

Applications

Some of the applications are as follows:

(i) Halogenation of alkanes

Chlorination of methane is induced by light and is a free radical substitution reaction. The mechanism for the reaction may be explained as follows:

In the initiation step a molecule of halogen (chlorine in this reaction) by absorption of energy from sunlight, gives two chlorine free radicals by homolysis. In the propagation step, this radical then abstracts a proton from hydrocarbon (methane) to give a methyl free radical and HCl molecule. This methyl free radical then cleaves a chlorine molecule by homolysis to form methyl chloride and chlorine free radical which may again start the propagation step till all methane and chlorine is used up, giving CH_2Cl_2, $CHCl_3$ and CCl_4. The reaction terminates when two free radicals combine to give a neutral molecule.

$$\text{Initiation} \qquad Cl_2 \xrightarrow[\text{Light}]{h\nu} 2Cl\cdot$$

$$\text{Propagation} \qquad \begin{cases} Cl\cdot + CH_4 \longrightarrow CH_3\cdot + HCl \\ CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot \end{cases}$$

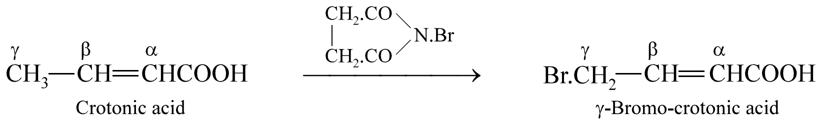
$$\text{Termination} \qquad \begin{cases} CH_{\dot{3}} + Cl\cdot \longrightarrow CH_3Cl \\ 2CH_3\cdot \longrightarrow CH_3—CH_3 \end{cases}$$

Allytic and benzylic bromination

Bromination with N-bromosuccinimide (NBS) used to introduce bromine adjacent to olefinic, aromatic and carbonyl groups (Wohl-Ziegler bromination) is also a free radical substitution reaction.

$$C_6H_5CH_3 \xrightarrow{\text{NBS}} C_6H_5—CH_2—Br$$

$$CH_2 = CH—CH_3 \xrightarrow{\text{NBS}} CH_2 = CH—CH_2—Br$$



$$\overset{\gamma}{C}H_3—\overset{\beta}{C}H=\overset{\alpha}{C}HCOOH \xrightarrow{(CH_2.CO)_2N.Br} Br.\overset{\gamma}{C}H_2—\overset{\beta}{C}H=\overset{\alpha}{C}HCOOH$$

The reaction is favoured at low concentrations of Br_2. The low energy of allylic C—H bond helps in honelysis to form a resonance stabilized radical.

(*ii*) Oxidation of hydrocarbons by oxygen

The photosensitized air oxidation of many organic compounds is a free radical substitution reaction initiated by oxygen in presence of initiators. The reaction proceeds as:

Initiation $$R—H \xrightarrow[\text{Initiator radical (I}^{\cdot}\text{)}]{O_2} R—\dot{O}_2 + I—H$$

Propagation $$\begin{cases} RO_2\cdot + R—H \longrightarrow R—O—O—H + R\cdot \\ R\cdot + O_2 \longrightarrow R—O_2\cdot \end{cases}$$

Termination $$RO_2\cdot + R\cdot \longrightarrow R—O—O—R \text{ etc.}$$

(*iii*) Arylation of aromatic compounds (Gomberg reaction)

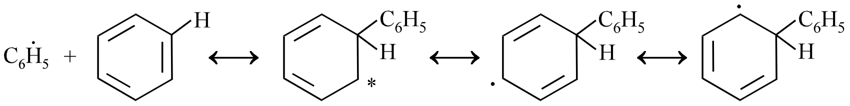
The reaction of benzene diazonium halide with benzene gives diphenyl by a free radical substitution reaction.

$$C_6H_5—H + \underset{\text{Benzene diazonium chloride}}{C_6H_5\overset{+}{N}_2\overset{-}{X}} \xrightarrow{\text{Alkali}} \underset{\text{Diphenyl}}{C_6H_5—C_6H_5}$$

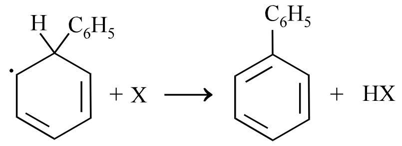
The mechanism of the reaction is as follows:

Initiation $$\underset{\text{(In neutral or basic medium)}}{C_6H_5—N{=}N—X} \longrightarrow C_6\dot{H}_5 + N_2 + \dot{X}$$

Propagation



Termination



Diphenyl

2.5.3 Free-Radical Addition

Free-radical addition is an addition reaction in organic chemistry involving free radicals. The addition may occur between a radical and a non-radical, or between two radicals.

The basic steps with examples of the free-radical addition (also known as radical chain mechanism) are:

- **Initiation by a radical initiator:** A radical is created from a non-radical precursor.
- **Chain propagation:** A radical reacts with a non-radical to produce a new radical species

- **Chain termination:** Two radicals react with each other to create a non-radical species

Free-radical reactions depend on a reagent having a (relatively) weak bond, allowing it to homolyse to form radicals (often with heat or light). Reagents without such a weak bond would likely proceed via a different mechanism. An example of an addition reaction involving aryl radicals is the Meerwein arylation.

2.5.4 Free Radical Rearrangement

In chemistry, a free radical is defined as an atom, molecule or ion that has unpaired valence electrons or an open electron shell, and therefore it can be possibly seen as having one or more 'Dangling' covalent bonds. These dangling bonds produce free radicals which are highly and chemically reactive towards other substances, or even towards themselves with some exceptions, these molecules may suddenly dimerize or polymerize when these molecules come in contact with each other. Most of the radicals are relatively stable only at very low concentrations in inert media or in a vacuum.

A significant example of a free radical is the hydroxyl radical (HO•), a molecule that is one hydrogen atom short of a water molecule and therefore has one bond 'Dangling' from the oxygen. Two other important examples include the carbene molecule ($:CH_2$) which has two dangling bonds, and the superoxide anion ($\bullet O^{-2}$), the oxygen molecule O_2 with one extra electron, which has one dangling bond. On the contrary, the hydroxyl anion (HO^-), the oxide anion (O^{-2}) and the carbenium cation (CH^{+3}) are not radicals, because the bonds that occur may be dangling and actually resolved by the addition or removal of electrons.

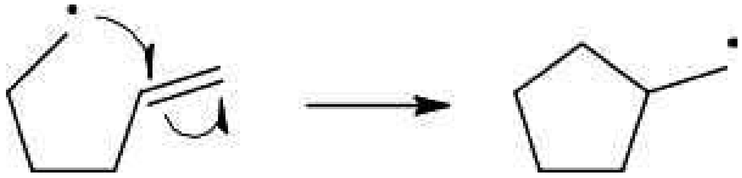
Free radicals can be produced by several methods, including synthesis with very diluted or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. This can be impacted by any specific process that gives sufficient energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Certainly, radicals are intermediate stages in many chemical reactions.

In chemical equations, free radicals are normally denoted by means of a dot placed immediately to the right of the atomic symbol or molecular formula as shown below:

$$Cl_2 \xrightarrow{UV} Cl\cdot + Cl\cdot$$

In the above reaction, the Chlorine gas is typically broken down by means of UV (Ultra-Violet) light forming atomic chlorine radicals.

Radical reaction mechanisms typically use single-headed arrows in order to depict the movement of single electrons, as shown below:



The homolytic cleavage of the breaking bond is specifically illustrated using a ‘Fish-Hook’ arrow for distinguishing it from the normal regular movement of two electrons which are depicted by means of a standard curly arrow. Remember that the second electron of the breaking bond also moves to pair up with the attacking radical electron.

Free radicals also actively participate in the radical addition reaction and radical substitution reaction as reactive intermediates. Chain reactions which involve free radicals can be typically divided into three distinct processes. These are referred as initiation, propagation, and termination.

- Initiation reactions are those reactions that result in a net increase in the number of free radicals. They may involve the formation of free radicals from stable species, or they may involve reactions of free radicals with stable species to form more free radicals.
- Propagation reactions are those reactions that involve free radicals in which the total number of free radicals remains the same.
- Termination reactions are those reactions which result in a net decrease in the number of free radicals. Characteristically, two free radicals combine to form a more stable species, for example: 2Cl·’! Cl_2.

Formation of Radicals

The formation of radicals includes homolytically breaking of covalent bonds, a method that needs substantial amounts of energy. For example, splitting of H_2 into 2H· needs ΔH° of +435 kJ/mol energy, and splitting of Cl_2 into 2Cl· needs ΔH° of +243 kJ/mol energy. This is termed as the homolytic bond dissociation energy and is generally abbreviated using the symbol ΔH°. The bond energy between two covalently bonded atoms is influenced by the structure of the molecule as a whole and not simply the identity of the two atoms. Similarly, radicals that require more amount of energy for forming free radicals are less stable as compared to the radicals requiring less amount of energy. Homolytic bond cleavage typically happens between two atoms of analogous electronegativity.

Reactive Oxygen Species

Reactive Oxygen Species or ROS are unique species, such as superoxide, hydrogen peroxide, and hydroxyl radical which are specifically correlated with cell damage. ROS formed as a natural by-product of the normal metabolism of oxygen and have significant role in cell signalling.

Oxybenzone forms free radicals in sunlight, and therefore can be correlated with cell damage. This only happens when combined with other ingredients generally found in sunscreens, like titanium oxide and octyl methoxycinnamate.

The **Hunsdiecker reaction**, also termed as the Borodin reaction or the Hunsdiecker–Borodin reaction, is a name reaction in organic chemistry where the silver salts of carboxylic acids react with a halogen to form or produce an organic halide. Typically, the Hunsdiecker reaction is an example of both a decarboxylation and a halogenation reaction as the product has one less carbon atom as compared to the starting or initial material (lost as carbon dioxide) and a halogen atom is introduced in its place. The reaction was first demonstrated by Alexander Borodin in his 1861 reports during the preparation of Methyl Bromide (CH_3Br) from Silver Acetate (CH_3CO_2Ag). Later, this approach was used in the degradation of fatty acids in the laboratory of Adolf Lieben. Consequently, it is named after Cläre Hunsdiecker and her husband Heinz Hunsdiecker, whose unique work in the 1930s developed it into a general method.

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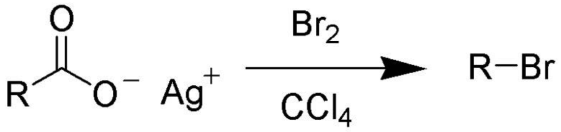
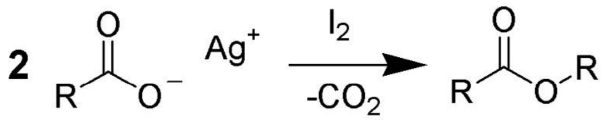


Alexander Borodin first observed the reaction in 1861 while preparing methyl bromide from silver acetate. The reaction is considered as a decarboxylation because the alkyl halide product has one less carbon atoms as compared to its parent carboxylate, lost as carbon dioxide.

CH_3COOAg + Br_2 ’! CH_3Br + CO_2 + AgBr

A carboxylate-to-iodine ratio of 1:1 forms an alkyl iodide in sequence with Borodin’s findings and the present interpretation of the Hunsdiecker reaction. However, a 2:1 ratio helps in the formation of an ester product that happens from decarboxylation of one carboxylate and coupling the resulting alkyl chain with the other.



A 3:2 ratio of reactants is used which forms or produces a 1:1 mixture of both the products.

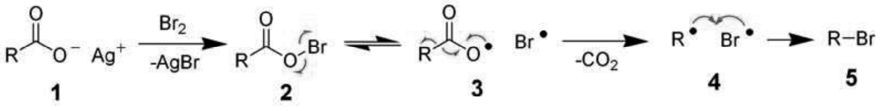
3 RCOOAg + $2I_2$ ’! RI + RCOOR + 2 CO_2 + 3 AgI

Now it is strongly recognized that mercuric oxide can also be used for effecting this transformation. The reaction was used in the preparation of ?ω-bromo esters having chain lengths between five and seventeen carbon atoms.

Mechanism

The reaction mechanism of the Hunsdiecker reaction includes organic radical intermediates. The following reaction of silver shows that it instantly reacts with bromine for forming acyl hypohalite intermediate **2**. Formation of the diradical pair **3** enables for radical decarboxylation for forming the diradical pair **4**, which will then immediately recombine and forms the desired organic halide **5**. The trend in the resultant yield of halide is given as,

Primary > Secondary > Tertiary



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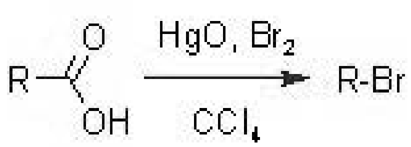
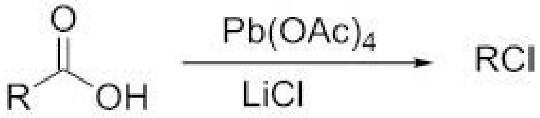
Variations of Hunsdiecker Reaction

- **Mercuric Oxide:** Lampman and Aumiller used mercuric oxide and bromine for preparing 1-bromo-3-chlorocyclobutane from 3-chlorocyclobutanecarboxylic acid as a modification of the Hunsdiecker reaction, also termed as Cristol-Firth modification.
- **Christol-Firth Modification:** The Cristol-Firth modification states that the Hunsdiecker reaction can be conveniently performed on the free carboxylic acid instead of the silver salt, which otherwise needs purification. In this modification reaction, the free carboxylic acid is specifically treated with a mixture of Mercuric Oxide (HgO) and Bromine (Br_2) in Carbon Tetrachloride or Tetrachloromethane (CCl_4). Isolation of an intermediate salt is not required.



- **Kochi Reaction:** The Kochi reaction is defined as a variation on the Hunsdiecker reaction which was typically developed by Jay Kochi who used Lead (IV) Acetate ($Pb(OAc)_4$) and Lithium Chloride (LiCl) in order to influence the halogenation and decarboxylation.



2.5.5 Barton, Sandmeyer, Ullmann, Pschorr and Hunsdiecker Reactions

Let us study them in detail.

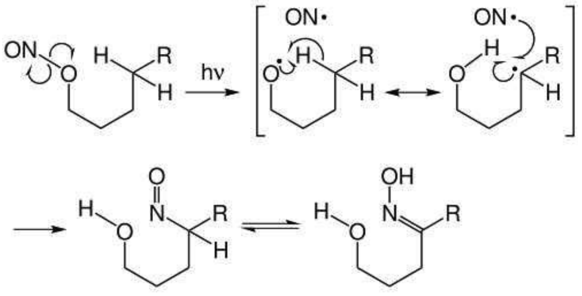
- **Barton Reaction**

The Barton reaction, also known as the Barton nitrite ester reaction, is a photochemical reaction that involves the photolysis of an alkyl nitrite to form a δ-nitroso alcohol.

The Barton reaction involves a homolytic RO–NO cleavage, followed by δ-hydrogen abstraction, free radical recombination, and tautomerization to form an oxime. Selectivity for the δ-hydrogen is a result of the conformation of the 6-membered radical intermediate. Often, the site of hydrogen atom abstraction can be easily predicted. This allows the regio- and stereo-selective introduction of functionality into complicated molecules with high yield.

Mechanism

The Barton reaction commences with a photochemically induced cleavage of the nitrite O-N bond, typically using a high pressure mercury lamp. This produces an alkyoxyl radical which immediately abstracts a hydrogen atom from the δ-carbon. In the absence of other radical sources or other proximal reactive groups, the alkyl radical recombines with the nitrosyl radical. The resultant nitroso compounds undergoes tautomerization to the isolated oxime product.



The carbon centered radical can be intercepted by other radical sources such as iodine or acrylonitrile. The first instance results in the δ-hydrogen being replaced with iodine, then subsequent cyclization to a tetrahydrofuran by an SN2 reaction. The second example results in a chain elongation product with the oxime formed 2 carbon units further from the oxygen than normal.

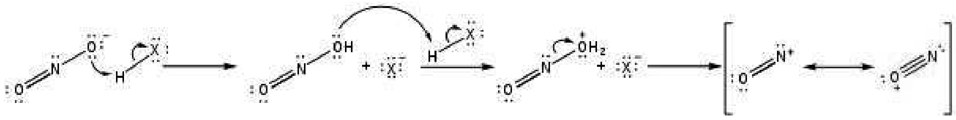
- **Sandmeyer Reaction**

The Sandmeyer reaction is a chemical reaction used to synthesize aryl halides from aryl diazonium salts using copper salts as reagents or catalysts. It is an example of a radical-nucleophilic aromatic substitution. The Sandmeyer reaction provides a method through which one can perform unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation, and hydroxylation.

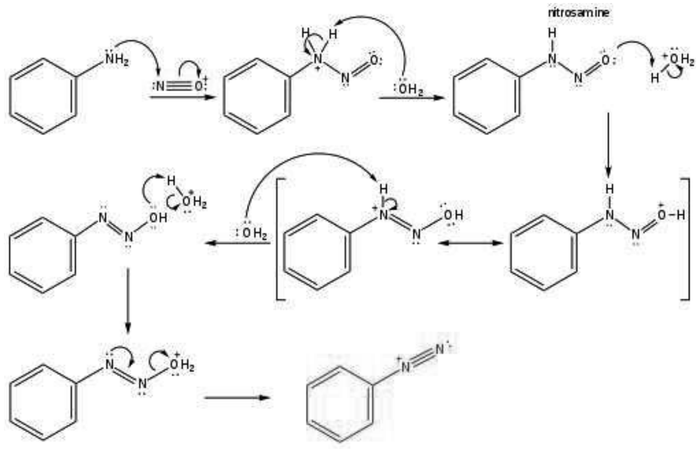
Mechanism

It involves the following:

Formation of the nitrosonium ion



Formation of the benzenediazonium ion



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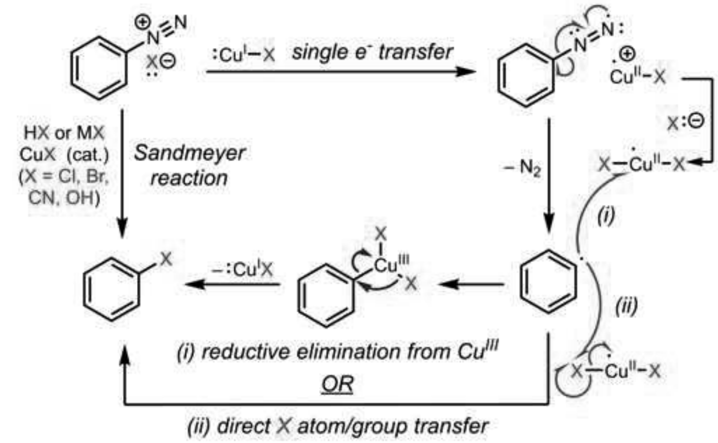
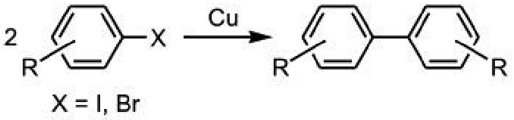


- **Ullmann Reaction**

The Ullmann reaction or Ullmann coupling is a coupling reaction between aryl halides and copper. The reaction is named after Fritz Ullmann.



Ullmann-type reaction is the copper-promoted conversion of aryl halides to aryl ethers, aryl thioethers, and aryl amines. Ullmann-type reactions are comparable to Buchwald-Hartwig reactions.

Mechanism

In the case of Ullmann-type reactions (aminations, etherifications, etc. of aryl halides), the reaction involves copper(I) alkoxide or copper(I) amides. The copper(I) reagent can be generated in situ from the aryl halide and copper metal. Even copper(II) sources are effective. A number of innovations have been developed with regards to copper reagents.

These copper(I) compounds subsequently react with the aryl halide in a net metathesis reaction:

$$\text{Ar–X} + \text{ROCu} \rightarrow \text{Ar–OR} + \text{CuX}$$

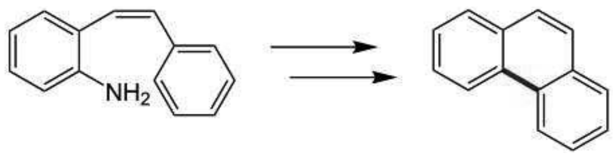
$$\text{Ar–X} + \text{RSCu} \rightarrow \text{Ar–SR} + \text{CuX}$$

$$\text{Ar–X} + 2\ \text{RNHCu} \rightarrow \text{Ar–NHR} + \text{CuX}$$

In the case of C-N coupling, kinetic studies implicate oxidative addition reaction followed by reductive elimination.

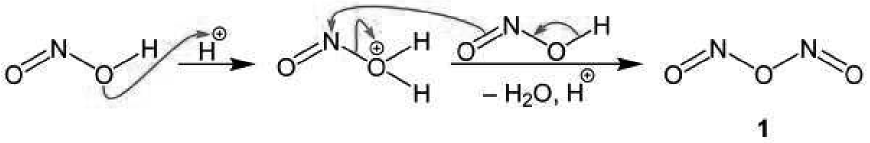
- **Pschorr Cyclization**

The Pschorr cyclization is a name reaction in organic chemistry, which was named after its discoverer, the German chemist Robert Pschorr (1868-1930). It describes the intramolecular substitution of aromatic compounds via aryldiazonium salts as intermediates and is catalyzed by copper. The reaction is a variant of the Gomberg-Bachmann reaction. The following reaction scheme shows the Pschorr cyclization for the example of phenanthrene.

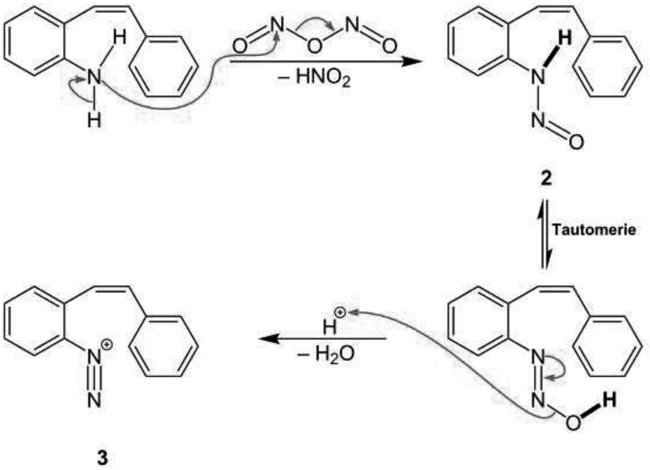


Mechanism

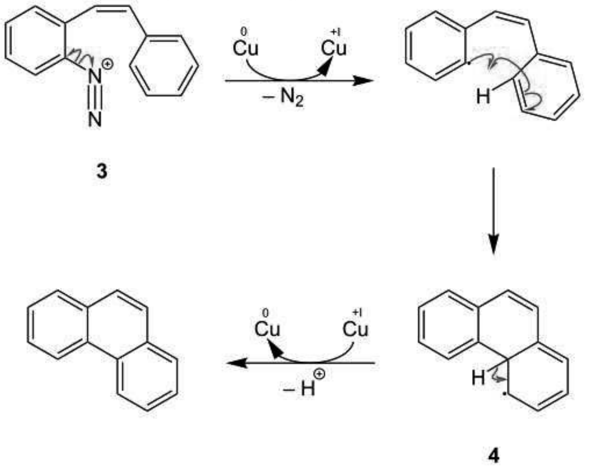
In the course of the Pschorr cyclization, a diazotization of the starting compound occurs, so that an aryldiazonium salt is formed as intermediate. For this, sodium nitrite is added to hydrochloric acid to obtain nitrous acid. The nitrous acid is protonated and reacts with another equivalent of nitrous acid to the intermediate 1 which is later used for the diazotization of the aromatic amine:



The intermediate **1** reacts in the following way with the starting compound:



Intermediate 1 replaces a hydrogen atom from the amino group of the starting compound. A nitroso group is introduced as new substituent, producing under the release of nitrous acid intermediate 2. Intermediate 2 then reacts via a tautomerism and dehydration to the aryldiazonium cation 3.



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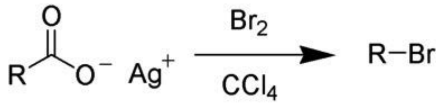
Nitrogen is then cleaved from the aryldiazonium cation 3 by the use of the copper catalyst. The aryl radical thus formed reacts via ring closue to the intermediate stage 4. Finally, rearomatization takes place using again the copper catalyst and phenanthrene is formed.

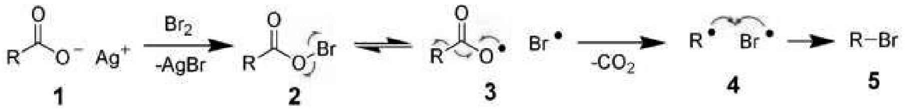
- **Hunsdiecker Reaction**

The Hunsdiecker reaction (also called the Borodin reaction or the Hunsdiecker–Borodin reaction) is a name reaction in organic chemistry whereby silver salts of carboxylic acids react with a halogen to produce an organic halide. It is an example of both a decarboxylation and a halogenation reaction as the product has one fewer carbon atoms than the starting material (lost as carbon dioxide) and a halogen atom is introduced its place. The reaction was first demonstrated by Alexander Borodin in his 1861 reports of the preparation of methyl bromide from silver acetate. Shortly after, the approach was applied to the degradation of fatty acids in the laboratory of Adolf Lieben. However, it is named for Cläre Hunsdiecker and her husband Heinz Hunsdiecker, whose work in the 1930s developed it into a general method. Several reviews have been published, and a catalytic approach has been developed.



Mechanism

The reaction mechanism of the Hunsdiecker reaction is believed to involve organic radical intermediates. The silver salt of the carboxylic acid 1 will quickly react with bromine to form acyl hypohalite intermediate 2. Formation of the diradical pair 3 allows for radical decarboxylation to form the diradical pair 4, which will quickly recombine to form the desired organic halide 5. The trend in the yield of the resulting halide is primary > secondary > tertiary.



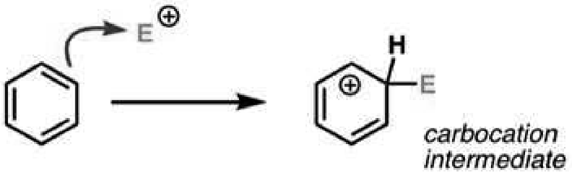
2.6 MECHANISM OF AN AROMATIC SUBSTRATE

The reactions of aromatic groups describe the activating and deactivating groups in Electrophilic Aromatic Substitution (EAS). The electron donating substituents on the aromatic ring increases the rate of reaction and electron withdrawing substituents decreases the rate of reaction. The mechanism includes the following steps:

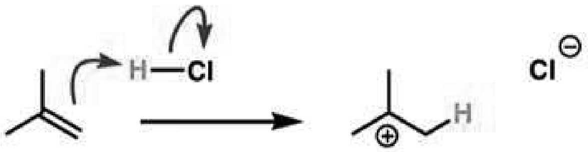
Step 1: The Electrophile (E) is attacked by a Pi-Bond of the Aromatic Ring.

In the first step of electrophilic aromatic substitution, the Electrophile (E+) is attacked by a Pi (π) bond of the aromatic ring. The uniqueness of the electrophile

E is particular to each reaction and generation of the active electrophile is referred as a mechanical step.



For example, the reaction of alkenes with a strong acid H-Cl forms a carbocation as shown below. The reaction is only applicable to an aromatic ring.

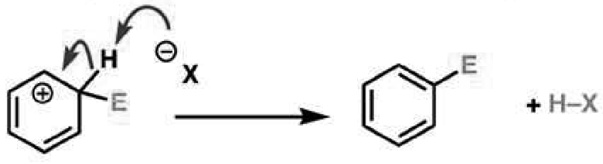


carbocation
intermediate

The addition of HCl to alkenes is defined as the attack of Cl on the carbocation, forming a new C-Cl bond, i.e., it is an electrophilic aromatic substitution.

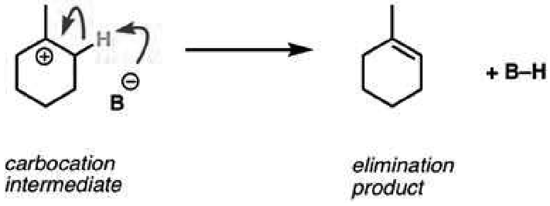
Step 2: Electrophilic Aromatic Substitution Mechanism - Deprotonation of The Tetrahedral Carbon Regenerates the Pi Bond.

In the second step of electrophilic aromatic substitution, the deprotonation takes place which breaks the C–H bond forming the C–C (π) bond and restores aromaticity. Aromaticity is a property of cyclic (ring-shaped), typically planar (flat) structures with Pi (π) bonds in resonance, those containing delocalized electrons, which gives increased stability compared to other geometric or connective arrangements with the same set of atoms. The resonance energy of benzene is approximately 36 kcal/mol. Following reaction illustrates the breakage of C–H bond in order to restore aromaticity.



Electrophilic aromatic
substitution product

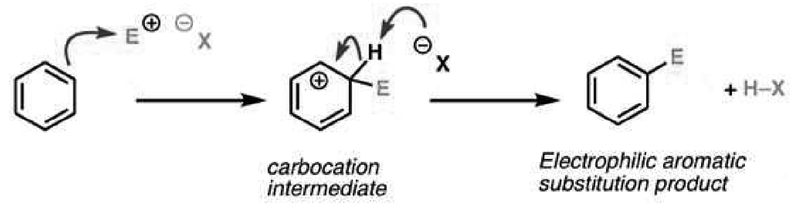
In the second step of E1 reaction, after loss of a leaving group, typically a carbon adjacent to a carbocation is deprotonated and forms a new C–C (π) bond.



In the above E1 reaction, a base (B) eliminates the proton from the carbon adjacent to a carbocation and forms a new C–C (π) bond.

Step 3: The Complete Mechanism - Combining the Two Steps.

The above mentioned two steps can be combined to illustrate the complete mechanism specifying how the electrophile E is generated unique to each reaction, as show below.



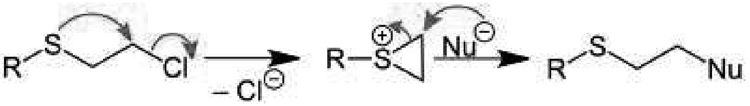
2.6.1 Neighbouring Group Assistance

In organic chemistry, the Neighbouring Group Participation (NGP), also known as **anchimeric assistance**, has been defined by IUPAC as the interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a Sigma (σ) bond or Pi (π) bond contained within the parent molecule but not conjugated with the reaction centre. Normally, the NGP increases the reaction rate. Compared to the normal NGP reaction, the stereochemistry of the reaction can be abnormal or unexpected. The neighbouring groups probably affect many reactions in organic chemistry, for example the reaction of a diene, such as 1,3-cyclohexadiene with maleic anhydride normally gives the endo isomer because of a secondary effect which is due to overlap of the carbonyl group (π) orbitals with the transition state in the Diels-Alder reaction. Here we will discuss about the neighbouring group effects with carbocations and S_N2 reactions.

- **NGP by Heteroatom Lone Pairs**

In the NGP by heteroatom lone pairs type of substitution reaction, one group of the substrate participates initially in the reaction and thereby affect the reaction. Because the NGP reaction rate is increased due to many folds 'Stoichiometry' product which undergoes attack of nucleophile changes. Stoichiometry refers to the relationship between the quantities of reactants and products before, during, and following chemical reactions.

A classic example of NGP is the reaction of a sulfur or nitrogen mustard with a nucleophile, the rate of reaction is much higher for the sulfur mustard and a nucleophile than it would be for a primary alkyl chloride without a heteroatom, as shown below. Nitrogen mustards are cytotoxic organic compounds with the chloroethylamine ($Cl(CH_2)_2NR_2$) functional group.

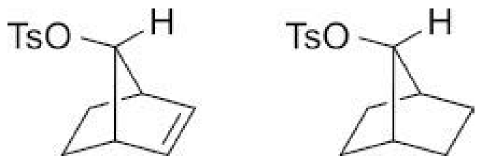


Ph-S-CH_2-CH_2-Cl reacts with water 600 times faster than CH_3-CH_2-CH_2-Cl. In this type of substitution reaction one group of the substrate participates initially in the reaction and thereby affect the reaction. Due to NGP, the reaction rate increases.

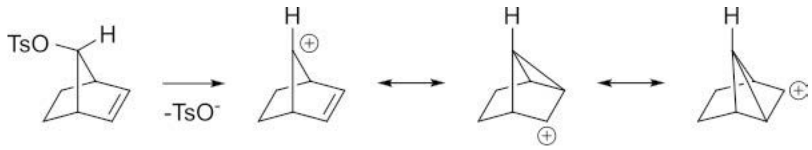
NOTES

- **NGP by an Alkene**

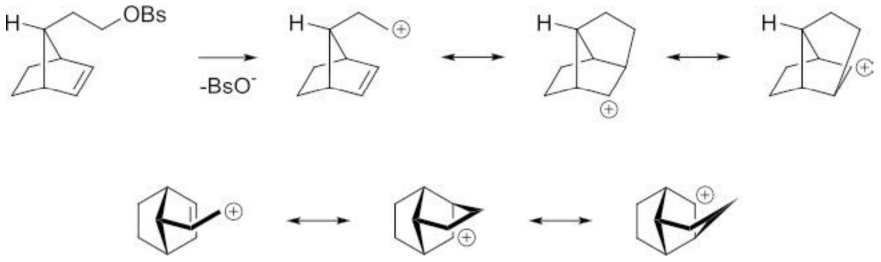
The (π) orbitals of an alkene can stabilize a transition state by helping to delocalize the positive charge of the carbocation. For example, the unsaturated tosylate will react more quickly, 10^{11} times faster for aqueous solvolysis, with a nucleophile as compared to the saturated tosylate, as shown below.



The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms, as shown below.



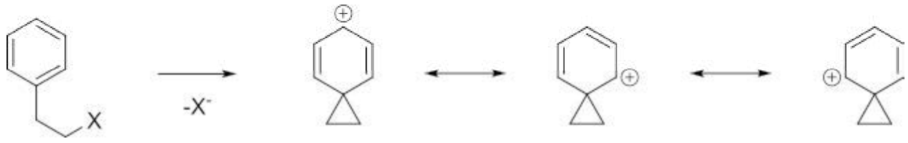
Even if the alkene is more remote from the reacting center the alkene can still act in this way. For example, in the following alkyl benzenesulfonate the alkene delocalises the carbocation.



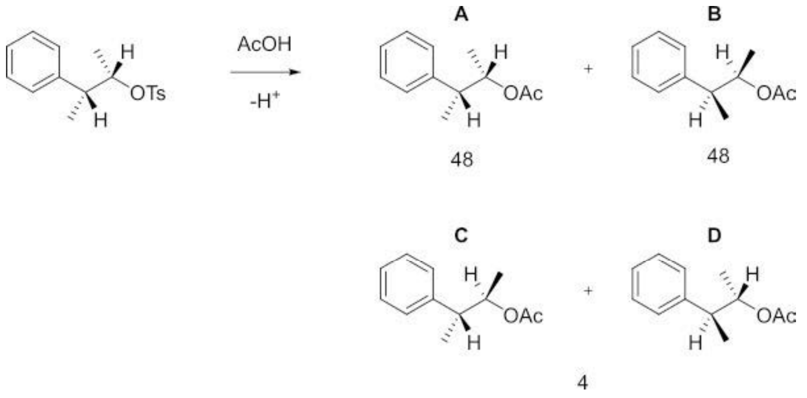
Additionally, the increase in the rate of the S_N2 reaction of allyl bromide with a nucleophile when compared with the reaction of n-propyl bromide states that it is because the orbitals of the (π) bond overlap with those of the transition state. In the allyl system the alkene orbitals overlap with the orbitals of a S_N2 transition state.

- **NGP by an Aromatic Ring**

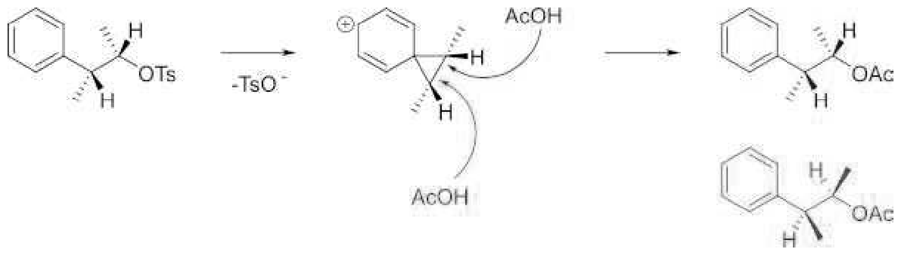
An aromatic ring can support in the formation of a carbocationic intermediate termed a phenonium ion by delocalising the positive charge.



When the following tosylate reacts with acetic acid in solvolysis then rather than a simple S_N2 reaction forming B, a 48:48:4 mixture of A, B, which are enantiomers, and C+D was obtained.



The mechanism of the formation of A and B is shown below.



In the example of benzyl halide, the reactivity is higher because the S_N2 transition state possesses an analogous overlap effect to that in the allyl system.

- **NGP by Aliphatic C–C or C–H Bonds**

Aliphatic C–C or C–H bonds can produce charge delocalization if these bonds are close and antiperiplanar to the Leaving Group (LG). Corresponding intermediates are referred to a nonclassical ions, with the 2-norbornyl system as the most recognised example.

2.6.2 Reactivity for Aliphatic and Aromatic Substrates at a Bridgehead

Bredt's rule is an empirical observation in organic chemistry that states that a double bond cannot be placed at the **bridgehead** of a **bridged ring system**, unless the rings are large enough. The rule is named after Julius Bredt, who first discussed it in 1902 and codified it in 1924. It primarily relates to bridgeheads with carbon-carbon and carbon-nitrogen double bonds.

For example, two of the following isomers of norbornene violate Bredt's rule, which makes them too unstable to prepare:

Norbornene   Forbidden norbornene isomers

In the above figure, the bridgehead atoms involved in Bredt's rule is illustrated on right side by means of forbidden norbornene isomers.

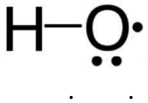
Bredt's rule states that having a double bond on a bridgehead can be equivalent to have a trans double bond on a ring, which is not stable for small rings (fewer than eight atoms) due to a combination of ring strain, and angle strain (nonplanar alkene). The p orbitals of the bridgehead atom and adjacent atoms are orthogonal and thus are not aligned properly for the formation of Pi (π) bonds.

Bredt's rule is significant for predicting which isomer is obtained from an elimination reaction in a bridged ring system. In addition, this rule can be applied to reaction mechanisms through carbocations and to a lesser degree through free radicals, because these intermediates have a planar geometry with 120 degree angles and sp^2 hybridization, similar to the carbon atoms involved in a double bond. For example, bicyclo[5.3.1] undecane-11-one-1-carboxylic acid undergoes decarboxylation on heating upto 132°C, but the similar compound bicyclo[2.2.1] heptan-7-one-1-carboxylic acid remains stable even beyond 500°C, in spite of both being β-keto acids with the carbonyl group on a one-carbon bridge and the carboxylate group on the bridgehead. The mechanism of decarboxylation involves an enolate intermediate, which is an S = 9 species in the bicyclo[5.3.1] undecane-11-one-1-carboxylic acid and an S = 5 species in the bicyclo[2.2.1] heptan-7-one-1-carboxylic acid, preventing the decarboxylation in the smaller ring system.

2.6.3 Reactivity in the Attacking Radicals

In chemistry, a radical is an atom, molecule, or ion that has at least one unpaired valence electron, these unpaired electrons make radicals highly chemically reactive. Many radicals spontaneously dimerize. A significant example of a radical is the hydroxyl radical (HO·), a molecule that has one unpaired electron on the oxygen atom. Two other examples are triplet oxygen and triplet carbene which have two unpaired electrons.

Radicals are intermediates in many chemical reactions, more so than is apparent from the balanced equations. Following is the Lewis structure of the hydroxyl radical containing one unpaired electron.



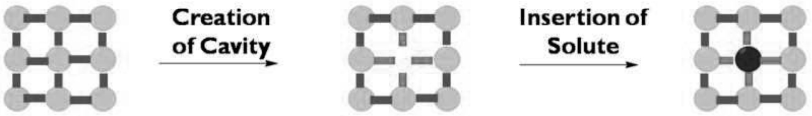
Radicals are either formed from spin-paired molecules or from other radicals. The formation of radicals from spin-paired molecules involves homolysis of weak bonds or electron transfer, also known as reduction.

2.6.4 Effect of Solvents on Reactivity

In chemistry, **solvent effects** are referred as the impact of a solvent on chemical reactivity or molecular associations. Solvents have specific effects on solubility, stability and reaction rates, hence selection of appropriate solvent provides thermodynamic and kinetic control over a chemical reaction.

Effects on Solubility

A solute is said to be dissolved in a solvent when it forms satisfactory interactions with the solvent. The process of dissolving all solvents depends upon the free energy change of both the solute and the solvent. The free energy of solvation is a combination of several factors.



The above reaction mechanism illustrates that at first a cavity has to be created in the solvent. The creation of the cavity must not be favourable entropically and enthalpically because the ordered structure of the solvent decreases and there are fewer solvent-solvent interactions. Secondly, the solute has to be separated out from the bulk solute. This is considered as enthalpically disadvantageous because the solute-solute interactions are broken although it is entropically satisfactory or favourable. Thirdly, the solute must occupy the cavity that is created in the solvent. This will result in the satisfactory or favourable solute-solvent interactions and is also entropically satisfactory or favourable as the mixture is more disordered as compared to the condition when the solute and solvent are not mixed. Dissolution often happens when the solute-solvent interactions are similar to the solvent-solvent interactions, denoted by the term 'Like Dissolves Like'. Consequently, polar solutes get dissolved in the polar solvents, whereas nonpolar solutes get dissolved in the nonpolar solvents.

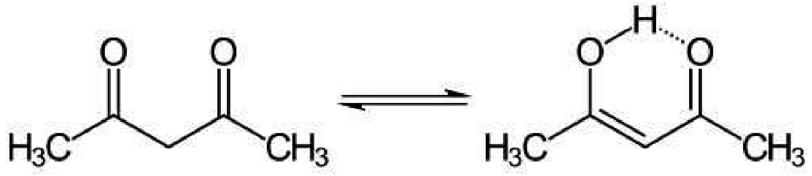
Effects on Stability

Different types of solvents can affect the equilibrium constant of a reaction through differential stabilization of the reactant or product. The equilibrium is uniquely shifted in the direction of the substance that is preferentially stabilized. Stabilization of the reactant or product can happen through any of the different non-covalent interactions with the solvent, such as H-bonding, dipole-dipole interactions, van der Waals interactions, etc.

Acid-Base Equilibria: The ionization equilibrium of an acid or a base is affected by means of a solvent change. The effect of the solvent is not only because of its acidity or basicity but also because of its dielectric constant and its ability to preferentially solvate and thus stabilize certain species in acid-base equilibria. A change in the solvating ability or dielectric constant can thus influence the acidity or basicity.

Keto–Enol Equilibria: Many of the carbonyl compounds exhibit keto–enol tautomerism. This keto–enol equilibria effect is specifically evident in 1,3-dicarbonyl compounds when the hydrogen-bonded enols are formed. 1,3-

dicarbonyl compounds were typically synthesized through the reaction of 9,10-phenanthrenequinone with acetylacetone and acetoacetic ester followed by the reduction and were uniquely characterized by means of spectroscopic and quantum-chemical methods. In the crystalline state and in solution, these compounds were found to exist in the keto form. The equilibrium constant specifically dependents upon the polarity of the solvent, with the cis-enol form prevalent at low polarity and the diketo form prevalent at high polarity. The intramolecular H-bond thus formed in the cis-enol form is more evident when there is no contest for intermolecular H-bonding with the solvent. Therefore, solvents of low polarity that do not readily participate in H-bonding permit cis-enolic stabilization by intramolecular H-bonding. Following reaction illustrates keto-enol tautomerization, diketo form on the left and cis-enol form on the right.



Effects of Solvent on Reactivity and Reaction Rates

Fundamentally, reactivity and reaction mechanisms are described as the actions of isolated molecules in which the solvent is regarded as a passive support. Even though, the nature of the solvent can essentially impact the reaction rates and order of a chemical reaction. When the reaction is performed without solvent then it can affect the reaction-rate for reactions with bimolecular mechanisms, for example by maximizing the concentration of the reagents.

Equilibrium-Solvent Effects

Solvents can affect rates through equilibrium-solvent effects that can be explained based on the transition state theory. In principle, the reaction rates are affected by differential solvation of the initial material and transition state by the solvent. When the reactant molecules continue to the transition state, the solvent molecules orient themselves to stabilize the transition state. If the transition state stabilises to a greater extent as compared to the initial material, then the reaction continues very fast. If the initial material stabilises to a greater extent as compared to the transition state, then the reaction continues slow. However, such differential solvation essentially involves fast reorientation relaxation of the solvent, i.e., from the transition state the orientation returns to the ground-state orientation. Consequently, the equilibrium-solvent effects can be seen in reactions that tend to have strong barriers and weak dipolar, speedy relaxing solvents.

Hughes–Ingold Rules

Originally, the effect of solvent on the elimination and nucleophilic substitution reactions was studied by British chemists Edward D. Hughes and Christopher Kelk Ingold, hence it is named as 'Hughes–Ingold Rules'. Using a simple solvation model that considered only pure electrostatic interactions between ions or dipolar molecules and solvents in initial and transition states, all nucleophilic and elimination reactions were organized into different charge types, namely neutral, positively charged, or negatively charged. Hughes and Ingold then defined certain assumptions about the extent of solvation which are possible in the following conditions:

- Increasing magnitude of charge will increase solvation.
- Increasing delocalization will decrease solvation.
- Loss of charge will decrease solvation more than the dispersal of charge.

Following examples illustrate the effect that are applicable to these general assumptions:

- An increase in solvent polarity accelerates the rates of reactions where a charge is developed in the activated complex from neutral or slightly charged reactant.
- An increase in solvent polarity decreases the rates of reactions where there is less charge in the activated complex in comparison to the starting materials.
- A change in solvent polarity will have little or no effect on the rates of reaction when there is little or no difference in charge between the reactants and the activated complex.

Check Your Progress

12. Define a radical.
13. Give an example of a stable radical.
14. Define polymerization reaction.
15. What are the three main features of free radical reactions?
16. Define Ullmann reaction.

2.7 ANSWERS TO 'CHECK YOUR PROGRESS'

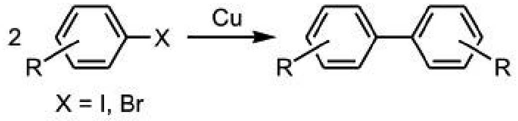
1. All the organic reactions can be broadly classified into the following five types.
    (i) Substitution Reactions
    (ii) Addition Reactions
    (iii) Elimination Reactions
    (iv) Molecular Rearrangement Reaction
    (v) Molecular Reaction
2. There are three fundamental events in these elimination reactions.
    (i) Removal of proton
    (ii) Formation of carbon-p bond
    (iii) Breaking of the bond to the leaving group.
3. If a covalent bond in which carbon is attached to a lesser electronegative atom breaks up by heterolysis the atom will leave without taking away the bonding pair of electrons. The resulting carbon anion is known as *carbanion.*

4. Classical definitions of acids and bases are given by Arrhenious who suggested that acids are those substances which give hydrogen ions when dissolved in water whereas bases are substances which give hydroxyl ions.
5. If a covalent bond, in which carbon is attached to a more electronegative atom or group, breaks up by heterolytic fission, the more electronegative atom will take away the electron pair and become negatively charged while the carbon will lose its electron and thus acquire a positive charge. Such cationic species carrying a positive charge on carbon are known as carbocations. These carbocations are called primary, secondary and tertiary depending upon the nature of the carbon atom bearing the charge.
6. Diradicals are molecules containing two radical centers. Multiple radical centers can exist in a molecule. Atmospheric oxygen naturally exists as a diradical in its ground state as triplet oxygen.
7. In the most simple nitrene, the linear imidogen (:N–H), two of the 6 available electrons form a covalent bond with hydrogen, two others create a free electron pair and the two remaining electrons occupy two degenerate p orbitals. Consistent with Hund's rule the low energy form of imidogen is a triplet with one electron in each of the p orbitals and the high energy form is the singlet state with an electron pair filling one p orbital and the other one vacant.
8. The effect of structure on reactivity of organic molecule may be classified into three major type field, resonance and steric. Resonance and field effect are collectively called as electrical effects.
9. Reactivity of the molecule due to presence of the bulky alkyl group hinders approach of the nucleophile to the carbon atom of the reacting molecule, this is called the steric factor (effect).
10. Hammett, proposed the equation for the cases of m and p - X C_6H_4Y as given below

$$\log \frac{k}{K_0} = \sigma p$$

11. The Taft equation is a linear free energy relationship used in physical organic chemistry in the study of reaction mechanism and in the development of quantitative structures activity relationships for organic compound. It was developed by Robert W. Taft in 1952 as a modification to the Hammett equation.
12. In chemistry, a radical is an atom, molecule, or ion that has an unpaired valence electron.
13. The prime example of a stable radical is molecular dioxygen (O_2). Another common example is nitric oxide (NO). Organic radicals can be long lived if they occur in a conjugated π system, such as the radical derived from α-tocopherol (vitamin E).
14. The combination of simple molecules repeatedly two or more times in some regular manner so that they combine to form a larger or long chain molecule is known as polymerisation.

15. Free radical reactions are characterized by the three important features (i) They are unaffected by the polar substances like acids, bases or polar solvents, (ii) They are initiated and accelerated by a free radical source, and (iii) They are inhibited by substances that scavenge free radicals, e.g., O_2, benzoquinone, etc.
16. The Ullmann reaction or Ullmann coupling is a coupling reaction between aryl halides and copper. The reaction is named after Fritz Ullmann.



2.8 SUMMARY

- An organic compound which is attacked by a reagent is known as substrate or reactant.
- A large variety of organic reactions may be placed in four major groups: (1) Substitution reactions (2) Addition reactions (3) Elimination reactions, and (4) Rearrangements.
- Reactions in which an atom or a group is replaced by another atom or group, are called substitution reactions.
- Compounds having unsaturation in the molecule have a tendency to add the attacking reagent molecule without eliminating any atom or group. Such reactions in which the attacking reagent adds to the substrate molecule are called addition reactions.
- The reverse of addition reactions are eliminations. In elimination reactions the number of groups or atoms attached to carbon decrease and the degree of unsaturation in the molecule increases.
- The reactions in which the carbon skeleton of the molecule is rearranged to give a structural isomer of the original molecule are known as rearrangement reactions.
- In the course of a reaction, the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the principle of microscopic reversibility.
- The feasibility of a particular reaction is based on the energetics (energy considerations) for that reaction. Thermodynamics is the study of the energy flow in a system.
- Product distribution in a chemical reaction in generally reaction is generally influenced by two factors: 1. Relative stability of the product (thermodynamic factor) 2. Rate of formation of the product (kinetic factor).

- Kinetics deals with the rate of reaction and factors affecting the rate.
- Polanyi-Hammond postulate states that mutual conversion between two species which are adjacent to each other on the reaction coordinate requires only a minor change in the structure provided they have nearly the same energy.
- A radical is an atom, molecule, or ion that has an unpaired valence electron. With some exceptions, these unpaired electrons make radicals highly chemically reactive. Many radicals spontaneously dimerize. Most organic radicals have short lifetimes.
- Radicals or charged species add to non-radicals to give new radicals. This process is the basis of the radical chain reaction. Being prevalent and a diradical, O_2 reacts with many organic compounds to generate radicals together with the hydroperoxide radical. This process is related to rancidification of unsaturated fats.
- Radical alkyl intermediates are stabilized by similar physical processes to carbocations: as a general rule, the more substituted the radical center is, the more stable it is. This directs their reactions. Thus, formation of a tertiary radical ($R_3C\cdot$) is favored over secondary ($R_2HC\cdot$), which is favored over primary ($RH_2C\cdot$). Likewise, radicals next to functional groups such as carbonyl, nitrile, and ether are more stable than tertiary alkyl radicals.
- Radical chain reactions play an important part in organic chemistry both as radical substitution and radical addition reactions. Radical addition chain reactions, for instance, may be found in radical polymerization.
- Free-radical addition is an addition reaction in organic chemistry involving free radicals. The addition may occur between a radical and a non-radical, or between two radicals.
- The important free radical substitutions are halogenation of alkanes; and arylation of aromatic compounds by diazonium salts (Gomberg reaction).
- The combination of simple molecules repeatedly two or more times in some regular manner so that they combine to form a larger or long chain molecule is known as polymerization.
- Nitrenes are nitrogen analogous of carbenes. The nitrogen atom possess only six valence electrons; in nitrenes the triplet state is lower in energy than the single state.
- There are two common ways to generate nitrenes: From azides by thermolysis or photolysis, with expulsion of nitrogen gas. This method is analogous to the formation of carbenes from diazo compounds and from isocyanates, with expulsion of carbon monoxide. This method is analogous to the formation of carbenes from ketenes.
- In Hofmann rearrangement, elimination takes place to give a nitrene intermediate (I) which then by migration of the group R with its pair of electrons to the electron deficient nitrogen atom gives an isocyanate. Addition of water followed with the elimination of CO_2 gives the amine with one less carbon atom.

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- Beckmann rearrangement is also intramolecular rearrangement. The most interesting feature of this rearrangement is that it is always the *trans*-alkyl group which migrates preferentially regardless of electron donating abilities or nucleophilicity of migrating group.
- The Curtius rearrangement (or Curtius reaction or Curtius degradation), first defined by Theodor Curtius in 1885, is the thermal decomposition of an acyl azide to an isocyanate with loss of nitrogen gas. The isocyanate then undergoes attack by a variety of nucleophiles such as water, alcohols and amines, to yield a primary amine, carbamate or urea derivative respectively.
- The Schmidt reaction is an organic reaction in which an azide reacts with a carbonyl group to give an amine or amide, with expulsion of nitrogen. It is named after Karl Friedrich Schmidt (1887–1971), who first reported it in 1924 by successfully converting benzophenone and hydrazoic acid to benzanilide. Surprisingly, the intramolecular reaction wasn't reported until 1991 but has become important in the synthesis of natural products.

2.9 KEY TERMS

- **Kinetics:** It is the branch of chemistry or biochemistry concerned with measuring and studying the rates of reactions.
- **Thermodynamics:** It is the study of the interrelation of heat and work with chemical reactions or with physical changes of state within the confines of the laws of thermodynamics.
- **Organic reaction:** Organic reactions are chemical reactions involving organic compounds.
- **Free radicals:** Radical, also called free radical, in chemistry, molecule that contains at least one unpaired electron.
- **Polymerization:** The combination of simple molecules repeatedly two or more times in some regular manner so that they combine to form a larger or long chain molecule is known as polymerisation.
- **Carbene:** Carbene, any member of a class of highly reactive molecules containing divalent carbon atoms—that is, carbon atoms that utilize only two of the four bonds they are capable of forming with other atoms.
- **Nitrene:** A nitrene (R–N) is the nitrogen analogue of a carbene. The nitrogen atom has only 6 valence electrons and is therefore considered an electrophile. A nitrene is a reactive intermediate and is involved in many chemical reactions.
- **Schmidt Reaction:** The Schmidt reaction is an organic reaction in which an azide reacts with a carbonyl group to give an amine or amide, with expulsion of nitrogen.
- **Steric effect:** Reactivity of the molecule due to presence of the bulky alkyl group hinders approach of the nucleophile to the carbon atom of the reacting molecule, this is called the steric factor (effect).

- **Taft equation**: The Taft equation is a linear free energy relationship used in physical organic chemistry in the study of reaction mechanism and in the development of quantitative structures activity relationships for organic compound.

2.10 SELF ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the types of reactions in chemistry?
2. What are the thermodynamic and kinetic parameters for the feasibility of chemical reactions?
3. Define Hammond's Postulate.
4. State the structure, stability and reactivity of carbocations.
5. Define the structure and bonding in carbenes.
6. Which kinetic factors influence the product distribution in a chemical reaction?
7. What are the kinetics and non-kinetics methods for determining organic reaction mechanisms?
8. What are nitrenes?
9. What is the effect of structure on reactivity?
10. Write the equation of oxidation of aldehydes to carboxylic acids.
11. Determine the reaction of Nitrene-C-Insertion.
12. Write the difference between polymerisation and condensation.
13. What is radical chain mechanism?

Long-Answer Questions

1. Explain the types of mechanism of organic reactions.
2. Describe the thermodynamic and kinetic requirements for any reaction.
3. Explain the methods of determining-mechanisms.
4. Discuss the structure of nitrenes.
5. Analyze the resonance and field effects.
6. Describe the process of formation of free radicals.
7. Explain the mechanism of free radical substitution reactions.
8. Explain Sandmeyer reaction and its mechanism.
9. Discuss the structure of nitrenes.

2.11 FURTHER READING

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UNIT 3 SUBSTITUTION REACTIONS

NOTES

Structure

3.0 INTRODUCTION

Although aromatic compounds have multiple double bonds, these compounds do not undergo addition reactions. Their lack of reactivity toward addition reactions is due to the great stability of the ring systems that result from complete p electron delocalization (resonance). Aromatic compounds react by electrophilic aromatic substitution reactions, in which the aromaticity of the ring system is preserved. For example, benzene reacts with bromine to form bromobenzene.

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Substitution at aromatic or unsaturated carbon atoms. The most important reactions of the aromatic compounds are the electrophilic substitution reactions like nitration, halogenation, sulphonation etc. Nitration is introduction of a nitro group (—NO_2) in place of hydrogen by electrophile (nitronium ion). Sulphonation is the replacement of a hydrogen by —SO_3H group and takes place by electrophilic attack of SO_3 on aromatic carbon.

A nucleophilic aromatic substitution is a substitution reaction in organic chemistry in which the nucleophile displaces a good leaving group, such as a halide, on an aromatic ring.The discovery of nucleophilic aromatic substitution (SNAr) pathways dates back to the early 20th century, yet, despite all the extraordinary advances in cross-coupling and related reactions, SNAr remains by some measures the second most frequently used reaction class in medicinal chemistry. This may occur in several ways, including aromatic SN1 mechanism, involving benzene intermediate and SNAr mechanism involving addition and elimination.

In aliphatic electrophilic substitution, an electrophile displaces a functional group. The four possible electrophilic aliphatic substitution reaction mechanisms are S_E1, S_E2 (front), S_E2 (back) and S_Ei (Substitution Electrophilic), which are also similar to the nucleophile counterparts S_N1 and S_N2. In the S_E1 course of action the substrate first ionizes into a carbanion and a positively charged organic residue. The carbanion then quickly recombines with the electrophile. The S_E2 reaction mechanism has a single transition state in which the old bond and the newly formed bond are both present.

In this unit you will study about aliphatic nucleophilic substitution, the neighbouring group mechanism, classical and nonclassical carbocations, phenonium ions and norbornyl system, common carbocation rearrangements, application of NMR spectroscopy in the detection of carbocation, nucleophilic substitution at an allylic, aliphatic trigonal and a vinylic carbon, reactivity effects of substrate structure, aliphatic electrophilic substitution, aromatic electrophilic substitution and aromatic nucleophilic substitution.

3.1 OBJECTIVES

After going through this unit you will be able to:

- Understand aliphatic nucleophilic substitution
- Discuss the neighbouring group mechanism
- Explain classical and nonclassical carbocations
- Discuss application of NMR spectroscopy in the detection of carbocation
- Explain nucleophilic substitution at an allylic, aliphatic trigonal and a vinylic carbon
- Analyze reactivity effects of substrate structure
- Describe aliphatic and aromatic electrophilic substitution
- Understand aromatic nucleophilic substitution

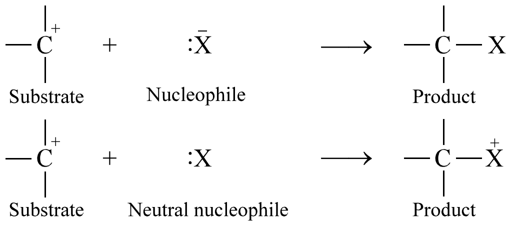
3.2 ALIPHATIC NUCLEOPHILIC SUBSTITUTION

Reagents having an unshared pair of electrons are known as *nucleophilic reagents* or *nucleophiles* because they have a tendency to share this pair of electrons with electron deficient substrate. They can also be classified into two groups (*i*) **negative nucleophiles**, and (*ii*) **neutral nucleophiles**. Negative nucleophiles are those which carry an electron pair and are negatively charged because of one extra electron. If a negative charge is present at carbon, such nucleophiles are known as *carbanions.* Some simple examples of such nucleophiles are given in Table 3.1.

Table 3.1 *Some Common Nucleophiles*

Negative nucleophile		*Neutral nucleophile*	
Halide ion (X = Cl, Br, I)	$:\ddot{\underset{..}{X}}:^{-}$	Trialkyl amine	$R_3N:$
		Ammonia	$:NH_3$
Alkoxy ion	$R-\ddot{\underset{..}{O}}:^{-}$	Water	$H-\ddot{\underset{..}{O}}-H$
Amino ion	$:\bar{N}H_2$	Alcohol	$H-\ddot{\underset{..}{O}}-C_2H_5$
Hydroxyl ion	$:\bar{\underset{..}{O}}H$	Dialkyl sulphide	$R_2\ddot{\underset{..}{S}}$
Cyanide ion	$:\bar{C}\equiv\ddot{N}$	Alkyl hydrosulphide	$R-\ddot{\underset{..}{S}}-H$
Carbanion	$-\overset{\vert}{\underset{\vert}{C}}:^{-}$		

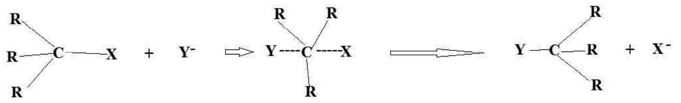
The neutral nucleophiles are rich in electrons because of the presence of unshared electron pair, but are not charged and are electrically neutral for example, H_2O: and $:NH_3$. The addition of negative nucleophile to a positively charged substrate results in a neutral molecule whereas the addition of a neutral nucleophile to a positively charged substrate will give a positively charged product. Thus:



$$\underset{\text{Substrate}}{-\overset{|}{\underset{|}{C^{+}}}} + \underset{\text{Nucleophile}}{:\bar{X}} \longrightarrow \underset{\text{Product}}{-\overset{|}{\underset{|}{C}}-X}$$

$$\underset{\text{Substrate}}{-\overset{|}{\underset{|}{C^{+}}}} + \underset{\text{Neutral nucleophile}}{:X} \longrightarrow \underset{\text{Product}}{-\overset{|}{\underset{|}{C}}-\overset{+}{X}}$$

A **nucleofuge** is the combination of two term Nucleo and Fugetake (*nucleo*-nucleus means the positive charge part in an atom and fuge, *fugitive mean* to escape) is a leaving group which retains the lone pair from its previous bond with another species. For example, in the S_N2 mechanism a nucleophile attacks an organic compound containing the nucleofuge which simultaneously breaks the bond with the nucleofugeo (in given reaction X^-) and make this a leave group or atom (*A leaving group that carries away the bonding electron pair).*



In this reaction the leaving group is X^-.

3.2.1 Kinetics of Aliphatic Nucleophilic Substitutions: S_N1, S_N2, and S_Ni Mechanism

Substitution reactions by nucleophilic reagents are known as nucleophilic substitution (S_N) reactions. Nucleophiles generally react at sites that are deficient in electrons. Consequently such reaction will be most important for compounds where a carbon is linked to greater electronegative atom or group (like halogen) and is thus deficient in electrons because of unequal sharing of bonding electrons. Like electrophilic substitution these can also be of two types—nucleophilic substitution at saturated or aliphatic carbon and at unsaturated or aromatic carbon. Unlike electrophilic substitution which predominates in aromatics and unsaturated compounds the nucleophilic substitution is more common in aliphatic compounds and has been extensively studied. Kinetic investigations of conversions of alkyl halides to alcohols by the action of alkali shows that there are two extreme types of reaction. In one type the reaction rate is proportional to the concentration of alkyl halide only and it is designated as S_N1 reaction. Here S stands for substitution, N for nucleophile and 1 for unimolecular. The term unimolecular is used here since the rate determining step involves only one molecule. In general S_N1 reactions follow *first order kinetics.* In the other type the rate of reaction is proportional to the concentrations of alkyl halide and alkali or hydroxyl ions and is a bimolecular reaction designated as S_N2 reaction. S_N2 reactions follow second order kinetics.

For S_N1: Rate $\propto$ [R—X] Independent of $[O\bar{H}]$.

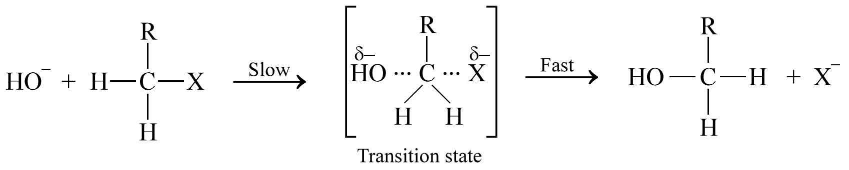
(Stepwise mechanism)

(*i*) $R—X \xrightarrow{\text{Slow}} \overset{+}{R} + \bar{X}$

(*ii*) $\overset{+}{R} + O\bar{H} \xrightarrow{\text{Fast}} R—OH$

For S_N2: Rate $\propto$ $[R—X][OH^-]$

(Concerted mechanism)

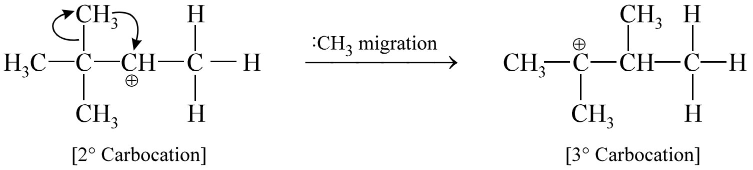


Some examples of the nucleophilic substitution reaction are hydrolysis of alkyl halides, acyl halides; cleavage of ethers with HI (Ziesel reaction and alkylation with alkyl halides (Williamson's synthesis).

The various factors guiding the reaction to follow S_N1 or S_N2 mechanism have been discussed below.

- **Structure of the substrate:** Alkyl halides have been extensively used as substrate for studying nucleophilic substitution reactions. It has been observed that the hydrolysis of primary and tertiary alkyl halides are fast although the former follows S_N2 and the latter S_N1 mechanism. The rate of hydrolysis of secondary alkyl halides is slow and they follow both S_N1 and S_N2 mechanism of hydrolysis. The rate of reactivity of various alkyl halides is iodide > bromides > chlorides for a particular alkyl group and tertiary > secondary > primary > CH_3 alkyl halides for a particular halogen. Amongst the primary alkyl halide the order of reactivity is $CH_3X > C_2H_5X > n\text{-}C_3H_7X > n\text{-}C_4H_9X$ etc.

  The reason from this transformation from S_N2 to S_N1 type mechanism in going from primary to tertiary is the structural difference in their molecules. Tertiary alkyl halides have three alkyl groups attached to the carbon atom joined to halogen. The (+I) effect of the three alkyl groups increases the electron density on the carbon to which they are joined and this increases the repulsion towards halogen thereby increasing the chance of formation of carbocation. Thus in tertiary alkyl halides the tendency to follow the path of S_N1 mechanism increases. Primary alkyl halides follow S_N2 mechanism.
- **Steric effect:** S_N2 mechanism involves the attack by a nucleophile from the side opposite to that of the leaving group. Now if the carbon atom has bulky alkyl group(s) attached to it then it will be difficult for nucleophile to reach the carbon atom hence the reaction will be slowed down. Since S_N2 mechanism operates better in primary alkyl halides therefore with the increase in the size of alkyl group the rate of reaction decreases i.e., $CH_3X > n\text{-}C_4H_9X$. Tertiary alkyl halides are not affected much because they follow S_N1 mechanism.
- **Rearrangement of carbocations:** Sometimes it is found that the attacking nucleophile joins a carbon atom other than that of the leaving group. This happens due to the rearrangement of the carbocation in S_N1 mechanism to a more stable cation. This is due to 1,2 alkyl or hydrogen shift which results in the formation of stabler cation. The formation of stabler



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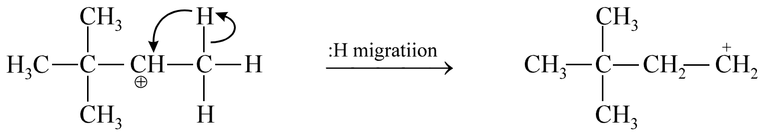


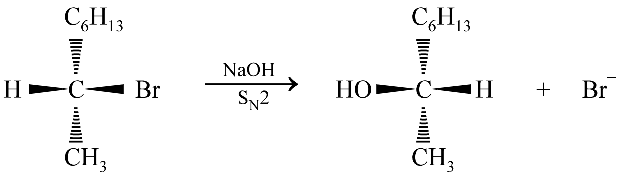
[2° Carbocation]

[1° Carbocation]
(This rearrangement not
possible forming less
stable carbocation)

cation decides the shift. In the above example of hydrolysis of 3-bromo- 2,2-dimethylbutane the carbocation formed rearranges to stable (3°) cation and therefore the alcohol obtained will be 2,3-dimethyl- butanol-2 and not 3,3-dimethylbutanol-2. It is also clear that in single step S_N2 mechanism such a rearrangement is not possible.

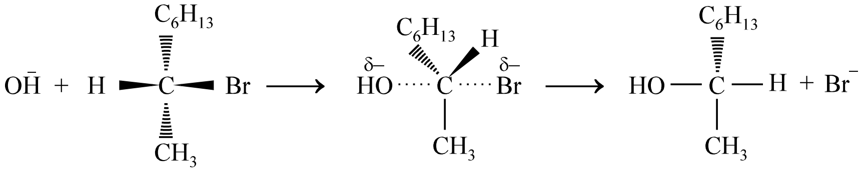
Stereochemistry of S_N2 and S_N1 reactions

In S_N2 reaction of hydrolysis of 2-bromo-octane, having a chiral centre, it is found that the laevorotatory 2-bromo-octane gives dextro-rotatory 2-octanol. This clearly means that there has been an inversion of rotation. Hence it shows that S_N2 reaction proceeds with complete inversion of configuration accompanied by inversion in rotation.



(–) 2-Bromo-octane (–) 2-Octanol

To explain this it is assumed that the nucleophile —OH attacks the carbon from the opposite side of the leaving group so as to avoid over crowding and starts forming a bond by sharing of its pair of electrons. At approximately the same time, the group which is leaving the molecule starts acquiring the bonding electron pair. Thus a negative charge spreads in the transition state from the nucleophile at one end to the departing group at the other end. The configuration of transition state is perhaps that of a triangular bipyramid with all the other groups in the same plane. Since the nucleophile enter the molecule from the opposite end of the departing group, the configuration of the molecule is turned upside down like an inverted umbrella. This therefore results in the inversion of configuration known as *Walden inversion*, when bromide ion is expelled and tetrahedral arrangement reverts back with arrangement opposite to that of the original molecule.



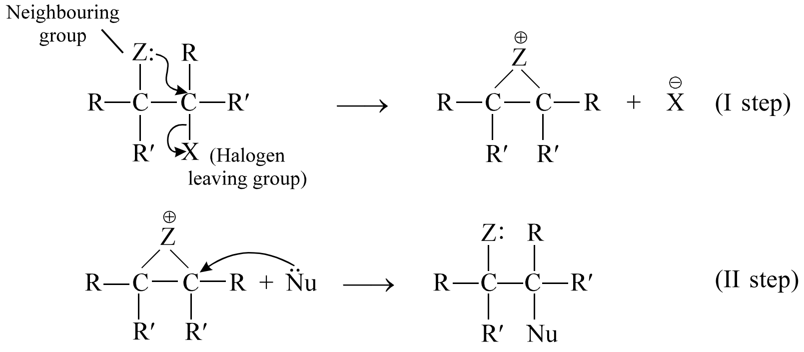
Transition state

3.2.2 Neighbouring Group Participation

The neighbouring group participation is defined as the interaction of the reaction centre either with a lone pair of electrons as adjacent atom or with electrons present in a sigma or pi-bonds (as in a double bond). It generally leads to increased reaction rates and sometimes results in unexpected stereochemical nature of the product.

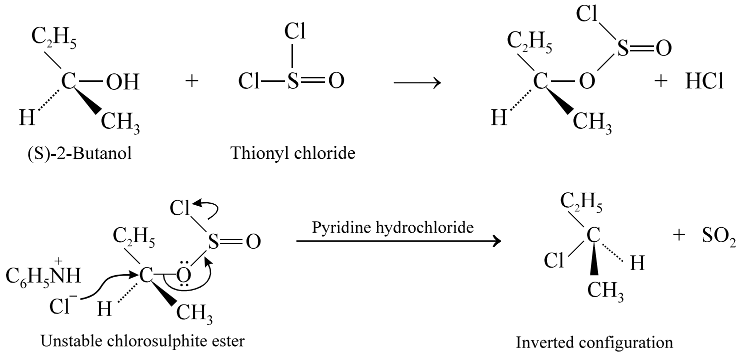
NOTES

If the neighbouring group (the group attached to the carbon which is next to carbon having leaving group) is an electron-rich substituent at a proper place then the configuration is retained. This is a two-step process.

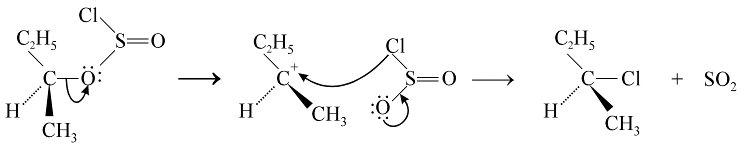


S_Ni

Substitution nucleophilic internal (S_Ni) are those substitution reactions in which substitution takes place by intramolecular process. In these reactions the configuration of the product may or may not change; depending upon the conditions employed in the reaction. Conversion of an alcohol (S)-2-butanol to corresponding chloride using thionyl chloride, is a reaction where the configuration changes only under a set of conditions and does not change under other conditions.

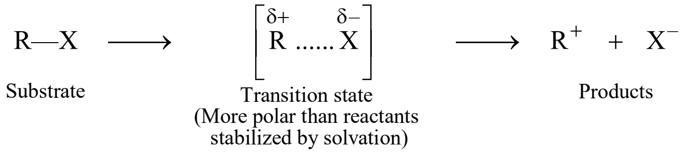


However, in the absence of pyridine the chlorosulphite ester decomposes to give the chloride having the same configuration.

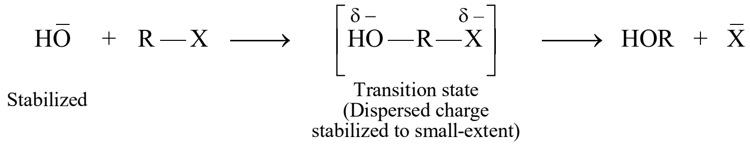


• Solvent Effect

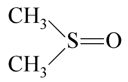
In S_N1 substitution reaction the bond breaking between carbon and halogen requires energy. The ions generated during heterolysis of the bond are surrounded by polar solvent molecules oriented with their negative end towards the carbocation and positive end towards anion. The substrate molecule is then pulled apart as solvated ions. Individually these ion-dipole bonds are weak but altogether they provide a great deal of energy. The transition state has a stretched carbon-halogen bond with well developed charges. Thesolvent thus stabilizes transition state more than the reactant, thereby lowering the energy of activation and speeding up the reaction. This lowering of energy compensates for the energy required for breaking the bond.

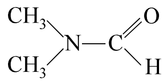


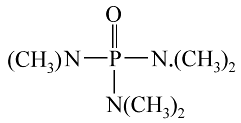
In S_N2 mechanism the solvent stabilizes the reactants specially the nucleophiles, more than it does the transition state and thus raises the energy of activation and slows down the reaction (stabilization deactivates the nucleophile)



Here we must understand that cations are solvated through unshared pair of electrons but the anions are chiefly solvated through hydrogen bonding. Hence protic solvents like water and alcohol are good for S_N1 mechanism but they slow down S_N2 reaction. (CF_3CH_2OH, HCOOH and CF_3COOH are other solvents which form strong H-bond with the leaving group and are better solvents for S_N1 mechanism.) In aprotic solvents like DMSO, DMF and HMPT, S_N2 reactions go 10^6 times as fast as in polar solvents like water and alcohol.


Dimethyl sulphoxide
(DMSO)


Dimethyl formamide
(DMF)

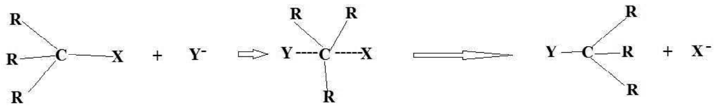

Hexamethyl phosphorotriamide
(HMPT)

- **Leaving Group**

Most of the leaving groups leave as negative ion and if they stabilize this charge most effectively as they will be considered as good leaving groups. Weak bases which are conjugate bases of strong acids do this best. The anions of strong acids like Cl^-, Br^-, I^- and $HS\bar{O}_4$ are good leaving groups in S_N2 reactions. Amongst the halogens Iodide ion is the best leaving group and fluoride is the poorest of the lot $I^- > Br^- > Cl^- > F^-$.

Kinetics of a Reaction

The rate of nucleophilic substitution in a reactions depends on the concentration of both the haloalkane and the nucleophile.



(a) If we double the concentration of either the haloalkane or the nucleophile, then the rate of the reaction would proceed twice as fast as the initial rate.

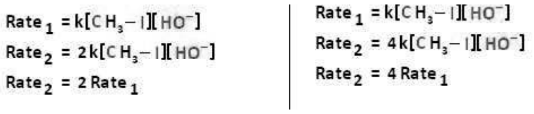
(b) If we double the concentration of both the haloalkane and the nucleophile,then that the rate of the reaction would proceed four times as fast as the initial rate.

Let as assume the initial reaction is:

$$HO^- + CH_3-I \longrightarrow CH_3OH + I^-$$

$$\text{Rate} = k[CH_3-I][HO^-]$$

Changing of Concentration:



$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2\,\text{Rate}_1$$

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4\,\text{Rate}_1$$

3.2.3 Neighbouring Group Participation (NGP): Anchimeric Assistance

A remarkable difference in the rate of following two substitution reactions is observed which are superficially very similar.

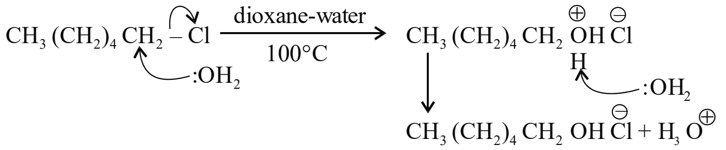
(i) $\underset{\text{(1-Chlorohexane)}}{CH_3(CH_2)_4CH_2Cl} + H_2 \xrightarrow[100°C]{\text{dioxane water}} CH_3(CH_2)_4CH_2OH + HCl$

(Second order Kinetics while)

(ii) $\underset{\beta\text{-Chloroethylethylsulphide}}{CH_3CH_2SCH_2CH_2Cl} + H_2O \xrightarrow[100°C]{\text{dioxane water}} \underset{\text{2-(ethylthio)ethanel}}{CH_3CH_2SCH_2CH_2OH}$

(First order kinetics)

At first sight both reactions appear to be simple S_N2 reactions in which chloride is displaced by hydroxyl group.

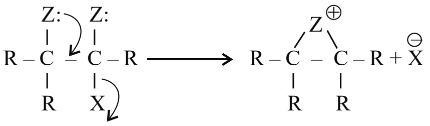


This reaction requires high temperature because water is such a poor nucleophile in the S_N2 reactions that the reaction is extremely slow at lower temperatures. As a matter of fact the presence of sulpher in S_N2 reaction should have little effect on the rate of S_N2 reaction as electronegative substituents are known to retarcts S_N2 reactions slightly.

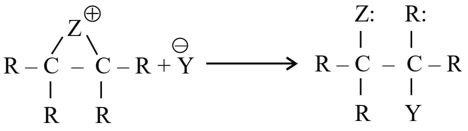
On the contrary the reaction (ii) is thousand times faster than the reaction (i). Furthermore, the reaction kinetics are first order i.e., the rate depends only on the concentration of substrate but not the nucleophile. This is a rathers surprising result for substitution at a primary carbon atom, a reaction expected to be S_N2.

When potential substrate for nucleophilic substitution consists a group which can act as a nucleophile then it is observed that the kinetics and stereochemistry of the substitution are strongly affected. Such groups (with unshared electron pairs) are generally located at β or some times further away to the leaving group. The mechanism operating in such cases is called as neighbouring group mechanism.

In the first step, the neighbouring group acts as a nucleophile pushing out the leaving group but still retaining attached to the molecule.



In the second step, external nucleophile displaces the neighboring group by backside attack.



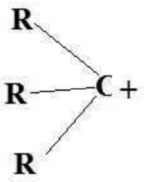
Anchimeric assistance

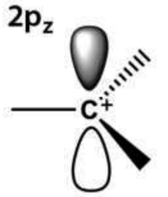
In neighbouring group mechanism, a large rate acceleration is typical of experimental evidence used to diagnose the involvement of neighbouring group in chemical reaction, neighbouring group provide "anchimeric assistance". The assistance given by group Z is termed as anchimeric assistance. Some of the important neighboring groups are $COO^{\ominus}$, $^{\ominus}OCOR$, $OR^{\ominus}$, $OH^{\ominus}$, $O^{\ominus}$, $NH_2^{\ominus}$, $NHR^{\ominus}$, $S^{\ominus}$, $SH^{\ominus}$, $SR^{\ominus}$, $I^{\ominus}$, $Br^{\ominus}$ and Cl^-. The effectiveness of halogen as neighboring group decreases in the order.

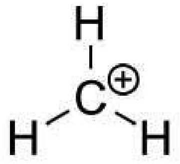
I > Br > Cl

3.2.4 Classical and Nonclassical Carbocations

The 'classical' carbocation, in which an electron deficient carbon bearing a positive charge. It means the carbon atom has a deficiency of electron, due to this deficiency the carbon has +ve charge on it.

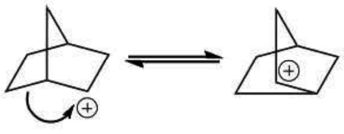




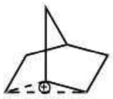


A carbocation the ground state of which has delocalized (bridged) bonding ð- or ó-electrons. There are many examples of 'non-classical' carbocations, like- 2-norbornyl carbocation.

classical

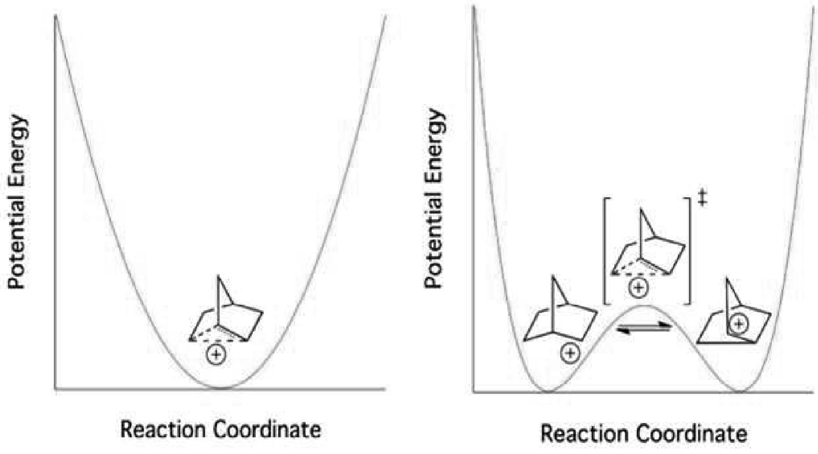


non-classical



Labeling experiments have shown that the positive charge resides on more than one carbon in the 2-norbornyl ion. Early on, the data was explained by equilibrating classical ions, but soon another possibility emerged - one involving a single non-classical ion.

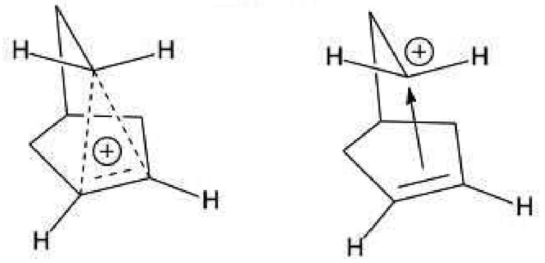
The problem comes down to: are the equilibrating classical ions ground state structures with the non-classical ion serving as the transition state, or is the non-classical ion the ground state? This debate went on for a very long period of time, but now most agree that the non-classical structure is the ground state in the 2-norbornyl system. In fact, a recent, and difficult to obtain, crystal structure for the 2-norbornyl cation has been published proving that the ion exists with the non-classical geometry.



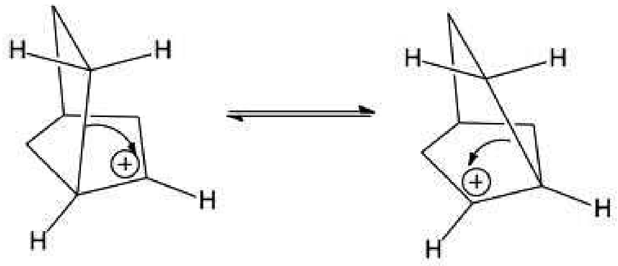
(a) (b)

A key difference between classical and non-classical structures is the bonding. As illustrated above, a classical ion has a carbon with a sextet of electrons and 3 other bonds. The non-classical ion, on the other hand, involves 3 carbons with 2 electrons spread over them. This is called a 3-center 2-electron bond (hypercoordinate bonding) and is **a clear marker for a non-classical ion.**

non-classical

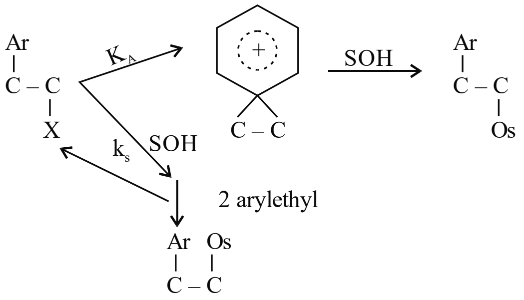


classical



3.2.5 Phenonium Ions and Norbornyl System

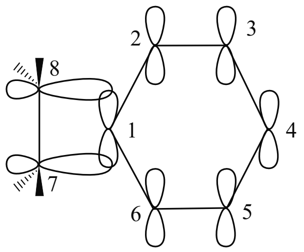
Neighboring group participation by an aromatic ring. An aromatic ring β to the leaving group can function as neighboring group.



Solvolysis of 2. arylethyl

This system follows two paths. In the first path, K_Δ aryl group pusher out the leaving group to give a bridge ion called "phenonium ion" which on reaction with solvent forms the product with retention of configuration. Second path is simple S_N2 .

An aromatic ring can assist in the formation of a carbocation intermediate called a phenonium ion delocalizing the positive change.



(Overlap of the cyclopropyl orbitals with the π system)

The bridged form of the β-phenyl eithyl cation can be observed in super-acid medium and characterized by cation and proton NMR spectra.

Let us study the norbonyl system in detail.

NOTES

In carbocation the positive charge is localized on cone carbon atom but when the positive charge is delocalized by a double ~~b~~ or triple bond that is not in allylic position or by a single bond then it is termed as "Non-classical or bridge carbocation".

Thus in organic chemistry non-classical ions are a special type of carbonium ions displaying delocalization of σ-bonds in 3-center-2-electron bonds of bridge system.

In 1949 Winstein explained the reactivity of certain nor bornyl compounds. General mechanistic possibility for 1, 2-shift are outlined A → B → C → D → E.

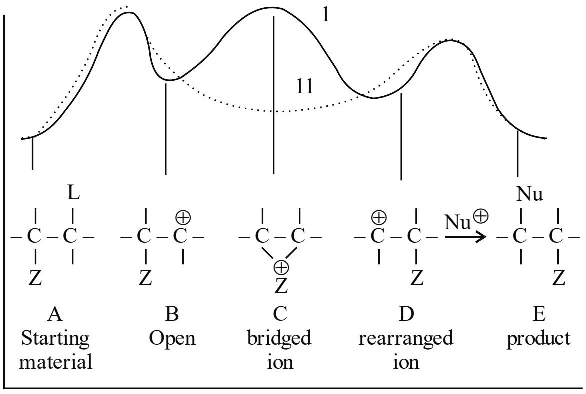
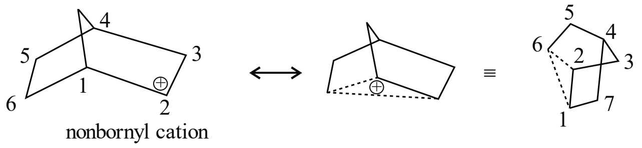
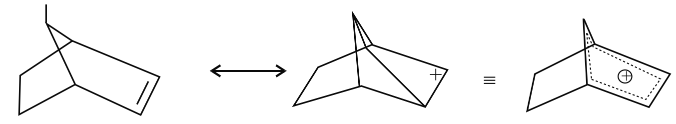


Fig. 3.1 *Mechanism and Energy Diagram of 1, 2 Shift*

The most popular application of non classical carbocation comes from nonbornyl cation, 7-non-bornenyl cation and cyclopropyl methyl cation.

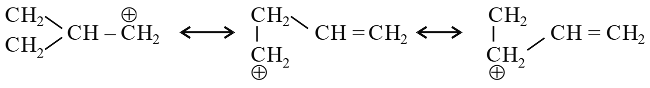


nonbornyl cation



7-non boryl cation

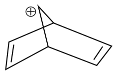
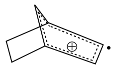
[homoallylic carbocation) achiral



$CH_2 \diagdown CH-\overset{\oplus}{C}H_2 \longleftrightarrow CH_2 \diagdown CH=CH_2 \longleftrightarrow CH_2\ CH=CH_2$; $CH_2 \diagup$; $\overset{\oplus}{C}H_2$; $\overset{\oplus}{C}H_2 \diagup$

Cyclopropyl methyl cation

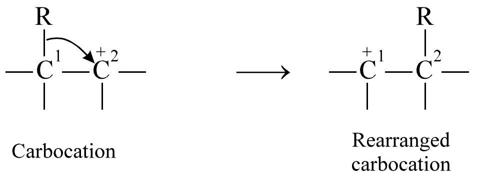
Evidence in support of existence of non-classical carbocation

NMR spectra of non bornadienyl cation shows  that 2, and 3 protons are not equivalent to 5 and 6 protons this shows that there is interaction between changed carbon and double bond which is evidence of existence of .

3.2.6 Common Carbocation Rearrangements

In a rearrangement reaction the atoms or groups within a molecule move from one atom to another, thus giving rise to structural isomer of the starting compound or the reactant. The product is the rearranged molecule. It is difficult to visualize these reactions separately from the addition, substitution or eliminate type because most of the rearrangements involve one or more than one of these processes. The atom or group which migrates is known as **migrating group**, the atom to which it was initially attached is known as **migration origin** and the atom which it finally joins is known as **migration terminus**. If the migrating group gets completely detached from the molecule during the rearrangement then it may as well go to the migration terminus of other molecules of the compound. Such rearrangements in which the migrating group actually becomes free even for a small fraction of time, are known as **Intermolecular rearrangements**. However if the migrating group remains attached to the molecule in some or the other way throughout the process of rearrangement then this type is known as **Intramolecular rearrangements**.

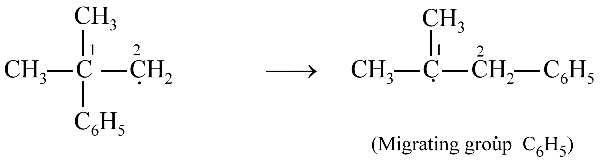
The migration of atoms or groups may occur with the pair of electrons through which it is attached to migration origin (known as **anionotropic migration**), or without this pair of electrons (**cationotropic migration**), or with just one unpaired electron (**free radical migration**).



$$-\overset{R}{\overset{|}{\underset{|}{C^1}}}-\underset{|}{\overset{+}{C}}{}^{2}- \longrightarrow -\underset{|}{\overset{+}{C}}{}^{1}-\overset{R}{\overset{|}{\underset{|}{C^2}}}-$$

Anionotropic Migration (Migration with the pair of the electrons)

(R = Migrating group; C1 = Migration origin; C2 = Migration terminus)

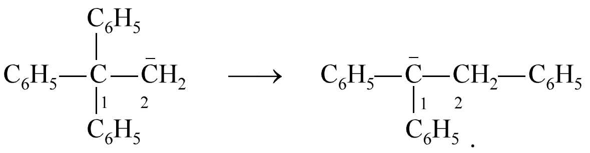


$$CH_3-\overset{CH_3}{\underset{C_6H_5}{C}}-\underset{\cdot}{C}H_2 \longrightarrow CH_3-\overset{CH_3}{\underset{\cdot}{C}}-CH_2-C_6H_5$$

(Migrating group C_6H_5)

Free Radical Migration

Examples of cationotropic rearrangements are few and these involve the formation of a carbanion which then may rearrange as follows:



$$C_6H_5-\overset{C_6H_5}{\underset{C_6H_5}{C}}-\overset{-}{C}H_2 \longrightarrow C_6H_5-\underset{C_6H_5}{\overset{-}{C}}-CH_2-C_6H_5\,.$$

(Migrating group $\overset{+}{C}_6H_5$)

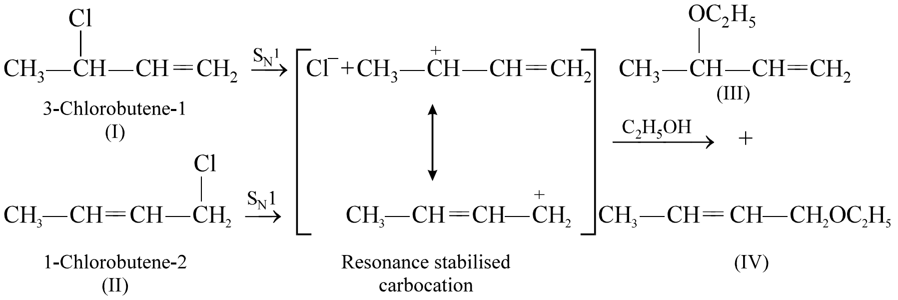
(Cationotropic Migration)

The most common type of rearrangements involve migration of the group with its pair of electrons (anionotropic) and these involve the formation of a carbocation in most cases. The carbocations in order to acquire greater stability tend to rearrange by the migration of hydrogen or alkyl group with its pair of electrons. Allylic and pinacol-pinacolone rearrangements are given here as examples of rearrangement by migration of a multiple bond or an alkyl or allyl group as a carbanion respectively.

NOTES

Allylic rearrangement

Substitution reactions at allylic positions usually occur by S_N1 mechanism forming an allylic carbocation which is resonance stabilised. This results in a mixture of two isomers in the product due to the migration of a double bond from its original position to an adjacent site. Such rearrangement reactions in which the carbon skeleton remains unchanged but multiple bonds rearrange are known as *allylic rearrangements*.

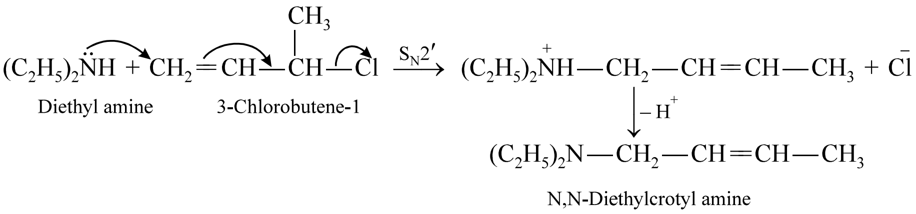


$$CH_3-\underset{}{\overset{Cl}{CH}}-CH=CH_2 \xrightarrow{S_N1} \left[Cl^- + CH_3-\overset{+}{C}H-CH=CH_2 \leftrightarrow CH_3-CH=CH-\overset{+}{C}H_2\right] \xrightarrow{C_2H_5OH} CH_3-\overset{OC_2H_5}{CH}-CH=CH_2 + CH_3-CH=CH-CH_2OC_2H_5$$

$$CH_3-CH=CH-\overset{Cl}{CH_2} \xrightarrow{S_N1}$$

Whether the starting material is (I) or (II), in either case it is always a mixture of (III) and (IV) which is obtained obviously due to two important resonance contributing structures of intermediate carbocation. Such substitution reaction occurring by S_N1 mechanism resulting in a rearranged product are S_N1' reactions.

Bernard David de la Mare and coworkers (1953) have shown that allylic rearrangements are also possible in S_N2 reaction which are designated as S_N2' reactions. These reactions occur as follows:

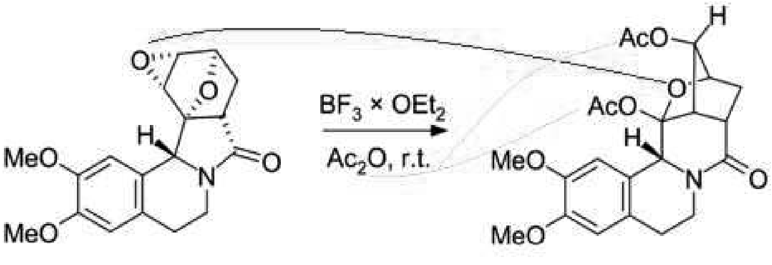


$$(C_2H_5)_2\ddot{N}H + CH_2=CH-\overset{CH_3}{CH}-Cl \xrightarrow{S_N2'} (C_2H_5)_2\overset{+}{N}H-CH_2-CH=CH-CH_3 + \overset{-}{Cl} \xrightarrow{-H^+} (C_2H_5)_2N-CH_2-CH=CH-CH_3$$

(i) Wagner-Meerwein rearrangement

A Wagner–Meerwein rearrangement is a class of carbocation 1,2-rearrangement reactions in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon.

Example: In the synthesis of bridged azaheterocycles:



Wagner–Meerwein Rearrangement in the synthesis of bridged azaheterocycles

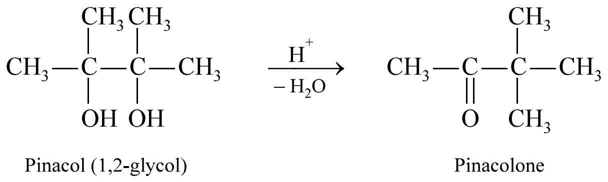
Wagner-Meerwein rearrangement mechanism used to convert an alcohol to an olefin using an acid catalyst.

Mechanism

Protonation of the alcohol by the acid which is then released as water to forms a carbocation. A 1,2-shift then occurs to form a more substituted and stabilized carbocation. A final deprotonation with water produces the final olefin product and regenerates the acid catalyst.

(ii) Pinacol-pinacolone rearrangement

Transformations of 1,2-glycols to aldehydes or ketones, involving the migration of an alkyl or aryl group, under acidic conditions are known as Pinacol-pinacolone rearrangement. Originally the term was applied to the conversion of pinacol to pinacolone

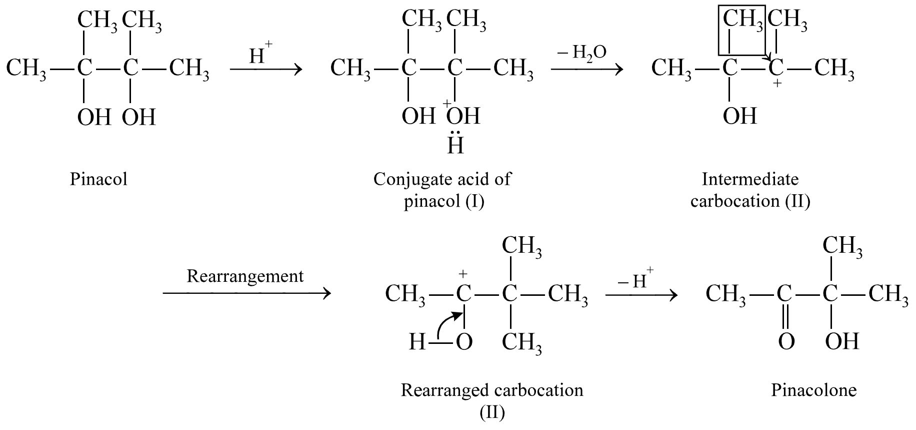


Pinacol (1,2-glycol)   Pinacolone

This is an intramolecular rearrangement in which alkyl group migrates to an electron deficient adjacent carbon atom.

Mechanism

Under acidic conditions pinacol forms its conjugate acid (I) which loses a molecule of water to form a carbocation (II). An alkyl group from adjacent carbon atom then migrates with its pair of electrons to the electron deficient carbocation carbon forming the rearranged carbocation (III) of pinacolone. This loses a proton to form the rearranged pinacolone (IV).



Pinacol

Conjugate acid of pinacol (I)

Intermediate carbocation (II)

Rearranged carbocation (II)

Pinacolone

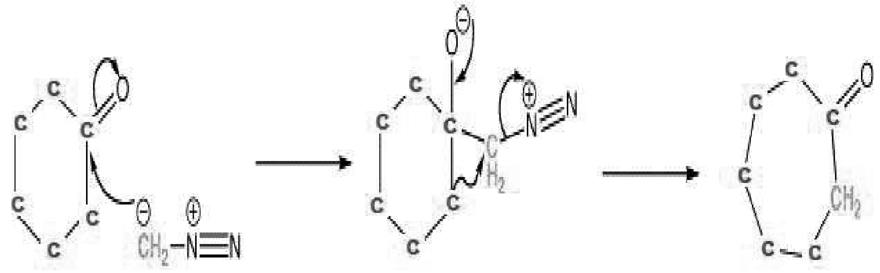
(iii) Semi-Pinacol Rearrangement

The **semipinacol rearrangement** is a rearrangement reaction in organic chemistry involving a heterosubstituted alcohol of the type $R_1R_2(HO)C–C(X)R_3R_4$. The hetero substituent can be a halogen (Cl, Br, I), a tosylate, a mesylate or a thiol group. This reaction proceeds by removal of the leaving group X forming a carbocation as electron deficient center. One of the adjacent alkyl groups then migrates to the positive carbon in a 1,2-shift. Simultaneously with the shift, a pi bond forms from the oxygen to carbon, assisting in driving the migrating group off its position. The result is a ketone or aldehyde. In another definition all semipinacol rearrangements "*share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C–C or C–H bond to terminate the process, generating a carbonyl group* ".

The rearrangement reaction can be classified into 4 types. Type 1 concerns all 2-heterosubstituted alcohols. Substrates in type 2 rearrangements are allyl alcohols. The carbocation is formed by electrophilic addition to the alkene group with electrophiles such as halonium ions, Brønsted acids and Lewis acids. In type 3 the substrates are epoxides, notably 2,3-epoxy-alcohols and type 4 concerns the reactions of alpha hydroxyketones and alpha hydroxy imines. Reactions of type 4 are also called acyloin rearrangements.

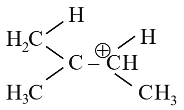
While similar to the pinacol rearrangement, the semipinacol rearrangement differs from the pinacol rearrangement in that the cation is not formed from a vicinal 1,2-diol. With diazoalcohols the reaction is known as the Tiffeneau–Demjanov rearrangement.

Example: When diazomethane mix in to ketone, the product undergoes a ring extension by rearrangement of the intermediate. Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone, so it ring expands cleanly to cycloheptanone.



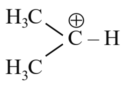
3.2.7 Application of NMR Spectroscopy in the Detection of Carbocations

The coupling between protons separated by more than three bonds is possible if the intervening protons are separated by sp^2 carbon and not by sp^3. Coupling constants are corresponding to sp^2 hybridised species.



$\tau = 5H_3$

In C^{13} NMR spectra, coupling constant (C^{13} - H) in the iso-propyl cation is in accordance with the predication of planner ion. Substitution of ethyl for methyl or methyl for H causes a down field shift indicating that the central carbon becomes more positive.



$\tau = 169H_3$

3.2.8 Nucleophilic Substitution at an Allylic, Aliphatic Trigonal and a Vinylic Carbon

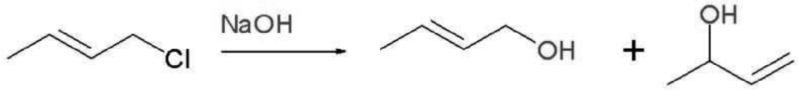
Let us study them in detail.

- **Allylic Carbon**

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 and is confronted in **nucleophilic substitution**.

In reaction, the conditions that facilitate a S_N1 reaction mechanism is referred as the intermediate which is a carbocation for which numerous resonance structures are possible. This describes the product distribution (or product spread) after recombination with **nucleophile Y**. This specific process is termed as an **S_N1' substitution**.

Alternatively, it is possible for nucleophile to directly attack at the allylic position, and displaces the leaving group in a single step, this specific process is referred as **S_N2' substitution**. This is possible in the specific situations when the allyl compound is unobstructed, and a strong nucleophile is typically used. The products probably be similar like those observed with S_N1' substitution. Consequently, reaction of 1-chloro-2-butene with sodium hydroxide produces a mixture of 2-buten-1-ol and 3-buten-2-ol, as shown below:



However, the product in which the OH group is on the primary atom is minor. In the substitution of 1-chloro-3-methyl-2-butene, the secondary 2-methyl-3-buten-2-ol is produced in a yield of 85%, while that for the primary 3-methyl-2-buten-1-ol is 15%.

In one of the reaction mechanism the nucleophile does not directly attack at the electrophilic site but in a conjugate addition over the double bond, as shown below:

Usually in the allylic compounds with a bulky Leaving Group (LG) in S_N2 conditions or bulky non-leaving substituent which produces significant steric hindrance increases the conjugate substitution. This type of reaction is termed as S_N1' or S_N2', depending on whether the reaction follows S_N1-type mechanism or S_N2-type mechanism. Similarly, the S_N1' and S_N2' equivalents are possible for the S_N1 and S_N2 reactions, respectively. In addition, there is also an equivalent for S_Ni', appropriate for reactions between allylic compounds and reagents, such as $SOCl_2$.

The synthetic utility can be extended to substitutions over butadiene bonds as shown below which illustrates the reaction in methanol and catalyst diisopropylethylamine.

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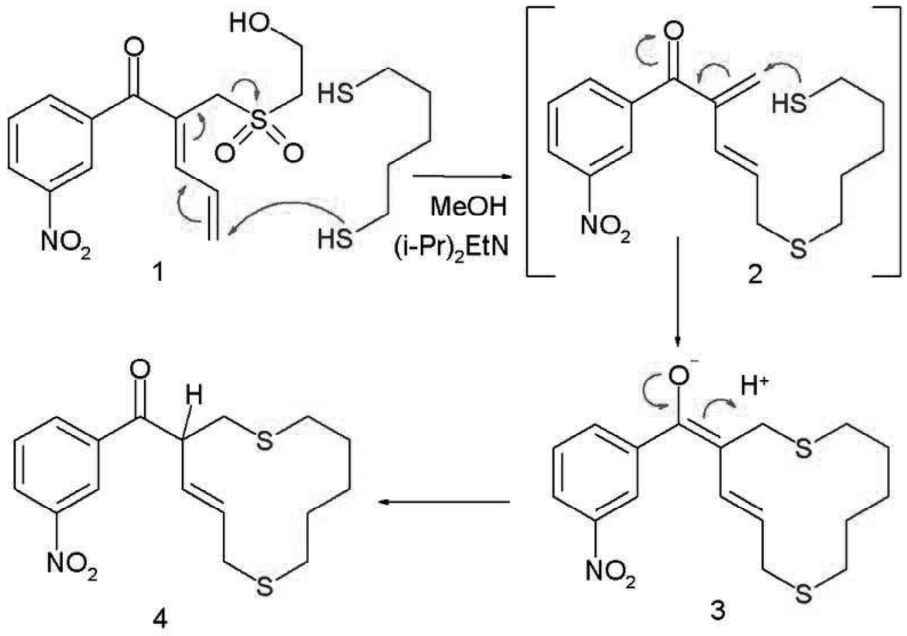
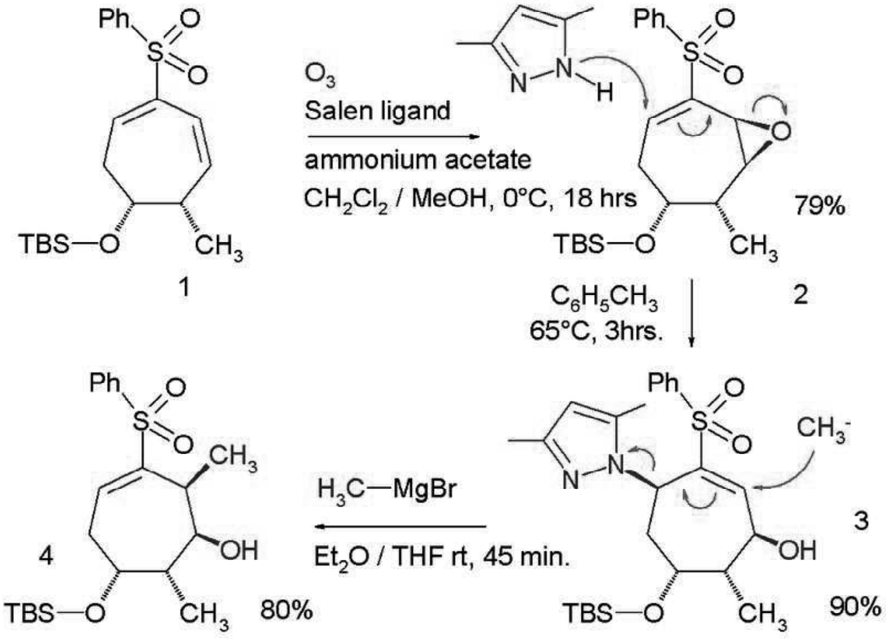


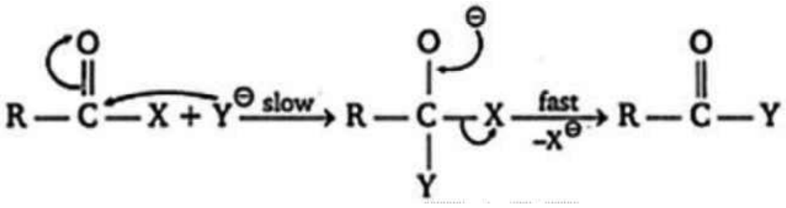
In the first step of the above macrocyclization reaction, the thiol group in one end of 1,5-pentanedithiol reacts with the butadiene tail in 1 to the enone 2 in an allylic shift with a sulfone leaving group which then reacts with the other end in a conjugate addition reaction. The detailed observation specifies that the allylic shift was used twice in a ring system.



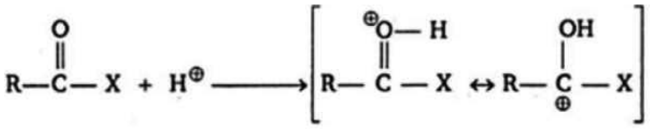
In this reaction sequence, a Jacobsen epoxidation is added as an epoxy group to a diene which acts as the leaving group in reaction with the pyrazole nucleophile. The second nucleophile is Methyl Magnesium Bromide ($H_3C - MgBr$) expulsing the pyrazole group.

- **Aliphatic Trigonal Carbon**

Nucleophilic substitution is very significant reaction at trigonal carbons, particularly when the carbon is double bonded to an oxygen, sulphur or a nitrogen. The nucleophilic substitution takes place as a result of tetrahedral mechanism, sometimes termed as addition-elimination reaction. Even though this mechanism demonstrates second order kinetics, but it is not equivalent to the S_N2 mechanism.

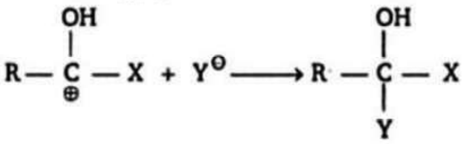


In tetrahedral mechanism, at first the nucleophile (Y) attacks for providing a tetrahedral intermediate that contains both X (Leaving Group) and Y and then the Leaving Group (X) leaves. The tetrahedral mechanism is typically supported through the second order kinetics and isotopic labelling. When the reaction is carried out in an acidic solution then the hydrogen ion acts as a catalyst. The reaction rate is increased since the nucleophile easily attacks the carbon when the electron density of it has decreased.

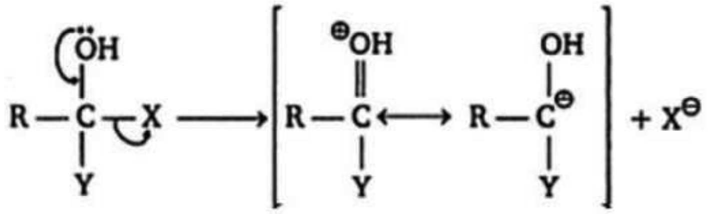


Mechanism

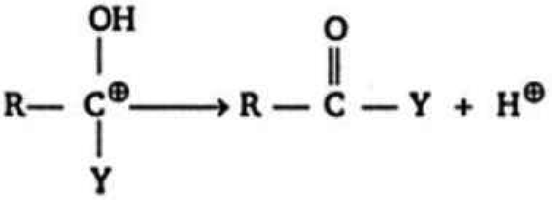
Step 1



Step 2

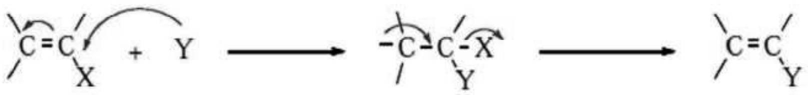


Step 3



- **Vinylic Carbon**

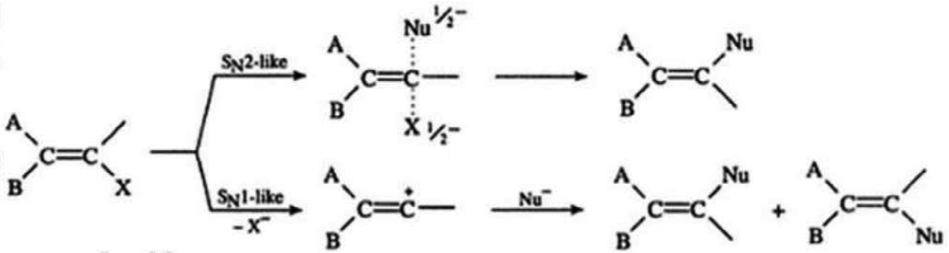
The vinylic substrates undergo addition and substitution reactions. The nucleophilic substitution at unsaturated carbon, such as vinyl chloride (CH_2=CHCl) is shown below.



Under normal conditions, nucleophilic substitution at vinylic carbon is exceptionally slow as compared to substitution at saturated carbon. Vinyl substrates are essentially inert towards nucleophiles. Following are the two key reasons for this lack of reactivity:

Reason 1: The first reason is Vinyl C–X bond (X–Halogens). Essentially, vinyl halides and related compounds are considered fundamentally inert towards nucleophiles. The vinyl C–X bond (X = Halogen, Oxygen, or Nitrogen) is stronger as compared to the alkyl C–X bond because of a resonance interaction between the double bond and an unshared pair on X. This interaction also weakens and polarizes the π-bond, because of which such compounds are reactive towards electrophilic addition.

Reason 2: The second reason for low reactivity of vinyl substrate towards nucleophilic substitution is that the S_N2 transition state and the S_N1 intermediate (a vinyl cation), are extremely high in energy to be readily accessible.



The vinylic cations can be readily made through solvolysis of the S_N1 type if the following two conditions are met:

1. The leaving group is extremely reasonable.
2. The vinylic group contains electron releasing substituents.

Substitution at Vinylic Carbon by Other Mechanism

Substitution at vinylic carbon is significantly facilitated in vinylic compounds of the type Z.CH=CH.X where Z is an electron withdrawing group, for example CHO, R_2CO, COOEt, $ArSO_2$, F. The mechanism possible in some other cases may be different from the established S_N1 reaction and S_N2 reaction. These are described as tetrahedral mechanism and addition-elimination mechanism.

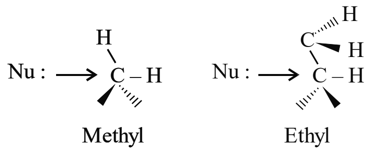
3.2.9 Reactivity Effects of Substrate Structure

Let us study them in detail.

I. Effect of Substrate Structure

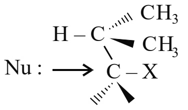
Variation in the structure of substrate affects S_N1 and S_N2 mechanisms in the following manner:

(a) **Branchign at α and β carbon atoms:** The effect of alkyl group at α and β carbon on reaction rate can be explained considered steric hindrance to the attack of attacking nucleophile.



Effect of a branching on S_N2

Similarly blocking by added methyl group to nucleophile attack can be seen in isobutyl and neopentyl compounds.



Isobutyl system

(b) **Unsaturation at α-carbon:** Such systems are rings, acetylenic or aryl substrate which are very unreactive toward both S_N^1 and S_N^2 mechanism because of the following reasons:

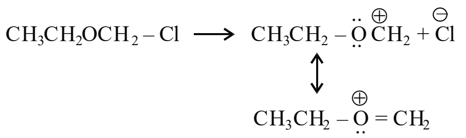
   (i) sp^2 carbon is more electronegative than sp^3 hence loss of X and X^- is difficult.

   (ii) Lone pair of leaving group are involved in n-π conjugation which gives double bond character to C-X bond and hence it is shorter and stronger.

(c) **Unsaturation at β-carbon:** Allylic and benzylic halides react rapidly by S_N^1 mechanism as the resulting carbocations are stabilized by resonance.

II. Effect of Substituent Group

Carbocation connected to heteroatom possessing nonbonding electrons are particularly well stabilised. Reaction of 1-chloro 2 oxobutane with ethanol proceeds at a rate over 109 faster than similar reaction of the tertiary haloalkane-2-chlro, 2 methyl propane.



$$CH_3CH_2OCH_2-Cl \longrightarrow CH_3CH_2-\ddot{O}\overset{\oplus}{C}H_2+\overset{\ominus}{Cl}$$
$$\updownarrow$$
$$CH_3CH_2-\overset{\oplus}{\underset{\cdot\cdot}{O}}=CH_2$$

If the group Z is electron withdrawing such as RCO, –CHO, –CN, etc. then S_N^1 rates are decreased due to destabilization of carbocation by (n-π) conjugation or high electronegativity of Z group.

NOTES

Some elctronic effects are observed because bond breaking and bond making do not necessarily occur to exactly the same extent at the transition state of an S_N^2 reaction. Electron donating group can aid in "lossening" the bond to leaving group by stabilizing any partial positive change which develops on the carbon atom.

Electron withdrawing Z decreases the rate by concentrating the change while electron donating group increases the rate by spreading the position change.

III. Effect of Attacking Nucleophile

A nucleophile is a species with unshared electron pair. The relative reactivity of a nucleophile is called nucleophilicity. Nucleophilicity is tendency to react with carbon while basicity is tendency to react with proton.

The factors that governs the effect of nucleophile on S_N^2 reactions are:

(i) A nucleophile with negative charge is more powerful than its neutral acid.

$OH^{\ominus} > H_2O, \quad CH_3O^- > CH_3OH$

(ii) For nucleophiles with same attacking atom, or attacking atom in the same row of the periodic table, i.e., having approzimately same size, nucleophilic activity increases with increase in basicity.

(iii) In a series of analogues ions or molecules with very different in size at least in protic solvent reactivity of nucleophile increases with increasing atomic number although basicity decreases.

$\overset{\ominus}{I} > \overset{\ominus}{Br} > \overset{\ominus}{Cl} > \overset{\ominus}{F}$

(iv) A nucleophilic anion must have an associated cation, which has no effect on the rate of substitution as long as it is freely dissociated in the solvent.

IV. Effect of Leaving Group

In S_N^2 reaction leaving group gains electron density in going from a reactant to transition state. The degree to which a group can accommodate negative charge is also related to its affinity for a proton, i.e., basicity.

A group which is a conjugate base of a strong acid can act as a good leaving group, such as $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, etc.

CN^-, N_3^- and CH_3COO^- being strong bases are poor leaving group.

Leaving group	**Relative rate**
CF_3SO_3	10^8
CH_3SO_3	10^4
I^-	91
Br^-	14
F^-	10^{-6}
CH_3COO^-	10^{-6}

V. Effect of the Reaction Medium

The nucleophilic substitutions are heterolytic processes which usually take place in solution. Dipolar interactions of the reaction medium with reactants, intermediates can influence the rate of reaction.

For S_N1 reactions, the nature of the medium in which heterolytic reaction is carried out has after profound influence on reaction rate.

For neutral substrate, charge is more in transition state than in starting compound hence the more polar the solvent, the faster the reaction. For example, alkyl halide is a neutral molecule with small dipole moment. In rate determining step carbon-halogen bond breaks, carbon becomes positively charged and helogen negatively charged. Charge is greater in rate determining step. The polar solvent stabilises the dispersed charge on the transition state more that it will stabilise the relatively neutral reactant.

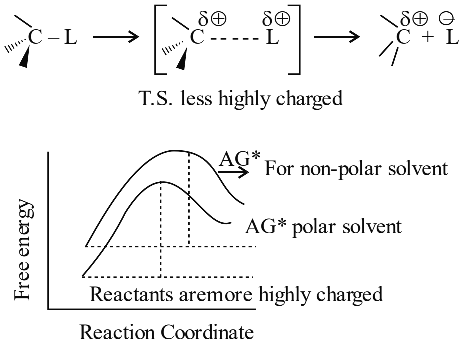


Fig. 3.2 Reaction Coordinate Diagram in which the Charge on the Reactant is Greater than the Charge on the Transition State

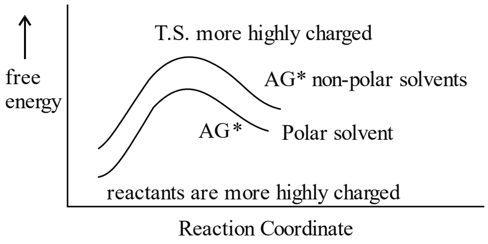


Fig. 3.3 Reaction Coordinate Diagram for a Reaction in which the Charge on the Transition State is Greater than the Charge on the Reactant

For S_N^1 mechanism, the effect of solvent has been treated quantitatively by a linear free-energy relationship of Greenwald-Wirsteiw equation.

$\log k/K_0 = my$

m = characteric of substrate (1.00 for t-BuCl)

y = characteric of solvent measuring-ring it ionizing power

K_0 is the rate in standard solvent, 80% aqueons ethanol at 25°C.

S_N^1 reactions of neutral substrate are more rapid in protic solvents (H_2O, ROH) which can form hydrogen bonding with the leaving group.

Specific reactant-solvent interaction on a molecular scale may also play a critical part in the reaction. A cation or anion is closely associated with numerous solvent molecules and is said to be solvated. Methanol and ethanol are polar protic solvents which are used extensively in organic reaction.

Solvation of the reacting nucleophile increases the energy required to attain the reaction transition state.

3.2.10 Phase Transfer Catalysis and Ultrasound

Generally in conducting those reaction in which the reactants do not mix, great difficulty is observed. This difficulty was overcomes in two ways:

(a) Using a solvent that dissolves both substrate and nucleophile

(b) Using phase transfer catalysts (PTS)

The principle of PTC is based on the ability of certain phase transfer agent from one. Phase into another phase wherein the other reagent exists. Thus reaction is made possible by bringing together the reagents which are originally in different phases.

Phase transfer catalyts find application in variety of reactions. Phase transfer catalyst reaction may be classified broadly into two main classes.

(i) Soluble phase tranfer catalyst reactions.

(ii) Insoluble phase transfer catalyst reaction.

In nucleophilic substitution, there are two principles types of phase transfer catalysts. Both types of catalysts transfer nucleophile from aqueous phase to organic phase.

(i) Quaternary ammonium or Phosphonium salt

(ii) Crown others or cryptands

Ultrasound

It is a technique to increase the reaction rate. The use of ultrasound in chemical reactions in solution provides specific activation based on physical phenomenon.

Acoustic Cavilation: Cavilation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by expansion, in which a sudden pressure drop forms small oscillating bubbles of gaseous substance. There bubbles expand with each cycle of the applied ultrasonic energy untill they reach an unstable size they can collid and collapse produces powerful shock waves. Cavilation converts the diffuse energy of sound into a chemical useful form.

These waves greatly increases the temperature aned pressure within the tiny regions resulting in an increase in reaction rate. This technique was found to be useful specidlly for those reaction which atleast partially involve free radical intermediate.

Applications of Ultrasound in Chemistry

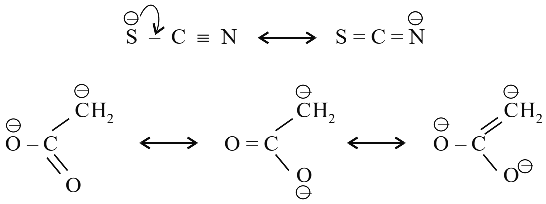
- (i) Decreases of reaction time
- (ii) Increase of yield
- (iii) use of less phase transfer catalyst
- (iv) Activation of metals and solid
- (v) Enhancement of the ractivity of reagents and catalysts
- (vi) Generation of useful reactive species

3.2.11 Ambident Nucleophile and Regioselectivity

A nucleophile can have more than one atoms carrying a pair of electrons or the electrons may be shared by two or more atoms. If such is the case the nucleophile may attact in two or more different ways to give different products. Such nucleophile are called ambident nucleophile.

A common example of ambident nuclephile is enolation with nuclepyhile centers.

Structure of some of the important ambident nucleophiles can be shown



Factors Influencing Ambident Reactivity

Which end of an ambident nucleophile should react predominantly under a particular set of condition? To answer this question, two most important factors are as follows:

- (i) Polarizability of the nucleophile
- (ii) Nature of solvent

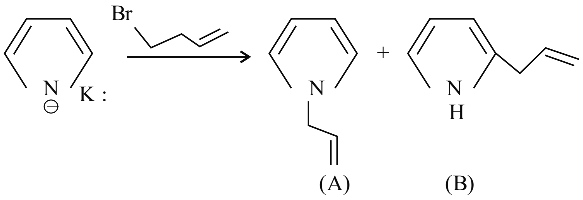
According to the principle of Hard and Soft acids and bases (HSAB), an ambident nucleophile the more electronegative atom is harden base than the less electronegative atom. Thus in enolate anion, the more electronegative oxygen atom with negative change is harden base than carbon atom.

For S_N1 mechanism, a carbocation intermediate is a hard acid that would preferably attacked by a hard base, i.e., attacked by oxygen of enolate.

On the other hand for S_N2 mechanism, the carbon at reaction centre is softer acid and would be preferably attacked by carbon atom of enolate ion.

In protic solvents, through hydrogen bonding the more electronegative atom is better solvated than the less electronegative atom. Thus less electronegative atom is more prone to attack.

In contrast, polar aprotic solvents offer no stabilization to either end of the nucleophile however, they stabilize the substrate cation by solvation.



The ratio of N-alkylation to C-alkylation changed dramatically as shown by the proportion of the products.

Solvent	**%A**	**%B**
Benzene	15	85
Toluene	14	86
Dioxane	71	29

Regioselectivity

Many reactions have a strong preference for forming one regiosomer over the possible other isomer. This property is known as regioselectivity.

Check Your Progress

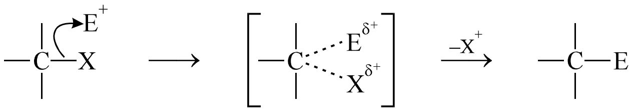
1. What are nucleophiles?
2. Define the term 'nucleofuge'.
3. What is Wagner-Meerwein rearrangement?
4. What is ultrasound technique in chemistry?
5. Give two examples of nucleophilic substitution reaction.
6. What is neighbouring group participation?

3.3 ALIPHATIC ELECTROPHILIC SUBSTITUTION: BIOMOLECULAR MECHANISMS

Substitution reactions initiated by electrophilic reagents are known as electrophilic substitution reactions. Obviously for such reactions the reactive site in the substrate must be rich in electrons. Two types of such reactions are electrophilic substitutions at saturated or aliphatic carbon atoms and at unsaturated or aromatic carbon atoms. The latter type is important. Electrophilic substitution reactions are designated as S_E reactions. If the reaction is unimolecular it is written as S_E1 and if it is bimolecular it is then written as S_E2 type of reaction. Usually the S_E1 reactions involve two steps—a slow ionization to give a carbanion and then a fast combination of this carbanion with electrophile. Thus:

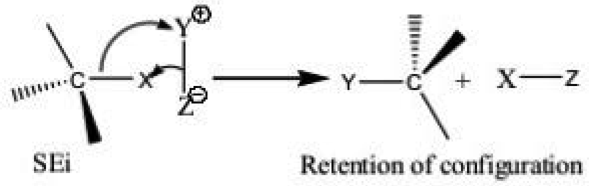
Step 1. $R—X \xrightarrow{\text{Slow}} R^- + X^+$ **Step 2.** $R^- + E^+ \xrightarrow{\text{Fast}} R—E$

The S_E2 reactions take place by a concerted mechanism. The incoming group approaches the reactive site from the front side and starts the formation of bond by overlapping with the orbital of carbon on the reactive site. At the same time the departing group is loosening its grip on the bonding pair of electrons. Thus:



This reaction will therefore proceed with the retention of configuration at reactive site whereas S_E1 reactions will result in racemic products because of the probability of attack of E^+ on carbanion from either side.

In S_Ei Mechanism, the final product forms with the same stereochemistry of a starting material i.e. S_Ei results in retention of configuration. S_Ei is also a bimolecular reaction.



Structure and Effect on Reactivity

Electrophilic substitutions at aliphatic carbon atom are usually observed in organometallic compounds where the metal is less electronegative than carbon. In such reactions, the chances for S_E1 type will decrease with the presence of electron donating groups and increase with the presence of electron withdrawing groups. The stability of the resulting carbanion also influences the course of reaction. The greater the polarity of bond C—X, the greater will be the S_E1 reaction rate. Similarly increase in the polarity of solvent favours S_E1 reactions. For S_E2 reactions the electron donating and withdrawing group do not have such rationalized influence. The solvent of greater polarity enhances the S_E2 reaction but lesser than the S_E1 reaction.

The reactivities in substitution at aromatic carbon atoms are strongly influenced by the nature of the substituents present in the ring.

Applications

Some examples of typical electrophilic substitution reactions are given below together with their mechanisms.

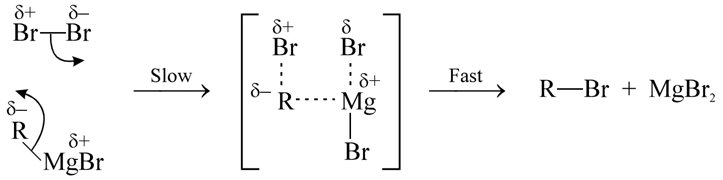
(1) **Substitution at aliphatic or Saturated carbon atom**

(*i*) Reaction of Grignard reagent with halogen:

$$\underset{\substack{\text{Alkyl magnesium}\\\text{bromide}}}{\text{R—Mg—Br}} + \text{Br}_2 \longrightarrow \underset{\substack{\text{Alkyl}\\\text{bromide}}}{\text{R—Br}} + \text{MgBr}_2$$

NOTES

The reaction proceeds by a S_E2 type mechanism.



Transition state

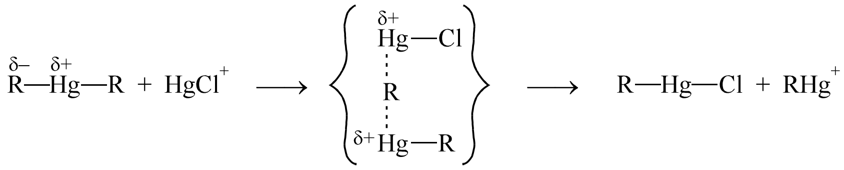
The replacement of —MgBr group by the electrophilic attack of bromonium ion (Br^+) occurs through a transition state resulting in the formation of alkyl bromide.

(*ii*) Reaction of dialkyl mercury with mercuric chloride:

$$\underset{\text{Dialkyl mercury}}{R—Hg—R} + HgCl_2 \longrightarrow \underset{\text{Alkyl mercuric chloride}}{2R—Hg—Cl}$$

This is another example similar to one described above.

$$HgCl_2 \longrightarrow HgCl^+ + Cl^-$$

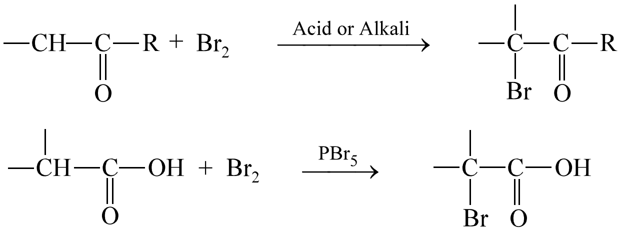


Transition state

$$R—Hg^+ + Cl^- \longrightarrow R—Hg—Cl$$

Here the Hg^+Cl electrophile replaces the Hg^+R group from the molecule by S_E2 mechanism.

(*iii*) Halogenation of aldehydes, ketones, and acids—The reaction may be represented as:

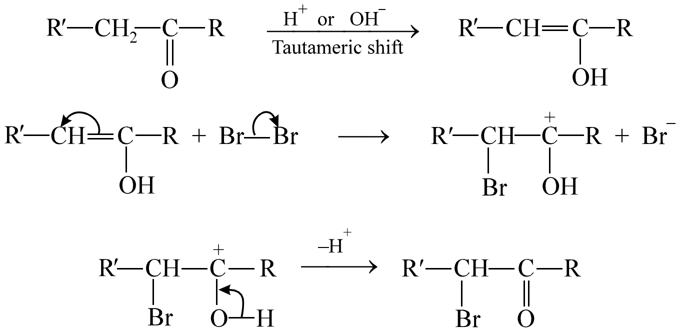


$$—CH—\underset{\underset{O}{\|}}{C}—R + Br_2 \xrightarrow{\text{Acid or Alkali}} —\overset{|}{\underset{\underset{Br}{|}}{C}}—\underset{\underset{O}{\|}}{C}—R$$

$$—\overset{|}{CH}—\underset{\underset{O}{\|}}{C}—OH + Br_2 \xrightarrow{PBr_5} —\overset{|}{\underset{\underset{Br}{|}}{C}}—\underset{\underset{O}{\|}}{C}—OH$$

(Hell-Volhard-Zelinsky reaction)

The mechanisms for these reactions too are explained by the application of electrophilic substitution.



$$R'—CH_2—\underset{\underset{O}{\|}}{C}—R \xrightarrow[\text{Tautameric shift}]{H^+ \text{ or } OH^-} R'—CH{=}\underset{\underset{OH}{|}}{C}—R$$

$$R'—CH{=}\underset{\underset{OH}{|}}{C}—R + Br—Br \longrightarrow R'—\underset{\underset{Br}{|}}{CH}—\underset{\underset{OH}{|}}{\overset{+}{C}}—R + Br^-$$

$$R'—\underset{\underset{Br}{|}}{CH}—\underset{\underset{O—H}{|}}{\overset{+}{C}}—R \xrightarrow{-H^+} R'—\underset{\underset{Br}{|}}{CH}—\underset{\underset{O}{\|}}{C}—R$$

Thus a bromonium ion has been substituted in place of a hydrogen ion.

(2) **Mechanism of haloform reaction**

When methyl carbonyl compounds (CH_3CHO, $CH_3CO.CH_3$, etc.) react with halogens in presence of alkali, haloform (CHX_3) is formed. The reaction is known as *haloform reaction.*

The reaction is given by all compounds containing the acetyl group attached to either carbon or hydrogen, or by compounds which are oxidised under the conditions of the reaction to derivatives containing the acetyl group for example, ethyl alcohol, isopropyl alcohol, lactic acid, etc. (Booth and Saunders in 1950 have shown that certain quinones and dihydric phenols also give haloform reaction.) Thus with ethyl alcohol the following steps are involved in preparation of chloroform:

(*i*) Oxidation of ethyl alcohol by chlorine to acetaldehyde:

$$CH_3.CH_2OH + Cl_2 \longrightarrow CH_3CHO + 2HCl$$

(*ii*) Chlorination of acetaldehyde to chloral (trichloroacetaldehyde):

$$CH_3CHO + 3Cl_2 \longrightarrow \underset{\text{Chloral}}{CCl_3.CHO} + 3HCl$$

(*iii*) Hydrolysis of chloral by calcium hydroxide yielding chloroform:

$$2CCl_3.CHO + Ca\,(OH)_2 \longrightarrow \underset{\text{Chloroform}}{2CHCl_3} + \underset{\text{Calcium formate}}{(H.COO)_2Ca}$$

In case of acetone the following steps are involved:

(*i*) Chlorination of acetone to trichloroacetone:

$$CH_3.CO.CH_3 + 3Cl_2 \longrightarrow \underset{\text{Trichloroacetone}}{C.Cl_3.CO.CH_3} + 3HCl$$

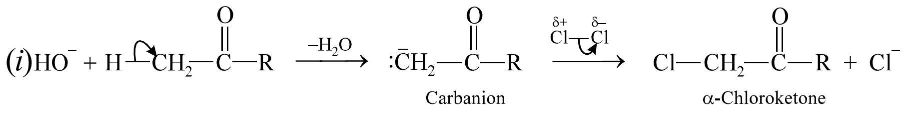
(*ii*) Hydrolysis of trichloroacetone by calcium hydroxide yielding chloroform:

$$2CCl_3.CO.CH_3 + Ca(OH)_2 \longrightarrow \underset{\text{Chloroform}}{2CHCl_3} + \underset{\text{Calcium acetate}}{(CH_3.COO)_2Ca}$$

Mechanism

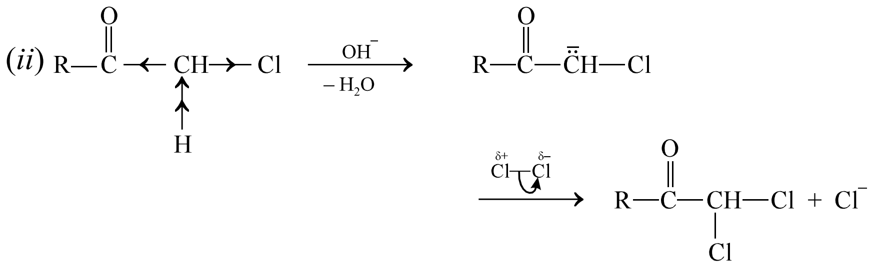
The hydrogen atoms at α-carbon to the carbonyl group are slightly acidic in nature due to the electron withdrawing effect of the carbonyl group.

In presence of base ($O\bar{H}$), these hydrogen atoms become still more reactive and are replaced easily by chlorine attacking as chloronium ion.



$$(i)\ HO^- + H-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R \xrightarrow{-H_2O} \underset{\text{Carbanion}}{:\bar{C}H_2-\overset{\overset{\displaystyle O}{\|}}{C}-R} \xrightarrow{\overset{\delta+}{Cl}-\overset{\delta-}{Cl}} \underset{\alpha\text{-Chloroketone}}{Cl-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R} + Cl^-$$

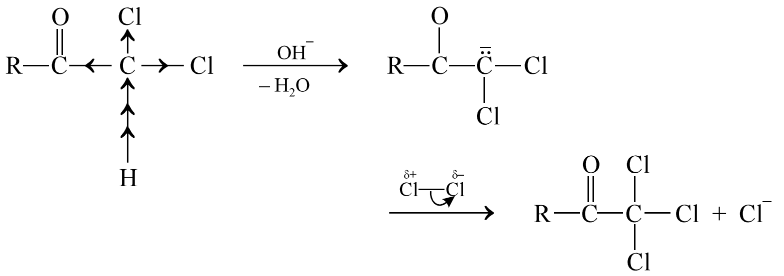
Once α-chloroketone is formed the other H atoms of the carbon having chlorine become more reactive on account of –I effect caused by chlorine and are replaced successively yielding trichloromethyl carbonyl compound.



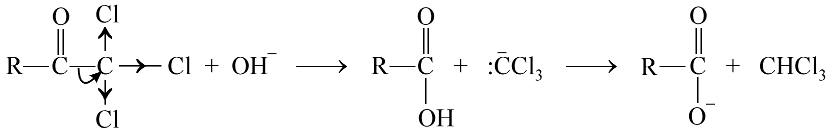
$$(ii)\ R-\overset{\overset{\displaystyle O}{\|}}{C}\leftarrow\underset{\underset{\displaystyle H}{\uparrow}}{CH}\rightarrow Cl \xrightarrow[-H_2O]{OH^-} R-\overset{\overset{\displaystyle O}{\|}}{C}-\ddot{C}H-Cl$$

$$\xrightarrow{\overset{\delta+}{Cl}-\overset{\delta-}{Cl}} R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle Cl}{|}}{CH}-Cl + Cl^-$$

(*iii*)



Trihalocarbonyl compound is then cleaved by alkali giving chloroform.



(Replacing R with H or CH_3, the reaction with CH_3CHO or CH_3COCH_3 can be written.)

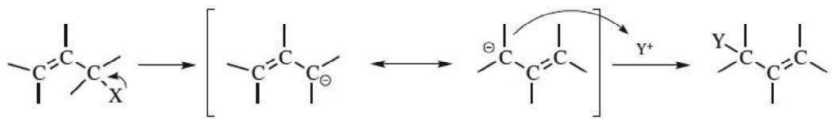
3.3.1 Electrophilic Substitution Accompanied by Double Bond Shifts

A double bond is defined as a covalent bond between two atoms involving four bonding electrons as opposed to two in a single bond. Double bonds occur most commonly between two carbon atoms, for example, in alkenes. Many double bonds exist between two different elements, such as in a carbonyl group between a carbon atom and an oxygen atom. Other common double bonds are found in azo compounds (N=N), imines (C=N), and sulfoxides (S=O). In the chemical skeletal formula, a double bond is drawn using two parallel lines (=) between the two connected atoms. Double bonds were first introduced in the chemical notations by Russian chemist, Alexander Butlerov.

When substitution reactions are carried out at an allylic substrate, the product may get rearranged based on thermodynamic stability of the intermediates and products. Such reactions are possible with nucleophilic substitution and also **electrophilic substitution**.

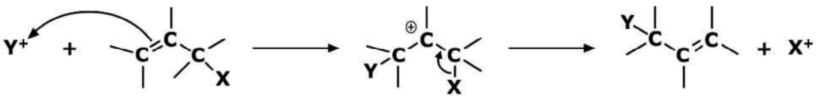
In an electrophilic substitution on allylic substrate, on attack of an electrophile, a displacement of double bond occurs leading to the formation of following product:

The mechanism of such substitutions is based on two different pathways. In the first pathway, when the substitution takes place by means of S_E1 mechanism, then the leaving group leaves first leading to resonance stabilized intermediate carbanion probably due to an adjacent double bond, which then attacks the electrophile.



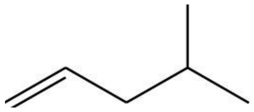
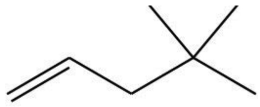
In an alternate mechanism, the electrophile is first attacked by the electron rich π-bond which leads in the formation of intermediate carbocation, which then loses the leaving group providing a double bond at the adjacent position.

NOTES



The groups that are adjacent to allylic system influences the stereochemistry of products to a remarkable extent. The following Table provides the experimental data on stereochemistry of products that are obtained using the specific substrates, when the reaction was typically carried out at 55ºC in DMSO as solvent with 0.77 M olefin and 0.70 M t-BuO$^-$K$^+$ as base.

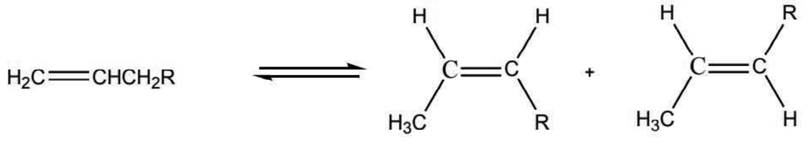
***Table 3.2** Dependence of Substrate on Stereochemistry of Double Bond Formation*

Starting or Initial Material	**(cis/trans)** $_{t\to 0}$ **(Kinetic Control)**	**(cis/trans)** $_{t\to\infty}$ **(Thermodynamic Control)**
	47.4	0.25
	10.8	0.23
	3.2	0.23
	0.25	<0.001

From the above table it can be stated that for adjacent alkyl groups the order of kinetically controlled cis product formation decreases in the following order:

$$CH_3 > CH_3CH_2 > (CH_3)_2CH > (CH_3)_3C$$

Initially at (t→0), the cis alkene products lead in the reaction. The prevalence of kinetically controlled cis product can be preserved under different solvent conditions with different base. When the olefin is substituted with an electron withdrawing functional groups, such as ester, carboxylic acids and ketones, then the geometry of the product is essentially trans as illustrated in the following example:



R= COOEt	15%	85%
R= COOH	6%	94%
R=COEt	-	100%

However, the trans products are thermodynamically more stable, therefore, eventually if long isomerization time is provided (t→∞) to the reaction then trans alkene product may become most significant.

Mechanisms of Double Bond Shift

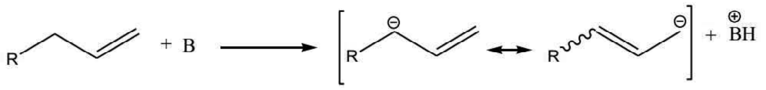
Following are the mechanisms of double bond shift:

(a) Base Catalysed Mechanism

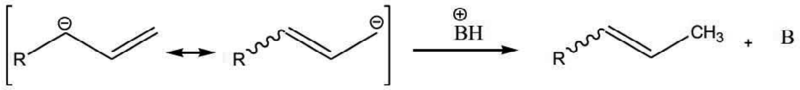
In unsaturated compounds, a strong base, such as $NaNH_2$, alkali metals, KOH, and $t\text{-}BuO^-K^+$, can accept or take a proton from the *sp*^{3} hybridized carbon atom adjacent to a double bond responsible in the formation of a carbanion which leads to equilibrium mixtures of product isomers upon substitution. Traditionally, the base catalysed double bond rearrangement was reported in 1892 by Griner *et al*. According to the theory, when 1,4-hexadiene is heated at 100ºC in a sealed tube in the presence of concentrated alcoholic KOH then it leads to the formation of 2,4-hexadiene. For such types of rearrangements, evidently the preferences support the formation of a double bond which may extend conjugation with already existing double bonds, if any. In addition, terminal alkenes isomerise to internal ones, nonconjugated alkenes to conjugated alkenes and exo-six-membered ring alkenes to endo alkenes.

Following two steps illustrate the mechanism of base catalysed electrophilic substitution on allyl system:

Step 1



Step 2



(b) Acid Catalysed Mechanism

Acid catalysed mechanism facilitates two step double bond migration, as shown below. In the reaction, first a proton is gained which first leads to a carbocation, and then another proton is lost to form the double bond.

Step I

$$H_3C{-}CH_2{-}CH{=}CH_2 + H^{\oplus} \longrightarrow H_3C{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3$$

Step II

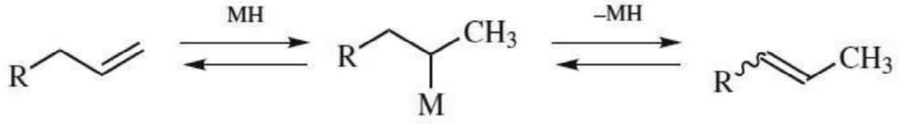
$$H_3C{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3 \xrightarrow{-H^+} H_3C{-}CH{=}CH{-}CH_3$$

The acid catalysed reactions are less synthetically effective because of possible rearrangements of carbocation that gives rise to multiple side products. Therefore, usually mixtures of all possible isomers are obtained.

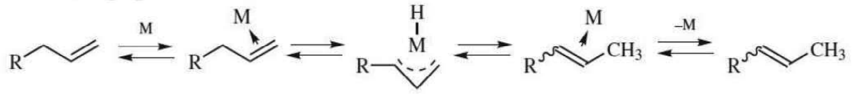
NOTES

(c) Metal Catalysed Mechanisms

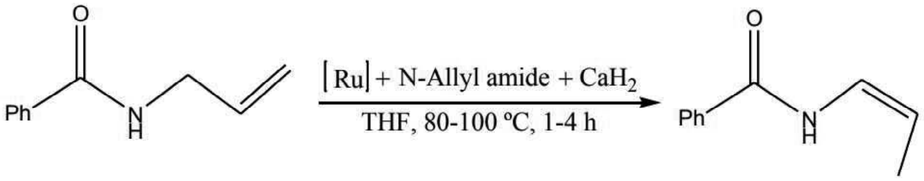
Metal ions under homogeneous or heterogeneous conditions have been used to obtain isomerization of olefins under electrophilic substitution conditions. Transition metal complexes, such as Pt, Rh, or Ru or metal carbonyls are commonly used. Basically, with the base catalysed methods possibly two mechanisms are used to define the shift. In the first method, termed as the 'Metal Hydride Addition–Elimination Mechanism', an external proton is required which is then abstracted from the substrate according to the following mechanism:



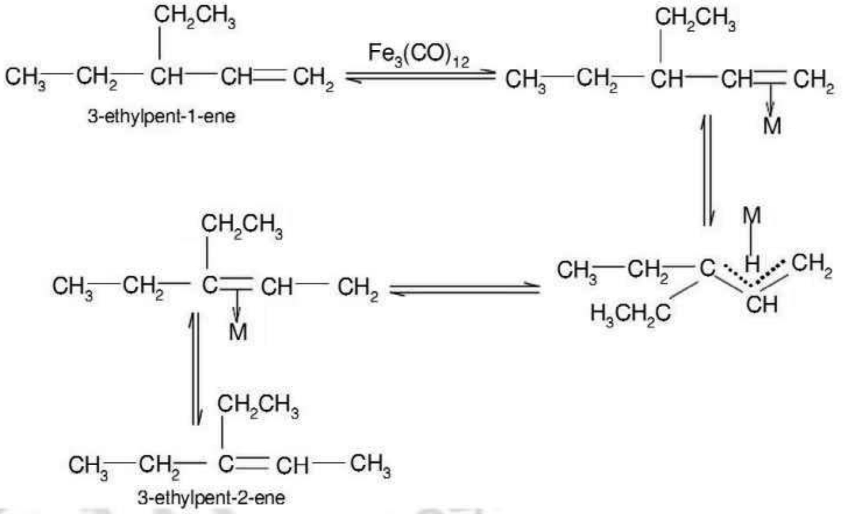
Isomerization of 1-butene by rhodium (I) is a significant example of a reaction that takes place through the metal hydride mechanism leading to **1,2-shift** in double bond. The second method is called π-allyl complex mechanism, which does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3-π-allyl complex.



Such a reaction when carried out on 3-ethyl-1-pentene with $Fe_3(CO)_{12}$-catalyst leads to **1,3-shift**. For example, in the mechanism of a catalytic system to yield quantitative Z-selective isomerization of N-allylamides to Z-enamides was found through in situ ruthenium based catalysis.



With the metal carbonyl catalyst, the isomerization of 3-ethyl-1-pentene involves **1,3-shift** producing 3-ethylpent-2-ene.



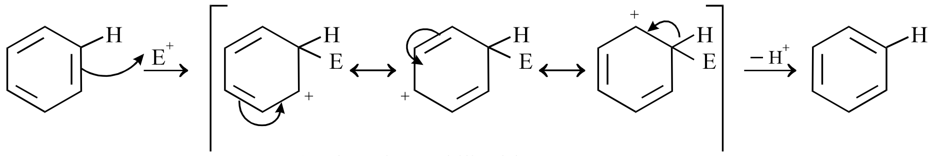
Double bond migration in allylic substrates, therefore, takes place by means of electrophilic substitution, and also in nucleophilic substitution.

Check Your Progress

7. What are electrophilic substitution reactions?
8. Define nitration.
9. What are the two types of electrophilic reactions?
10. How are unimolecular electrophilic substitution reactions represented?

3.4 AROMATIC ELECTROPHILIC SUBSTITUTION REACTIONS

The most important reactions of the aromatic compounds are the electrophilic substitution reactions like nitration, halogenation, sulphonation, etc. Nitration is introduction of a nitro group (—NO_2) in place of hydrogen by electrophile $\overset{+}{N}O_2$ (nitronium ion). Sulphonation is the replacement of a hydrogen by —SO_3H group and takes place by electrophilic attack of SO_3 on aromatic carbon. However the mechanism of a general electrophilic substitution in benzene by electrophile (E^+) is given below:



(Carbocation stabilised by resonance)

$\overset{+}{E}$ can be:

- $\overset{+}{N}O_2$ for nitration $(HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3\overset{+}{O} + 2HSO_4^-)$
- Cl^+ for chlorination $(Cl_2 + FeCl_3 \rightarrow Cl^+ + FeCl_4^-)$
- Br^+ for bromination $(Br_2 + FeCl_3 \rightarrow Br^+ + \overset{-}{F}eCl_3Br)$

The carbocation formed as intermediate in an aromatic electrophilic substitution is an arenium ion, also known as *Wheland intermediate* or a sigma (σ) complex. The smallest arenium ion is a protonated benzene $C_6H_7^{\oplus}$ called *benzenium ion* which can be isolated as a stable compound when benzene is protonated by the carborane super acid.

Electrophilic substitution of a monosubstituted benzene derivative can give rise to three *regioisomeric* products in which the new substitutent is placed at C–2 (ortho), C–3 (meta) or C–4 (para) position. There are two ortho- and two meta positions available but a statistical distribution of products is not observed and the actual proportion is dependent upon whether the group present is activating or deactivating.

A vast majority of electrophilic substitution reactions proceed under kinetic control where the rate- and product-determining step is the formation of a Wheland intermediate which is a highly endothemic process. Hammond's postulate states that the factors stabilizing the transition state should also operate in Wheland intermediate. Hence the stabler the intermediate faster is its formation.

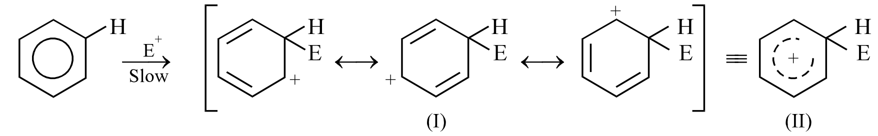
When *o*-, *p*-directing and activating groups (for example, —NH_2, —OH, etc.) are attached to benzene then the wheland intermediate resulting from *o*- or *p*-attack is more stabilized by resonance. In case of *o*-, *p*-directing but deactivating group (like —Cl) the Wheland intermediate from *o*- or *p*-attack are stabilized by resonance involving lone pair of chlorine, whereas when *m*-directing and deactivating groups (for example, —NO_2, —CN, etc.) are attached to benzene then Wheland intermediate from *m*-attack is less destabilized as compared to their *o*- or *p*-counterparts.

3.4.1 Aremium Ion Mechanism

The π electrons of benzene ring are losely held and are available to an electrophilic reagent seeking electrons *hence typical reactions of benzene are electrophilic substitution reactions. In the reactions, the attacking electrophile may be produced in different ways but what happens to the aromatic ring is basically same in all the cases.*

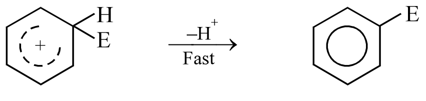
The attacking electrophile may be a positive ion or a dipole. If it is a positive ion it attacks the ring removing a pair of electron from the sextet to give a carbocation which gets resonance stabilized as shown in (I) and is represented as shown in (II).

Step 1

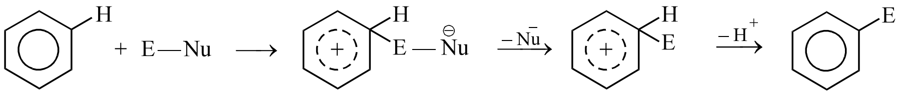


Ions of the type (II) are called *carbocation*, *Wheland intermediates*, σ-*complex* or *arenium ions*. In case of benzenoid system they are called cyclohexadienyl cations. The arenium ion has been isolated and is quite stable but it stabilizes itself by the loss of either E^+ or H^+. The aromatic sextet is then restored. This is the second step of the mechanism in which the proton is accepted by a proton acceptor (base) to revert the system to stable benzenoid structure. The second step is faster than the first step. Lars Melander (1949, 1950) while studying the nitration of a variety of aromatic compounds established that first step is slower.

Step 2



If the attacking species is not an ion but a dipole, the product must have a negative charge, unless part of the dipole with its electron pair, is broken off at some stage in the process.



The arenium ion formed and isolated is commonly called σ-*complex*. However, it was found that the relative reactivity and the percentage of *o*, *m* and *p* products formed depended not only a particular reaction but also on the nature of the reagent employed. This led some chemists to believe that a π-complex is formed during the electrophilic *substitution* between the substrate and the electrophile before the formation of arenium ion (σ-complex) and that influences the reaction rate.

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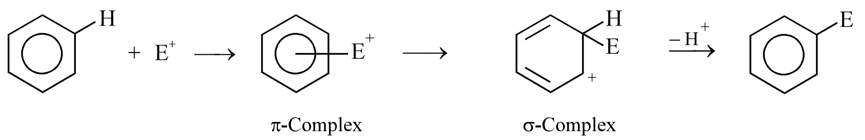
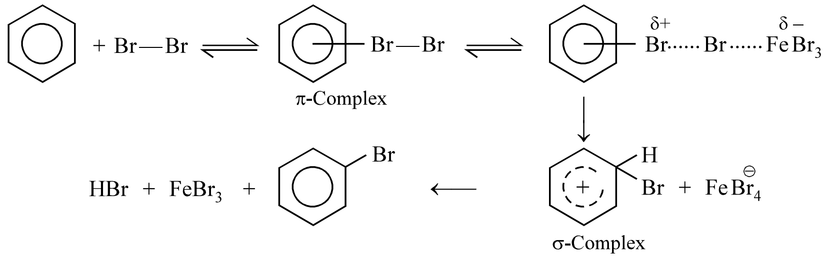


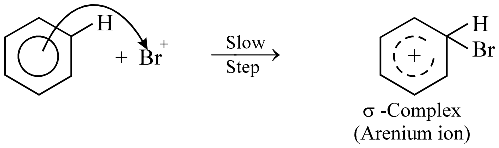
In the electrophilic substitution of bromine, kinetic data has shown that the rate of bromination depends on the concentration of catalyst $FeBr_3$ also besides halogen and benzene. The positive end of the dipole attacks the aromatic ring forming π-complex and the negative end is complexed with the catalyst. The formation of σ-complex (arenium ion) between Br^+ and carbon of the benzene ring is the slow step of the reaction. The reaction may be represented as given below:



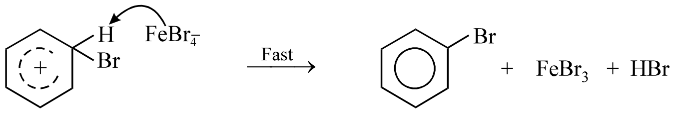
However, since σ-complex is formed, substitution can also be represented by the steps given below.

(*i*) $\underset{\text{Lewis base}}{Br—Br} + \underset{\text{Lewis acid}}{FeBr_3} \rightleftharpoons \underset{\text{Electrophile}}{Br^+} + FeBr_4^-$

(*ii*)



(*iii*)



In the substitution reactions given below there are three steps in the reactions. The first step is the production of electrophile, the second step is the formation of arenium ion or σ complex and the third step is the removal of the proton to form the substitution product.

1. **Nitration:** Nitration of benzene is carried out with a mixture of conc. nitric and conc. sulphuric acid.

$$C_6H_6 + HNO_3 \xrightarrow{H_2SO_4} C_6H_5NO_2 + H_2O$$

Mechanism

In the first step of the reaction $\overset{+}{NO_2}$ is produced (strong sulphuric acid causes nitric acid to ionise as $\bar{OH} + \overset{+}{NO_2}$) which reacts with benzene in the second step to give the arenium ion. The arenium ion transfers a proton to some base in the mixture, *e.g.*, $H\bar{S}O_4$ to give nitrobenzene.

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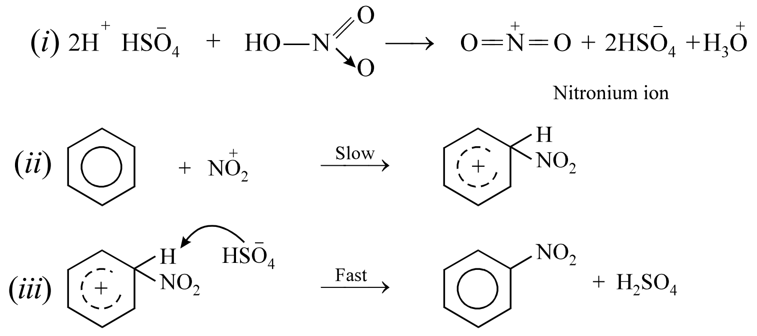


The energy changes taking place have been shown in the energy profile Figure 3.4.

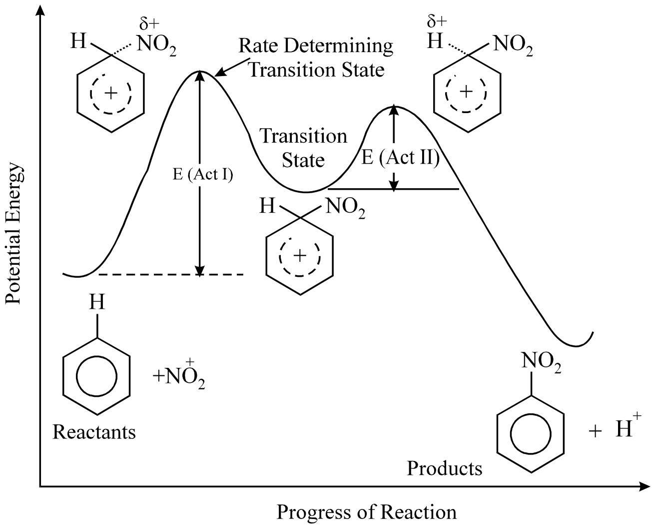
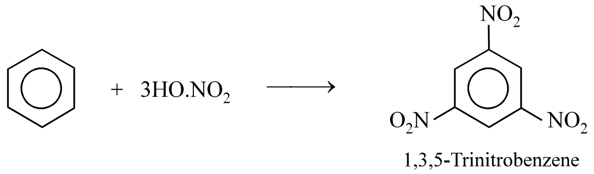


Fig. 3.4 *Energy Changes*

If fuming nitric acid is used for the reaction it is possible to introduce two or three nitro groups.



2. **Halogenation:** Benzene undergoes chlorination and bromination forming monochloro or monobromobenzene. The reaction takes place in presence of $FeCl_3$ or $AlCl_3$ at room temperature.

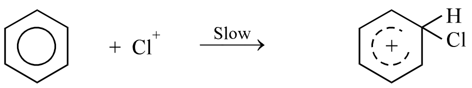
$$C_6H_6 + Cl_2 \xrightarrow{FeCl_3} C_6H_5Cl + HCl$$

Mechanism

In the first step, the electrophile is formed which in the second step attacks the π electrons to form arenium ion (σ-complex). The arenium ion loses the proton to the base in the last step to give monohalo substituted benzene.

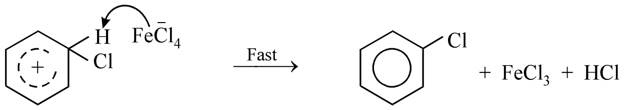
$$(i)\ Cl-Cl + FeCl_3 \longrightarrow Cl^+ + Fe\bar{C}l_4$$

(*ii*)



Arenium ion
(σ-complex)

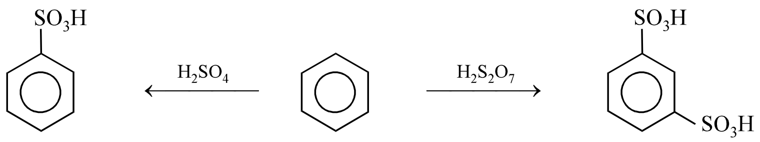
(*iii*)



The reaction with bromine is given just above. Reaction with iodine presents some difficulty since iodine is the least active among the halogens but if carried out in presence of some oxidising agent, *e.g.*, nitric acid or mercuric oxide, the reaction takes place with good yield of iodo-compound.

$$2C_6H_6 + I_2 \xrightarrow[{[O]}]{HNO_3} 2C_6H_5I + H_2O$$

3. **Sulphonation:** With hot and concentrated sulphuric acid benzene forms benzene sulphonic acid. If fuming sulphuric acid is used *m*-benzene disulphonic acid is formed.



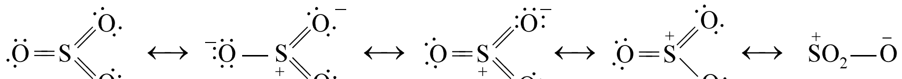
Benzene sulphonic acid

m-Benzene disulphonic acid

Mechanism

In the first step of reaction, H_2SO_4 acts both as an acid and a base to produce the electrophile SO_3 which is a resonance hybrid of many forms in which the following dipolar form predominates.

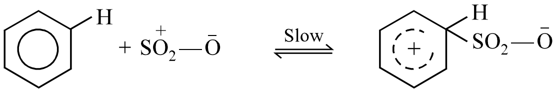
$$(i)\ 2H_2SO_4 \rightleftharpoons H_3\overset{+}{O} + HS\bar{O}_4 + SO_3$$



Electrophile

The electrophile SO_3 attacks π electrons of the ring to form arenium ion.

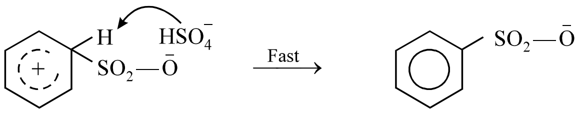
(*ii*)



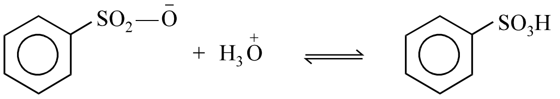
Sigma complex

Sigma complex loses a proton to base $HS\bar{O}_4$ to give resonance stabilized substitution product.

(*iii*)



The product in step (*iii*) accepts a proton to give the acid which remains dissociated.

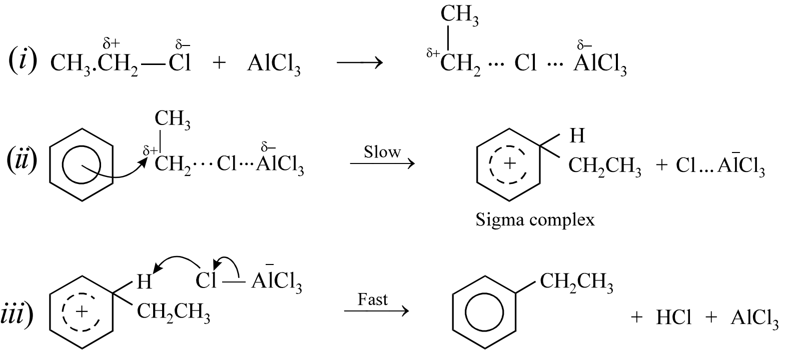


4. **Friedel-Crafts alkylation of benzene:** Benzene on being treated with alkyl halide in presence of $AlCl_3$ form alkyl benzenes in which the alkyl group comes from alkyl halide.

$$C_6H_6 + CH_3Cl \xrightarrow{AlCl_3} \underset{\text{Toluene}}{C_6H_5.CH_3} + HCl$$

Mechanism

In Friedel-Crafts alkylation, the electrophile is a carbocation which is easily formed if the alkyl halide is secondary or tertiary. The available evidence suggests that the alkyl halide (say on alkyl chloride) reacts with the $AlCl_3$ used to form a ion-pair type complex. This complex attacks the benzene ring in step II to form sigma complex.



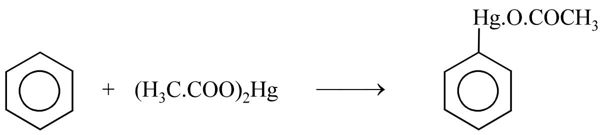
In the last step sigma complex loses a proton to base $Cl—\bar{A}lCl_3$ to give the alkyl benzene.

Friedel-Crafts reaction is also used to introduce groups like R.CO— or $(CH_3)_3C$— in benzene nucleus. In each case the electrophile is produced which then reacts in the manner indicated above. Production of electrophile has been indicated in a rather simplified manner here.

(*i*) $R.COCl + AlCl_3 \longrightarrow R.\overset{\delta+}{C}O\cdots Cl\cdots \overset{\delta-}{Al}Cl_3$ or $R.C\overset{+}{O}$ $\bar{A}lCl_4$

(*ii*) $(CH_3)_3C\ddot{\underset{..}{O}}H + BF_3 \rightleftharpoons (CH_3)_3\overset{+}{C} + H—\ddot{\underset{..}{O}}—\overset{\ominus}{B}F_3$

5. **Mercuration:** When benzene is heated to (90–160°C) with mercuric acetate for about an hour, one hydrogen atom is replaced by acetoxy-mercuric group. *Conditions of the reaction are such that electrophile* $H_3C.COOHg^+$ *is created for the reaction.*



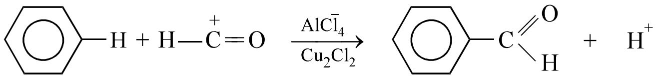
Acetoxymercuribenzene
or
Phenyl mercuric acetate

Mercurated compounds are of great medicinal value.

6. **Formylation:** During some reactions given below an aldehydic group gets introduced into the nucleus. This is called *formylation.*

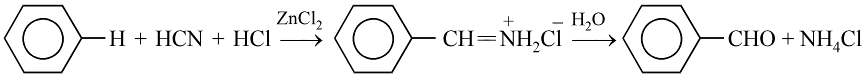
- **Gattermann Koch Reaction:** When a mixture of carbon monoxide and hydrogen chloride is passed in an ethereal solution of benzene in presence of anhydrous $AlCl_3$ and cuprous chloride, an aldehyde is obtained.

$$\text{CO} + \text{HCl} \longrightarrow \underset{\text{Formyl chloride}}{\text{Cl.CHO}} \;:\; \text{ClCHO} + \text{AlCl}_3 \longrightarrow \overset{+}{\text{C}}\text{HO} + \text{Al}\overline{\text{Cl}}_4$$



$$\text{H}^+ + \text{Al}\overline{\text{Cl}}_4 \longrightarrow \text{AlCl}_3 + \text{HCl}$$

- **Gattermann Aldehyde Synthesis:** When benzene is treated with liquid hydrogen cyanide and dry hydrogen chloride in presence of anhydrous $AlCl_3$ or $ZnCl_2$ then an aldimine is formed which on being hydrolysed gives an aldehyde.

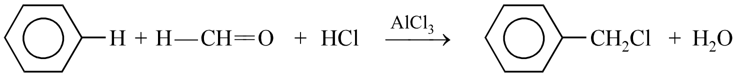


This is also an electrophilic substitution reaction and the attacking electrophile is $\overset{+}{\text{C}}\text{H}=\text{NH}$.

$$\text{H—C}\equiv\text{N} + \text{HCl} \longrightarrow \text{Cl.CH}=\text{NH} \xrightarrow[-\text{Al}\overline{\text{Cl}}_4]{\text{AlCl}_3} \overset{+}{\text{C}}\text{H}=\text{NH}$$

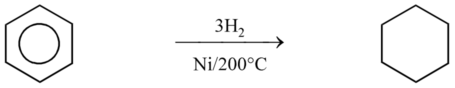
The reaction can also be applied to toluene, xylene, etc.

7. **Chloromethylation:** Introduction of the chloromethyl group (— CH_2Cl) in the benzene nucleus is also an electrophilic substitution reaction and is known as chloromethylation. This can be done by heating benzene or its homologues with formaldehyde and HCl in presence of anhydrous $AlCl_3$ or $ZnCl_2$.



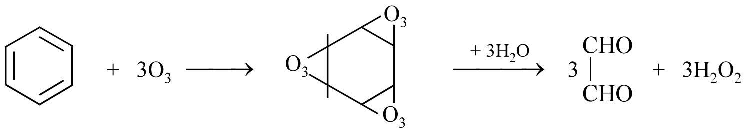
Benzyl chloride

8. **Hydrogenation:** Benzene undergoes hydrogenation in presence of finely divided metal catalyst like nickel, platinum, etc., at about 200°C and form corresponding saturated cyclohexane.



Benzene Cyclohexane

9. **Ozonide Formation:** Benzene adds up one ozone molecule at each one of the three double bonds to form a triozonide.



Benzene Benzene triozonide

10. **Addition of Halogen:** In bright sunlight and absence of halogen carrier, benzene react with chlorine and bromine to form hexahalides, *e.g.*,

$$C_6H_6 + 3Cl_2 \longrightarrow \underset{\text{Benzene hexachloride}}{C_6H_6Cl_6}$$

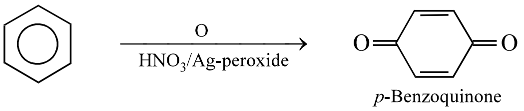
Benzene hexachloride (BHC) exists in several isomeric form. Its γ-isomer is a powerful insecticide sold under the name Gammexane (or 666).

(C) Miscellaneous Reactions

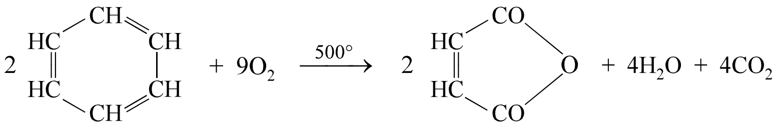
11. **Combustion:** Benzene is highly inflammable liquid and burns with a sooty (smoky) flame forming carbon dioxide and water vapour.

$$2C_6H_6 + 15O_2 \longrightarrow 12CO_2 + 6H_2O$$

12. **Oxidation:** Benzene is very stable to oxidising agents like chromic acid, alkaline potassium permanganate or dilute nitric acid. Thus benzene does not decolourise potassium permanganate. However, when oxidised with nitric acid in presence of silver peroxide, it forms *p*-quinone.



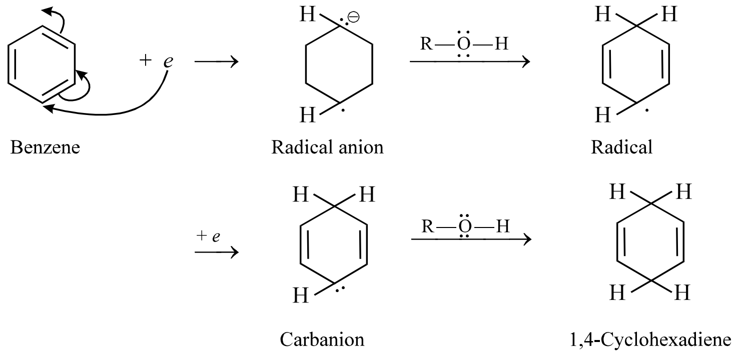
Vapours of benzene mixed with air, when passed over heated vanadium pentoxide form maleic anhydride by oxidation.



13. **Birch Reduction:** Partial reduction of aromatic ring can be achieved by dissolving lithium, sodium or potassium in liquid ammonia or amine in presence of ethyl, isopropyl or isobutyl alcohol.

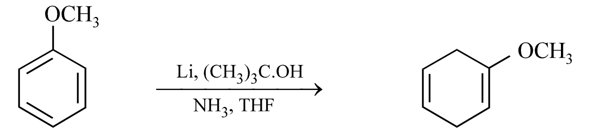
$$Na + (x + y)NH_3 \longrightarrow [Na(NH_3)_x]^+ + [e(NH_3)_y]^-$$

The mechanism of Birch reduction involves solvated electron which are transferred from metal to solvent and then to the ring. The reaction begins with addition of an electron to form a radical anion which is resonance stabilized. Protonation of the radical ion gives neutral radical. Addition of electron and protonation repeats itself to yield 1,4-cyclohexadiene.

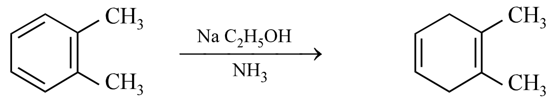


The double bonds in 1,4-cyclohexadiene are isolated and are much less reducible, hence the reaction steps. The presence of electron releasing groups like alkyl or alkoxy retard the electron transfer hence retard the reaction whereas the presence of electron withdrawing group like —COONa facilitates reduction:

Electron **releasing** groups present in benzene nucleus and Birch reduction:

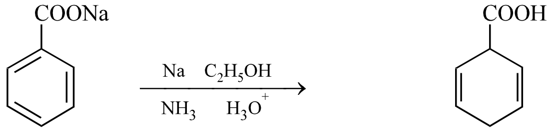


Methoxybenzene (Anisole) 1-Methoxy-1,4-cyclohexadiene



1,2-Dimethylbenzene (*o*-Xylene) 1,2-Dimethyl-1,4-cyclohexadiene

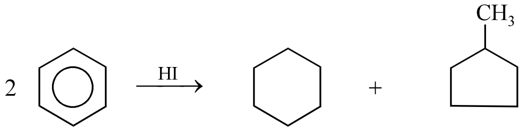
Electron **withdrawing** group present in benzene nucleus and Birch reduction



2,5-Cyclohexadiene-1-carboxylic acid

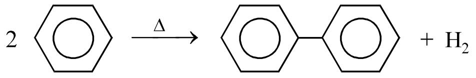
It is to be noted that electron releasing groups remain on the unsaturated carbon atom whereas electron withdrawing groups remain on the saturated carbon atom in the product.

14. **Action of HI:** Benzene on prolonged heating with HI forms a mixture of cyclohexane and methylcyclopentane.

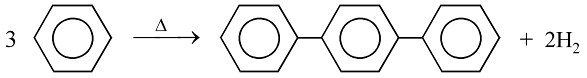


Cyclohexane Methylcyclopentane

15. **Formation of Polynuclear Hydrocarbons:** Vapours of benzene when passed through a red hot tube form a mixture of polynuclear hydrocarbons, e.g., biphenyl and terphenyl.



Biphenyl



Terphenyl

Uses of Benzene

Some of the common uses of benzene are as follows:

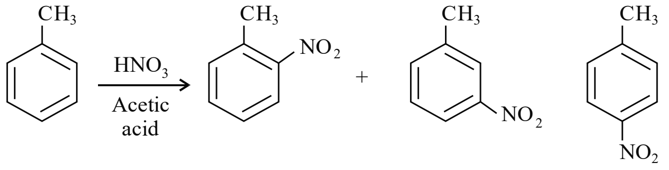
- As a solvent for extraction of fats and oils

- As a motor fuel along with petrol
- As a starting material for synthesis of various substances to be used for the preparation of dyes, drugs, plastics, perfumes, explosives, etc.
- In the manufacture of maleic acid by catalytic oxidation

NOTES

3.4.2 Ortho/Para Ratio

In benzene ring the presence of ortho, para directing group leads to the formation of both ortho and para isomers. But it is usually difficult to predict what percentage of ortho and para isomers will be formed. On the pure statistical basis one could expect 40% of ortho isomers and 40% of meta and 20% of para as in benzene ring there are two ortho, two para and one meta position but in practice it is not always realised.



	O-nitroboluene	M-nitrotoluene	P-nitrotoluene
Statistical	40%	40%	20%
Actual	60%	3%	37%

Similarly chlorination of toluene gives an ortho/para ratio any where from 62 : 38 to 34 : 66. According to Brown and Nelson the product distribution of toluene is given as:

isomer	Ortho	Meta	Para
%	58.4	4.4	37.2

The distribution of isomers does not appear to be altered significantly by changes in concentraion of nitrating agent but variations in reaction conditions can have a marked effect on product ratio. The factors that affect the reactivity to these positions can be, however, summarised as:

(a) **Steric Factor:** The isomer ratio of the product is influenced by the steric effect of the group which is either already present in the aromatic ring as well as in the attacking reagent.

The size of attacking electrophile also causes steric hindrance and inhibits the formation of the ortho product and increases the amount of para isomer.

(b) **Solvent Effect:** Electrophilic substitutions are carried out in different solvent media both polar and non polar. Solvent also plays a great role in some electrophilic substitutions. When acylation is carried out in presence of CS_2, product is 9-acetyle anthracene while in nitrobenzene, the product is 1-acetyl anthracene.

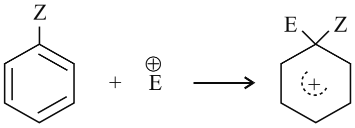
(c) **Polar Effect:** In some cases polar effect also play role in influencing o/p ratio. For example, in the nitration of halobenzenes, it was observed that amount of ortho isomers increases from fluoro to iodo derivatives. This can be attributed to electron withdrawing nature of substituent.

(d) **Resonance Effect:** Resonance effect also plays an important role in the absence of other complicating factors. For resonance effect planarity of the ring is desired so that orbirtal overlap is effective.

3.4.3 IPSO Attack

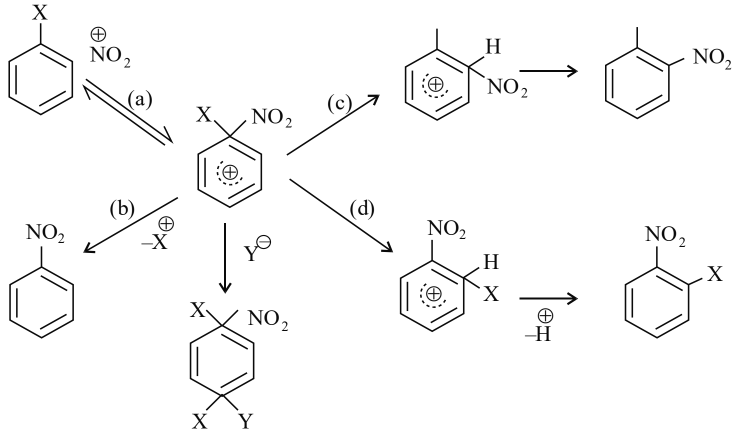
The attachment of an entering group to a position in an aromatic compound already carrying a substituents group (other than hydrogen) is term as ipko attack. Ths entering group may displace that substituent group but may also itself be expelled or migrate to the different position in s subsequent step.

Ipso effect is not easily explained by the usual theory of aromatic electrophiolic substitution. The term ipso substitution is not used since it is synchronons with substitution.



Where E is an electrophile and Z is substituents other than hydrogen.

The mechanism of nitration is complicated by imporatne of ipso attack. When the nitronium ion attack at ipso position, there are five possible fates of the ipso wheland intermedfiate.



(a) Return to starting material

The arenium ion can lose NO_2^+ and can return to the starting material and after undetectable.

(b) Loss of X^e i.e. ipso substitution

(c) Rearrangement by 1, 2 or 1, 3 migration of the nitro group with the loss of proton

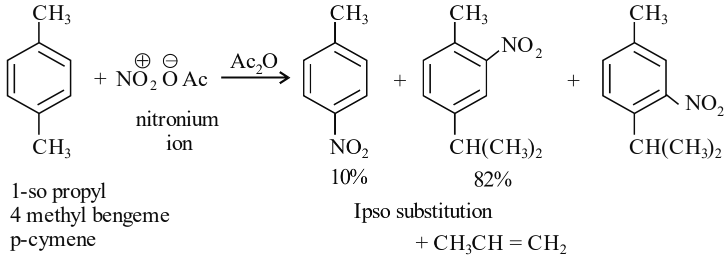
(d) Similar migration of substituent already present in benzene ring.

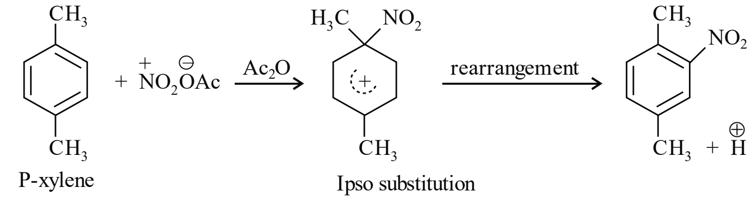
(e) Capture of nucleophile

Ipso substitution is limited to substrate in which there is same tendency for a group originally on the ring to depart.

If the substituent already on the ring is not a cationic leaving grouk, the electrophile can rearrange to provide a proton leaving group and the "normal" substitutional product.

NOTES

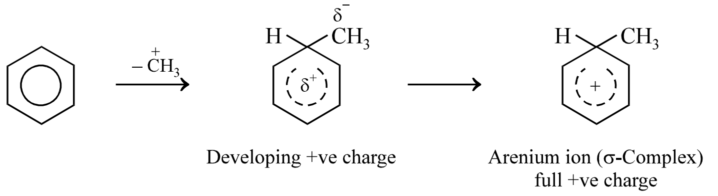




Ipso substitution usually requires base assisted removal of original substituent- z.

3.4.4 Activation and Deactivation of Benzene Nucleus and Orientation in Other Ring Systems

In benzene ring the electron density is uniform at all the carbon atoms, hence the attacking electrophile has no preferential choice and may occupy any position. However in presence of a substituent the uniform electron density of benzene ring is disturbed and the nucleus is either activated or deactivated for further substitution. For example, if a —CH_3 group is present in the nucleus of benzene (it is toluene) the sulphonation becomes twenty to twenty-five times faster under identical conditions. In other words we can say that the presence of methyl group has activated the nucleus. Methyl group has +I effect and at the time when methyl group is joining the nucleus +I effect stabilizes the developing positive charge and this lowers the activation energy in the rate determining step resulting in the faster reaction and the nucleus is said to be activated. Such groups which can release electrons into the nucleus by inductive or resonance effect, activate the nucleus. Halogens exert resonance effect, due to non-bonding lone pair of electrons and thus release the electrons to the nucleus but their strong –I effect more than neutralises this effect and thus they deactivate the nucleus. Such groups which activate the nucleus are *ortho* and *para*-directing and halogens though they deactivate the nucleus yet they are also *ortho-para*-directing.



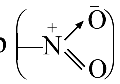
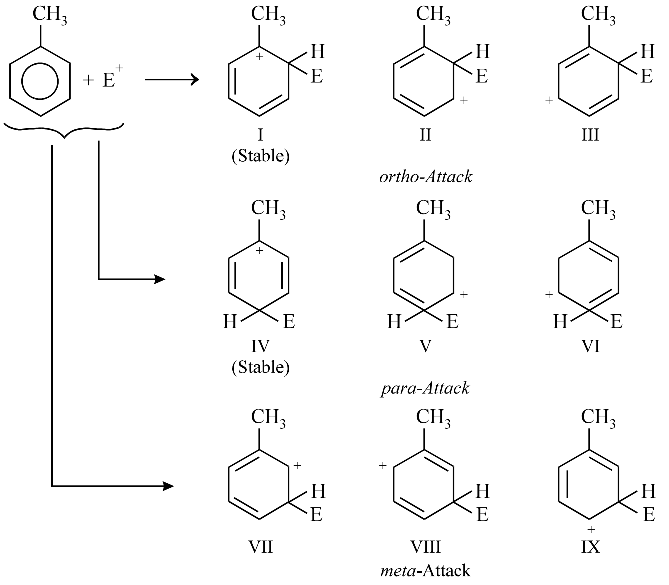
Again consider the nitro group  which has a positive charge at nitrogen. If this group is joined to the nucleus through nitrogen then it will try to withdraw electrons from the nucleus and thus intensify the positive charge and thus destabilize the carbocation because of the rise in the activation energy of the rate determining step. This will deactivate the nucleus. Such groups which withdraw electrons from the nucleus and deactivate it are *meta*-directing.

Table 3.3 *Reactivity and Orientation of the Groups*

	Polar Character			
Groups	*Inductive*	*Resonance*	*Hyperconjugation*	*Orientation and activity*
— C_6H_5— CH_3 and other alkyl groups	+ I	—	— CH_3 group shows hyper-conjugation	*o* and *p*-directing and weakly activating
—NH_2, —NHR, —NR_2 —OH	– I	+R	–	*o* and *p*-directing and strongly activating
OR (—OCH_3, —OC_2H_5 etc.), —NHCOR, —O.CO.R	– I	+R	–	*o* and *p*-directing and moderately activating
— F, — Cl, — Br, — I	– I – I	+R +R	–	*o* and *p*-directing but moderately deactivating
				o and *p*-directing and activating
$—\overset{+}{N}H_3$, $—\overset{+}{N}R_3$, —C.Cl_3	– I	—	—	*meta*-directing and deactivating
—NO_2, —CN, —SO_3H, —COR, —CHO, —COOH, —COOR	– I	– R	—	*meta*-directing and strongly deactivating

Theory of Orientation

When we say that a particular group activates the nucleus and is *ortho* and *para*-directing then it does not mean that it will direct the new entrant only to *ortho* and *para* and that there will be no *meta* substituted compound formed. In fact the groups activating the nucleus form *ortho* and *para* compounds in greater proportion than *meta*. Sometimes the proportion of *o* and *p* is very high and *meta*-compound formation is very low. The presence of *o*, *p*-directing group gives a stable cation only when the substituents enter the *ortho* and *para* position with respect to the substituent already present. Let us examine the *ortho*, *para* and *meta* substitutions in case of toluene.



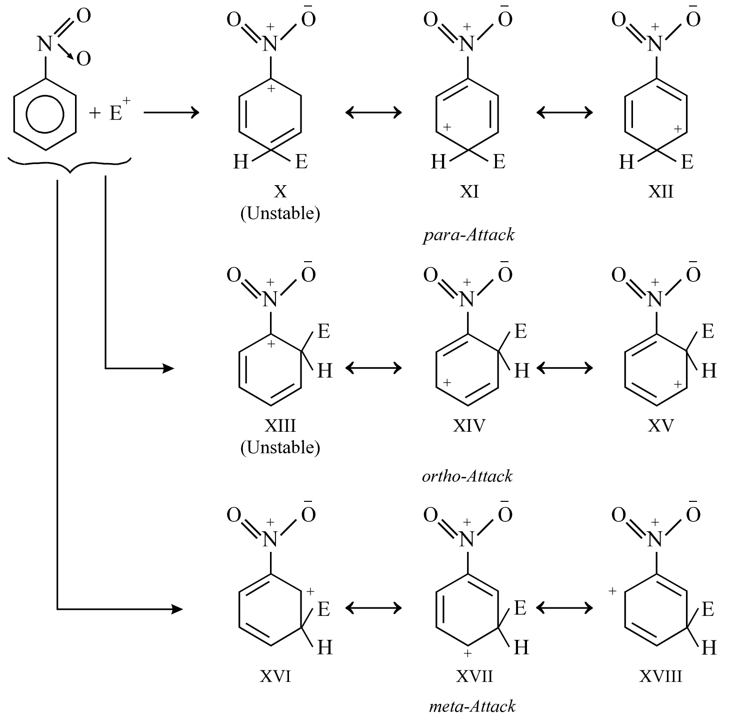
Out of the three hybrid structures for *ortho* attack (I to III) we can see that structure I has the positive charge on the tertiary carbon atom to which —CH_3 group is joined. Although —CH_3 group releases electrons uniformly to all the six positions of the hexagon but it does so most effectively to carbon atom nearest to it (I) at *ortho* position. Thus structure I provides stability to the hybrid carbocation resulting form the *ortho* attack on toluene.

Similarly it can be seen that the attack at the *para* position yields a stable carbocation IV which provides stability to the hybrid carbocation resulting from the *para*-attack on toluene.

Attack at *meta* position by the substituent does not provide a stabler carbocation hence methyl group gives a poor yield of the *meta* product. It can be seen from VII to IX structures that only secondary carbocation is formed in each case as against the tertiary carbocation formed in case of *ortho* and *para* substitution.

Next let us take an example of electron withdrawing group joining the nucleus. Nitro group is such a group which has a positive charge on nitrogen and when joined to nucleus will withdraw electrons. When a new substituent joins nitrobenzene at *ortho*, *para* or *meta* positions the resonance structures associated with the intermediates are given below.

In these structures, we can see that in X and XIII structures the positive charges are located on the adjacent atoms and therefore they have very high energy as compared to other intermediates where the positive charges are separated by one or more atoms. This results in the destabilization of intermediates leading to *ortho* and *para*-substitution of nitrobenzene. The positive ions produced by *meta* substitution are more stable and all the three intermediate structures (XIV to XVI) contribute equally to the stability of resonance structure. Hence *meta* substitution is more favoured in comparison to *ortho* and *para* substitution in cases where electron withdrawing group is attached to the nucleus.



On the basis of similar arguments it can be shown that all groups which release electrons through I or R effect will have *ortho* and *para*-directing influence and those with electron withdrawing effect through I and R effect will prefer *meta* orientation.

Electronic Explanation of O- and P-directive Influences

From an examination of the electronic structure and polar characteristics of *o*- and *p*-directing groups it is evident that with the exception of alkyl groups all of them posses at least one lone pair of electrons at the atom adjacent to the benzene ring known as *key atom.* Also that their polar characteristics are –I and +R type, except alkyl group which is +I type and halogens which have strong +E effect in addition. This lone pair of electrons is in conjugation with the π electrons of the ring and exhibits a strong +R effect, thus increasing the overall electron density in the benzene ring. Although the –I effect opposes the +R effect but latter predominates. Such groups, for example, —OH, —OR, —NH_2, —NHR, —NR_2, etc., therefore activate the benzene ring towards electrophilic substitution. However, the *relative increase of electron density is greater at o- and p-positions* due to the nature of conjugation and hence the substitution occurs at these positions.

The resonance contributing structures of such substituted benzene derivatives make it clear as to how the electron density is increased at these positions. The molecule being a hybrid of the contributing structures, the actual state of the molecule is having a small negative charge at the *o*- and the *p*-positions. Thus:

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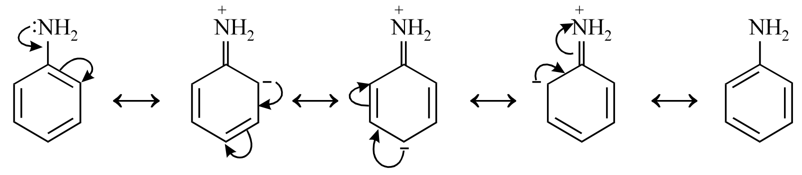
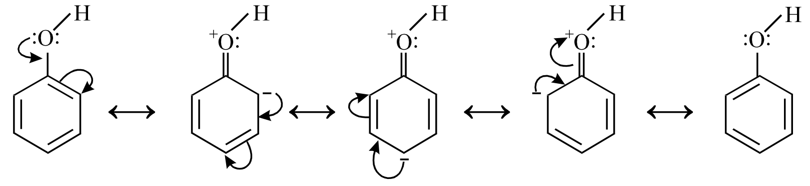
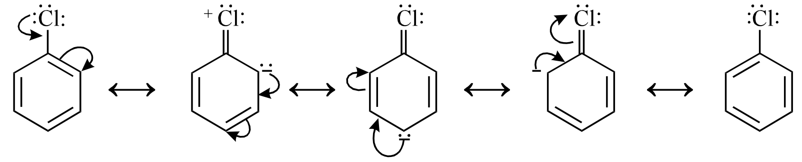


Resonance in aniline



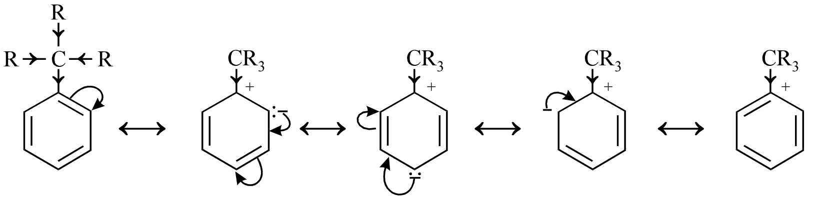
Resonance in phenol

The *o*- and *p*-directing effect of halogens is somewhat anomalous in that they exert strong –I effect and thus deactivate the ring. According to Ingold (1933), the +R effect of chlorine is too small to be of any significance. In presence of an attacking reagent the +E (electromeric) effect is brought into play and the *o*- and *p*-positions are raised in electron density above *m*-position. However, there is an overall decrease in the electron density as compared to benzene. Hence, although chlorine is *o*- and *p*-directing, it is weakly deactivating.



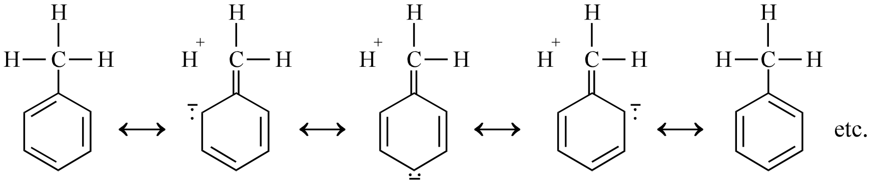
Resonance in chlorobenzene

Methyl or other alkyl groups repel electrons towards the ring by inductive and hyperconjugation effects and hence activate the ring moderately. For example, toluene is 25 times and *t*-butylbenzene is 16 times as reactive as benzene.



Activation and increase of electron density at o- and p-positions due to +I effect

For toluene, consideration of hyperconjugation contributing structures is also important.



Hyperconjugation in toluene

Although the alkyl substituent increases the electron density in the ring as a whole, but more so at *o*- and *p*-positions with respect to the alkyl group. Therefore, further electrophilic substitution occurs at these positions and not at *m*-position.

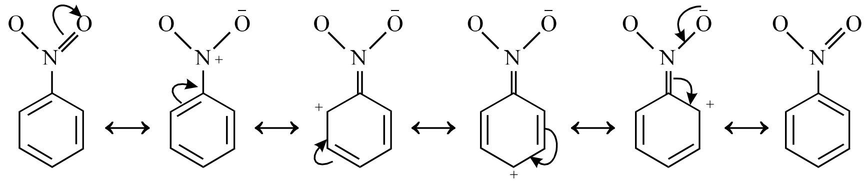
Electronic Explanation of M-directive Influence

The polar characteristics of these groups are –I and –R with the exception of —$\overset{+}{N}R_3$ and —CCl_3 groups which exhibit only –I effect. Hence —$\overset{+}{N}R_3$ and —CCl_3 groups *deactivate* the benzene ring in general by decreasing electron density due to –I effect. However, the withdrawal of electrons from *o*- and *p*-positions is much greater as compared to *m*-position. Thus *m-position remains the point of comparatively high electron density* and electrophilic substitution occurs preferentially at *m*-position.

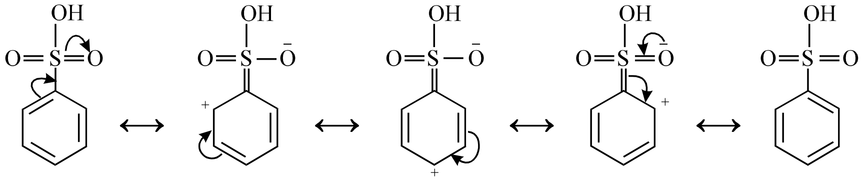
NOTES

The groups like —NO_2, —CN, —SO_3H, —CHO, —COOH, etc., have a multiple bond conjugated to the benzene ring and a strongly electron attracting atom linked through this multiple bond. Due to conjugation the electron attracting atom causes withdrawal of electrons away from the ring and towards the group by a –R effect, thus deactivating the nucleus. However the effect is more pronounced at *o*- and *p*-positions leaving the *m*-position as point of relatively high electron density. The –I effect assists the –R effect.

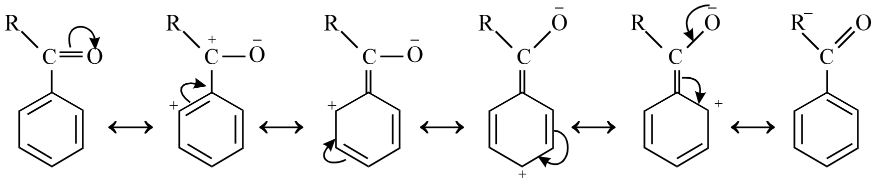
As the molecule is a resonance hybrid of various contributing structures there is a small positive charge at the two *o*- and the *p*-positions. The *m*-position remains the position of relatively high electron density and is attacked by electrophiles resulting in *m*-substitution.



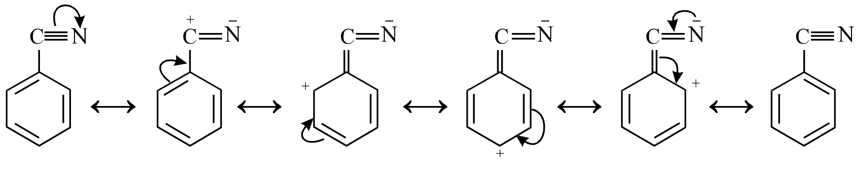
Resonance in nitrobenzene



Resonance in benzene sulphonic acid



[For substituent —CHO, R = H; for —COOH, R = OH etc.]



Resonance in phenyl cyanide

Other Factors Affecting Aromatic Substitution

Other factors like nature of incoming substituent and reaction conditions *e.g.*, temperature, concentration, solvent used, etc., also affect the orientation in a substitution reaction. However, these factors are of only minor importance.

Ortho-para Ratio

Since there are two *ortho*- and only one *para*-position in a monosubstituted benzene derivative, it might be expected that the ratio of *o*- and *p*-isomers formed should be 2 : 1. In actual practice, however, the ratio is seldom 2 : 1, indeed for some reactions *o*-substitution is favoured and for the others *p*-substitution.

As the electron density both at *o*- and *p*-positions are same, the abnormal behaviour is explained on the basis of *steric hinderance.* Thus it had been observed that as the size of the substituent already present in the ring increases, the amount of *o*-isomer decreases.

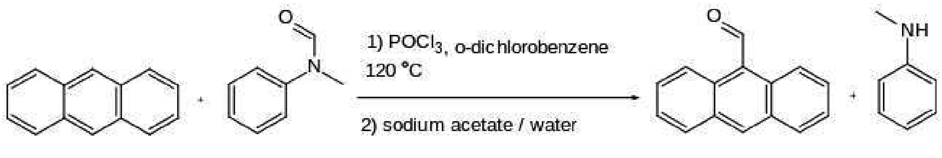
Similarly, greater the size of incoming substituent, the smaller is the proportion of *o*-isomer formed. Besides these the nature of solvent also affects the *ortho-para* ratio.

Vilsmeier–Haack Reaction

The Vilsmeier–Haack reaction, also termed as the Vilsmeier reaction, is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone. The reaction is named after Anton Vilsmeier and Albrecht Haack.

The Vilsmeier-Haack reaction is a common method used for introducing a formyl group into electron rich aromatic compounds and can also be applicable to electron rich alkenes. The process and the reaction conditions are simple. In chemistry, the addition of a formyl functional group is termed formylation. A formyl functional group consists of a carbonyl bonded to hydrogen. When attached to an R group, a formyl group is called an aldehyde.

For example, benzanilide and dimethylaniline react with phosphorus oxychloride to produce an unsymmetrical diaryl ketone. Similarly, anthracene is formylated at the 9-position. The reaction of anthracene with N-Methylformanilide, using the phosphorus oxychloride, is shown below.



Mechanism

The reaction of a substituted amide with phosphorus oxychloride gives a substituted chloroiminium ion (2), also termed as the Vilsmeier Reagent. The initial product is an iminium ion (4b), which is hydrolyzed to the corresponding aldehyde.

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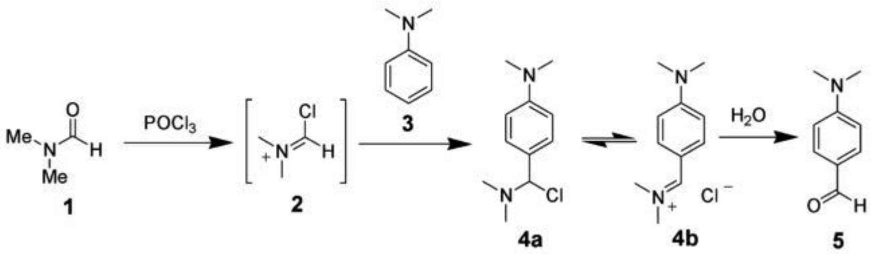
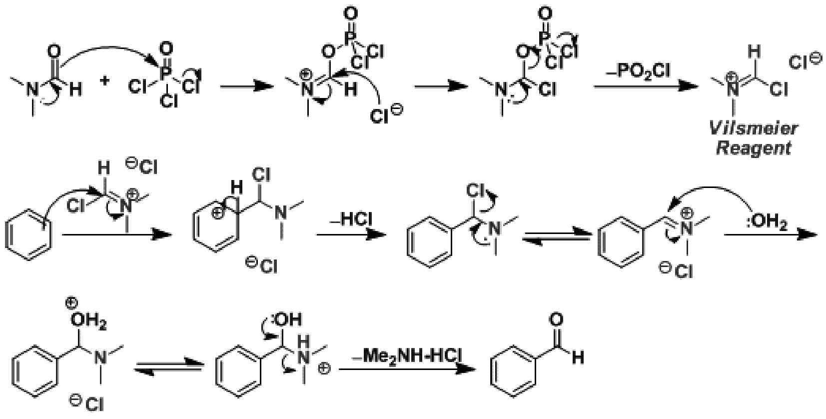
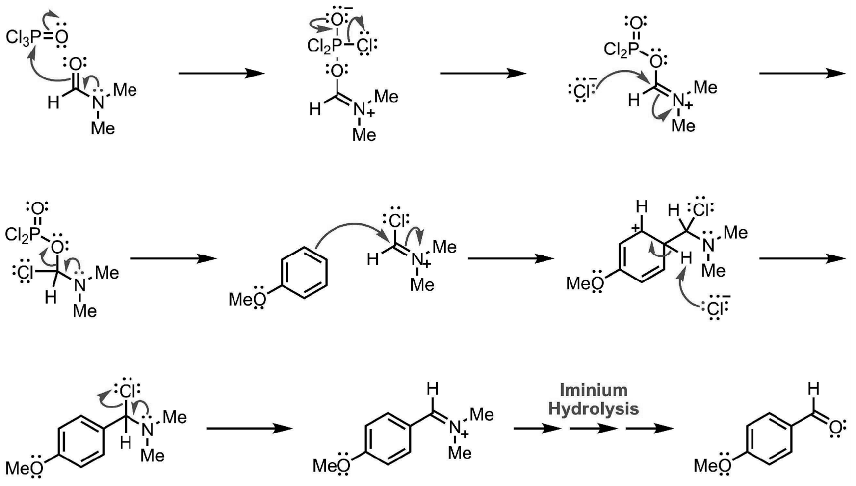


Following is the detailed reaction mechanism of N, N-Dimethylformamide (DMF) and phosphorus oxychloride (POCl3) oxychloride reaction which react to form the Vilsmeier Reagent or Vilsmeyer-Haack Reagent or Formylating Agent, which further undergoes S_EAr reaction.

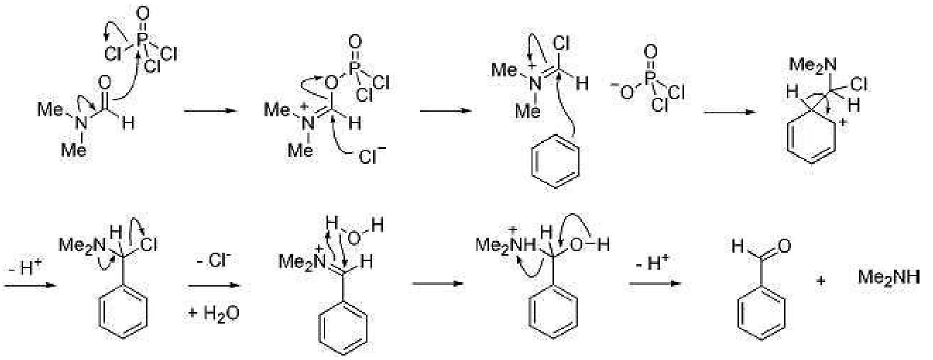


Typically, the formylating agent or the Vilsmeyer-Haack Reagent is formed from DMF and phosphorus oxychlorid due to an electrophilic aromatic substitution which leads to α-chloro amines, which are rapidly hydrolyzed during the reaction process to give the aldehyde.

Hydrolysis of the iminium intermediate gives the formylated product. Mechanism of the Vilsmeier-Haack Formylation reaction is shown below.

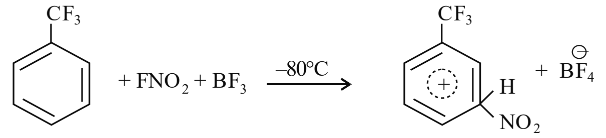


The Vilsmeier reaction allows the formylation of electron-rich arenes. The reaction of the amide with phosphorus oxychloride produces an electrophilic iminium cation. The subsequent electrophilic aromatic substitution produces an iminium ion intermediate, which is hydrolyzed to give the desired aryl ketone or aryl aldehyde.



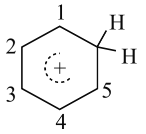
Electrophilic aromatic substitution proceeds; in large, by just one mechanism arenium ion mechanism. The IUPAC designation for this mechanism is $A_E + D_E$. Arenium ion mechanism is multistep process jUnit II Types of mechanism].

Strong evidence for the arenium ion mechanism comes from the isolation of arenium ion in number of instances and eventually found to be the σ-complex mentioned in the mechanism when benzotrifluoride was treated with nitrylfluoride and borontrifluoride at about –80°C a yellow crystalline sigma complex was detected and isolated.



Similary mesitylene also forms a crystalline σ-complex with m.p.–18°C.

Even the simple arenium ion, benzenonium ion (a) has been prepared and defeated by NMR at low temperature. B_C NMR spectra of benzenonium ion and pentamethyl benyenonium ion give graphci evidence for charge distribution as shown below

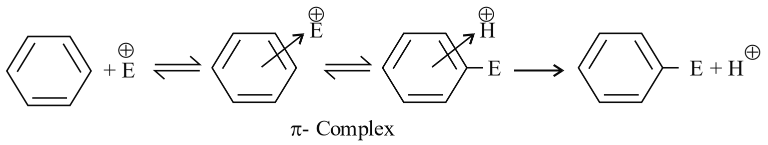


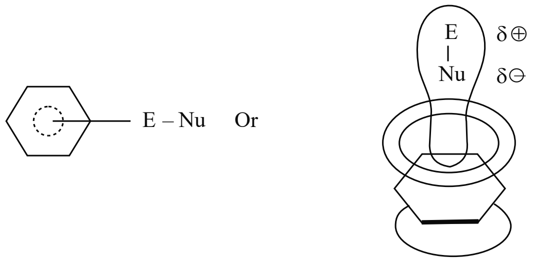
According to it, 1, 3, 5 carbon eachn of which bear change of about + 1/3 should have a greater chemical shift in NMR than 2 and 4 carbons. Which are unchanged.

An increase in base concentration increase the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting material.

The π-complex is donoe-acceptor type of complex with the π-electrons of the dramatic ring donating electron density to the acceptor electrophile. Although these complexes are readily observed by spectroscopic mraurements, they generally are of modest stability.

A was Dewar who originally proposed that compplexes may play an important role in electrophilic aromatic substitution.





π- Complex

Consequently the rate of substitution should parallel the stabilikty of π-complex.

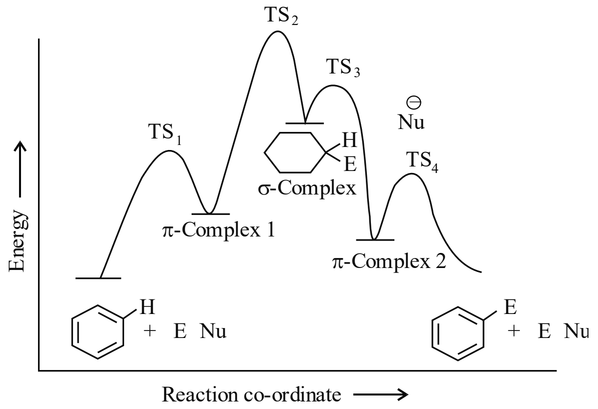
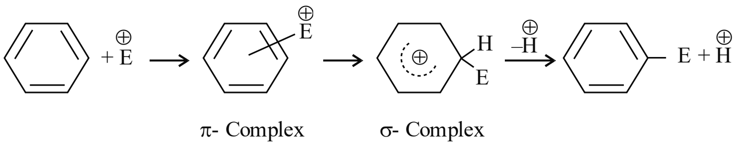


***Fig. 3.5** Energy Profile for Aromatic Substitution showing π Complex Formation. This Profile Suggests that s Complex Formation is Rate Determining*

Evidence for the formation of p complex as an intermediate state has been found in some reactions but not for all since the chemical interaction in π-complexes is very weak. Stable solution of arenium ion or π-complex can be formed with bromine, iodine, picric acid or HCL.



When atomatic hydrocarbon is treated with HCl alone, a π-complex is formed but when hemis acid is used along with HCl, arenium ion is formed. Both the solution have different properties. In case of π complex formation, the solution is:

(i) Colourless

(ii) do not conduct electricity

(iii) When DCl is used in place of HCl, no isotope exchange is observed as there is no true covalent bond formation during π-complex formation

On the contrary in arenium ion formation:

(i) Solution is coloured

(ii) Solution conducts electricity

(iii) denterium isotope exchange is observed when DCl and $AlCl_3$ are used.

In case if π complex formation is there, the mechanism may follow following two paths:

(a) π-complex formation is rate etermining step which is followed by a rapid conversion to arenium ion.

(b) π-complex formation is rapid and its conversion to arenium ion is rate determining step.

To ascertain this, the relative arenium ion stabilizes and π complex stabilities were determined using relative basicity of the substrate towards HCl in the former case and by equilibrium constant for the reaction between aromatic hydrocarbon and HCl in later case.

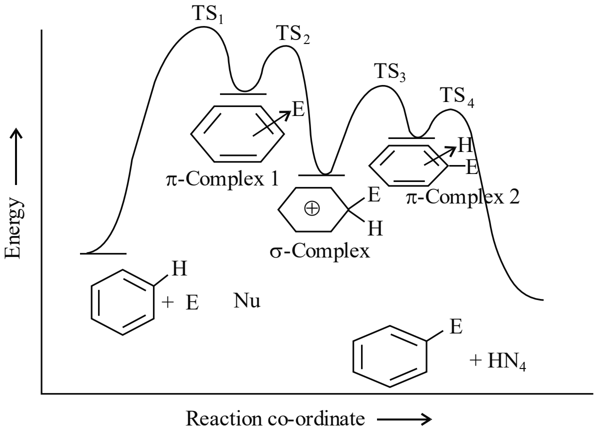


Fig. 3.6 *Energy Profile Diagram Showing Formation of π-complex in rate Determining Step.*

3.4.5 Quantitative Treatment of Reactivity in Substrate

In aromatic substitution quantitative rate studies are complicated as compared to such studies in nucleophilc substitution as in nucleophiolic substitution there is only on leaving grouping in the substrate while in aromatic substitution there are usually serveral hydrogen that can leave. So the total reactivity of the various mono-subsituted benzene towards electrophile is considered.

Most of the aromatic substitutions are kinetically controlled. Under kinetically controlled conditions the rate ratio can be obtained from overall rates and careful determination of the proportions of isomers formed.

Partial rate factor: Partial rate factor for a given group and for a given reaction may be defined as the rate of substitution at a single position relative to the rate of substitution at a single position in partial rate factors for a specific reaction are calculated by relating the percentage of ortho, meta and para isomers formed to the reactivity of the total molecule relative to benzene. As an example consider nitration to toluene. Analysis of product isomers indicates that it gives 56.5% ortho; 3.0% meta and 40% para nitro toluene.

Nitration of benzene reaction is 24 times slowes than the nitration of toluene in acetic anhydride. Hence the reactivity at para position of toluene is $40 \times \frac{24}{100} = 9.7$ tkmes the reactivity of benyene.

Since we want to eompare the reactivity at the single para position of toluene with that of at one position of benzene, it is necessary to multiply the reactivity at that one position of toluene by six to account for the six equivalent position of benzene which would actually be reacting. The partial rate factor for the reactivity of para position of toluene relative to one position in benzene is therefore.

$$P_F CH_3 = \frac{6k(C_6h_5CH_3)}{k(C_8h_6)} \frac{\%\text{para}}{100}$$

$$= 6 \times 24 \times .040$$

$$= 58$$

$k(C_4h_5CH_3)$ and $k(C_8h_6)$ are for the total reaction of $C_6h_5CH_3$ and C_8h_6 respectively.

This shows that the para position of toluene is 58 times more reactive than a single position in benzene ring for nitration reaction. Similarly arto and meta partial rate factor are calculated.

$$\text{O or } m_f^z = \frac{6k(C_6h_5z)}{2k(C_6h_6)} \frac{\%\text{ ortho or meta}}{100}$$

Partial rate factors for acetylation of toluene are:

for the ortho polsition = $O_f^{Me} = 4.5$

for the meta position = $O_f^{Me} = 4.8$

for the para position = $P_f^{Me} = 749$

Partial rate factors differ from:

(i) One reaction to another

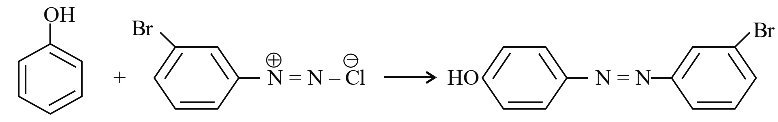
(ii) For the same reaction under different condition.

When two or more groups are present in the ring, one can predict the propertion of the isomers by making an assumption that the efect of substitution is additive.

3.4.6 Diazonium Coupling, Vilsmeier Reaction and Gattermann-Koch Reaction

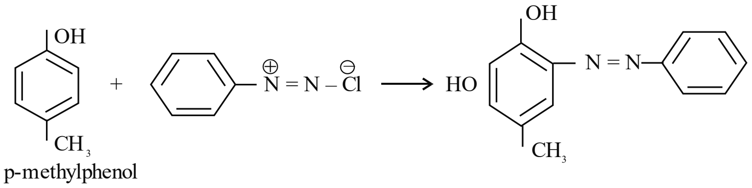
Azo coupling is the most widely used industrial reaction of arenediazonium ion in the production of dyes, lakes and pigments. Diazo coupling is an aromatic electrophilic substitution reaction in which the diagonium salt is an electrophile and the activated arene is the nucleophile. As the arenediazonium ion is unstable at room temperature, and can be used as an electrophile in only those electrophilic substitution reactions that can be carried out well below room temperature.

The –N = N– linkage is called an azo linkage. Since the electrophile is so large, substitution takes place prefuentially at the less sterically hindred para position.



Phenol m-bromobenzene 3-bromo-L'hydroxy axobenzyme

However, if the para position is blocked, substitution will occur at ortho position, e.g.,

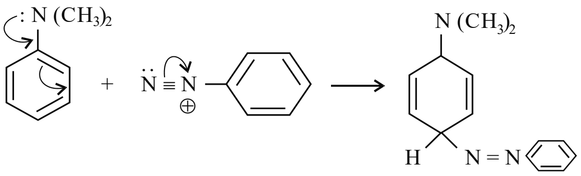


p-methylphenol

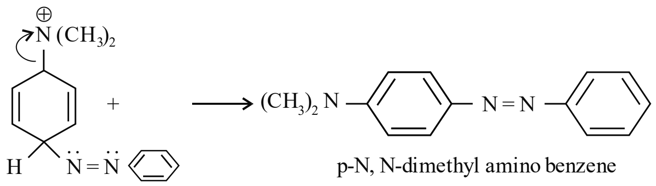
The pH of the solution is quite important, it must be mildly acidic or neutral,

Mechanism

(a) Attack of electrophile:



(b) Removal of proton:



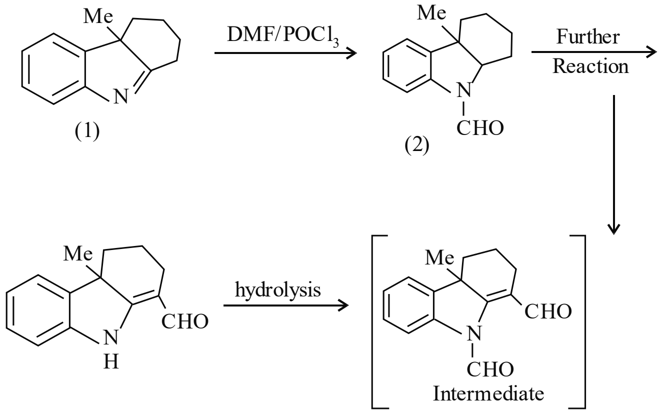
p-N, N-dimethyl amino benzene

Vilsmeier Reaction

The vilsmerier-Haack reaction (also called the vilsmerier reaction) is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron rich arene to produce an aryl aldehyde/ketone.

Chloro methyleneiminium salts (Vilsmerier-Haack reagent) are used for formylation, cyclohaloaddition, cyclization and ring annulations. A wide variely of alkene derivatives, carbonyl compound, as well as nitroghen nucleophiles undergo the reactions with vilsmerier reagent to yield the corredsponding iminium salt.

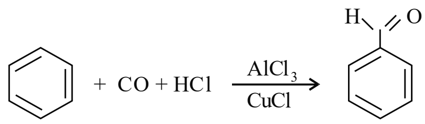
In 1959, frity reported the N-formylation of a 3, 3 disubstituted 3H-indole (indolenine) 1 leading to 2 by utilization of Vilsmerier reagent formed from DME and $POCl_3$. Further reaction of 2 with the Vilsmerier reagent, followed by hydrolysis produced compound 4. Formation of this product probably involves the intermediate 3 promo which the N-Formyl group is hydrolytically removed.



This reaction is formylation of an electron-enriched aromatic or heterocyclic compound using N, N disubstituted formamide (DMF) as the acylating reagent in the presence of an activating reagent $POCl_3$.

Gattermann-Koch Reaction

Gattermann Koch reaction begins with the formation of the reactive species with the help of the acid.



Mechanism

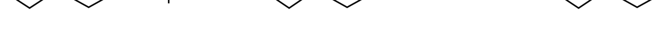
It includes the following steps:

Step 1. The first step of the reaction is the genration of reactive species. CO acts as a lemis base, it can accept a proton from the HCl. This results in a possitively charged molecule which has different resonance structure.

$$Cl-H|^{-}\ C\equiv O^{+}\ |\rightarrow H\equiv O^{+}\ |\leftrightarrow H-C^{+}O\rangle$$

Step 2. When a hemis acid is added, it easily removes a chlorine ion from the species.

Step 3. An electrophilic aromatic substitution occurs at the aromatic ring. The aromatic ring acts as a nucleophile and donates an electron pair to the formyl cation.



NOTES

Check Your Progress

11. What is Wheland intermediate?
12. Write the equation of halogenation.
13. State about Friedel-Crafts alkylation of benzene.
14. What does Hammond's postulate states?
15. What happens when o-, p-directing and activating groups are attached to benzene?
16. How is nitration of benzene carried out?
17. What is Gattermann Koch reaction?

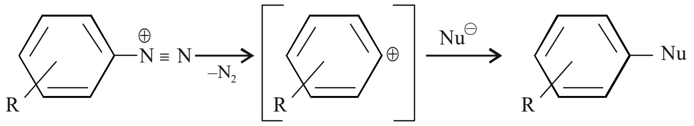
3.5 AROMATIC NUCLEOPHILIC SUBSTITUTION

Let us study these reactions and their mechanism in detail.

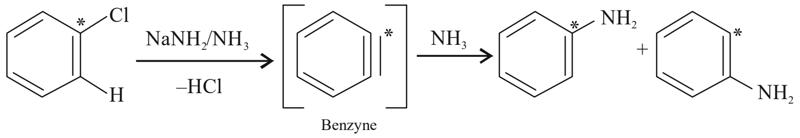
3.5.1 S_N1, S_NAR, Benzyne and S_RN1 Mechanisms

This may occur in several ways, including (i) aromatic S_N1 mechanism, (ii) involving benzyne intermediate and (iii) S_NAr mechanism involving addition and elimination.

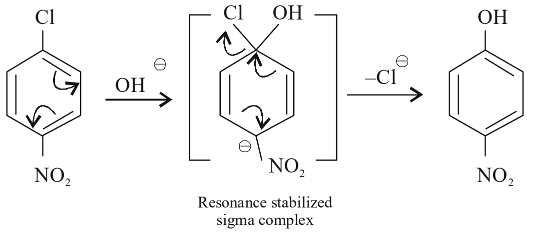
(i) Aromatic S_N1 mechanism is observed in diazonium salts



(ii) Benzyne mechanism is observed in reaction of chlorobenzene with $NaNH_2$.



(iii) S_NAR mechanism is observed when an electron withdrawing group like $–NO_2$ activates the ring towards nucleophilic attack.



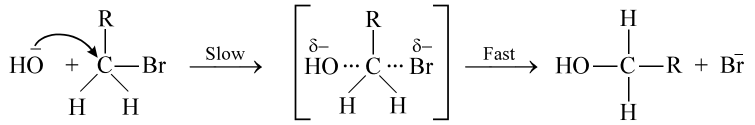
NOTES

Applications

The mechanisms of the hydrolysis of alkyl halides have been successfully explained by nucleophilic substitution. Some examples are given below:

(1) **Hydrolysis of Alkyl Halide (Primary and Secondary)**

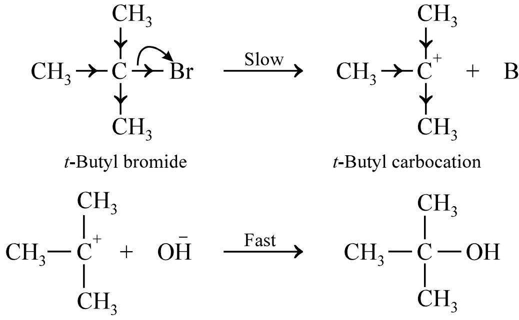
S_N2 mechanism



Primary alkyl halide   Transition state

Hydrolysis of t-butyl Bromide

S_N1 Mechanism



t-Butyl bromide   *t*-Butyl carbocation

t-Butyl alcohol

In the S_N2 mechanism the nucleophile hydroxide ion approaches the alkyl halide molecule preferably from the side opposite to that occupied by the departing group. As the carbon atom involved in carbon to halogen bond is slightly deficient in electron density because of greater electronegativity of halogen (bromine in above example) the hydroxide ion offers a pair of electrons for the formation of bond with this carbon. Simultaneously bromine starts taking hold of the electron pair through which it is bonded to carbon and a transition state or activated complex is visualized for such reactions in which five groups are linked to carbon. Finally bromine leaves the molecules as a bromide ion and hydroxide ion forms a covalent bond with the carbon giving alcohol as the reaction product.

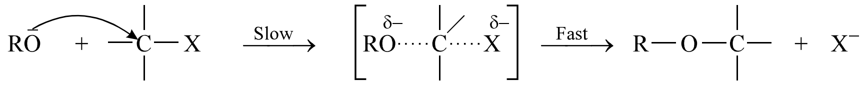
In the hydrolysis of *t*-butyl bromide which occurs by S_N1 mechanism, the first step is the slow dissociation of alkyl halide to give a bromide ion and tertiary butyl carbocation, which is stabilised due to hyperconjugation. The tertiary butyl carbocation then combines with a hydroxide ion to form the tertiary butyl alcohol.

(2) **Alkylation with Alkyl Halides (Williamson Synthesis of Ethers)**

$$R{-}X \ + \ R'{-}ONa \ \longrightarrow \ R{-}O{-}R' \ + NaX$$

S_N2 mechanism for the reaction is given below:

$$R'{-}ONa \ \longrightarrow \ R{-}O^- \ + \ Na^+$$



Alkoxide ion   Alkyl halide   Ether

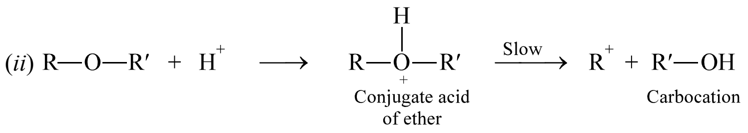
(3) **Cleavage of Ethers (Ziesel's Method for Determining Alkoxy Groups)**

$$R{-}O{-}R' + HI \longrightarrow RI + R'{-}OH$$

The mechanism is similar to above reaction and may be S_N1 or S_N2

S_{N1} mechanism

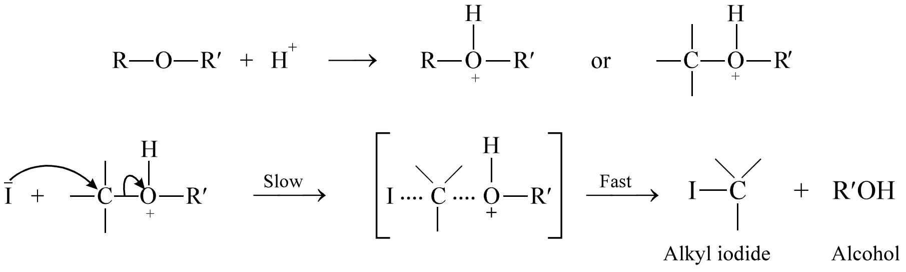
(*i*) $HI \longrightarrow H^+ + I^-$



(*ii*) $R{-}O{-}R' + H^+ \longrightarrow \underset{\text{Conjugate acid of ether}}{R{-}\overset{H}{\underset{+}{O}}{-}R'} \xrightarrow{\text{Slow}} \underset{\text{Carbocation}}{R^+} + R'{-}OH$

(*iii*) $R^+ + I^- \longrightarrow \underset{\text{Alkyl halide}}{R{-}I}$

S_N2 mechanism



$$R{-}O{-}R' + H^+ \longrightarrow R{-}\overset{H}{\underset{+}{O}}{-}R' \quad \text{or} \quad {-}\overset{|}{\underset{|}{C}}{-}\overset{H}{\underset{+}{O}}{-}R'$$

$$\bar{I} + {-}\overset{|}{\underset{|}{C}}{-}\overset{H}{\underset{+}{O}}{-}R' \xrightarrow{\text{Slow}} \left[I \cdots C \cdots \overset{H}{\underset{+}{O}}{-}R' \right] \xrightarrow{\text{Fast}} \underset{\text{Alkyl iodide}}{I{-}C} + \underset{\text{Alcohol}}{R'OH}$$

3.5.2 Reactivity-Effect of Substrate, Leaving Group and Attacking Nucleophile

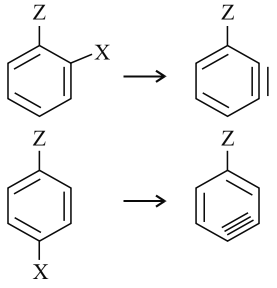
Let us study the effects of them on reactivity in detail.

- **Substrate**

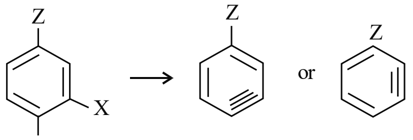
  (a) **S_NAr Mechanism:** Electron withdrawing group specially in the position of ortho and para to leaving group accelerate nucleophilic aromatic substitution, on the other hand electron donating group hindu. Activating group stabiloize the intermediate and transition state by withdrawing electron density of the ring.

  (b) **Benzyne Mechanism:** The position of attack of nucleophile depends. Upon two factors:

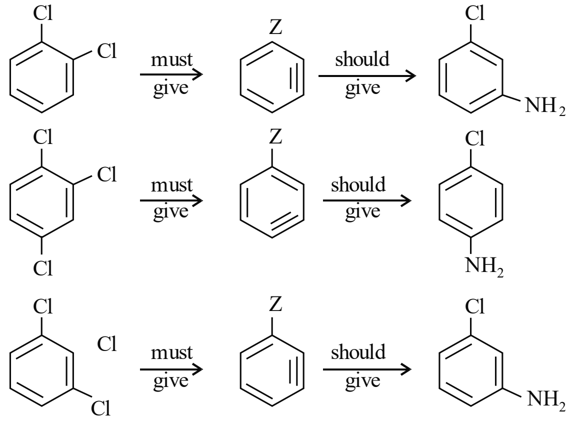
  (i) The direction in which aryne is formed if a group z is present ortho or para to leaving group x, there is no choice in aryne formation.



When group (2) is present meta to the leaving group, aryne can be formed in two different ways depending upon the nature of z, in each case more acidic hydrogen is removed the field effect of z affects the acidity of hydrogen, if z is on electron attracting group, removal of ortho hydrogen is preferred and if it is electron donating group para hydrogen is removed.



(ii) Attack of nucleophile on aryne such as attack can occur at two position the favoured position is one that leads to more stable cabanion intermediate, and this is turn depends upon the field effect of 2.



–I group the more stable carbanion is one in which negative change is closes to the substituent.

- **Leaving Group**

In aromatic nucleophilic substitution the order of leaving ability os F > NO_2 > OT_5 > SOPh > (1, Br) > N_3 > NH_2, however it greatly depends on nature of nucleophile. The leaving group order is quite different from that for S_N^1 and S_N^2 mechanism.

This is because in S_NAr mechanism the first step is rate determining which is promoted by strong-I effect. In benzyne mechanism fluoro group is poorest leaving group as it involves in rate determining step.

- **Attacking Nucleophile**

Nucleophilicity is generally dependent on base strength and nuclelphilicity increases as the attacking atom moves down a column of the periodic table.

In aromatic nucleophilic substitution cyanide ion acts as nucleophile only in von Ritches, Rosenmund, Von-Braun reaction and for sulphoric acid salts.

3.5.3 Sommlet-Hauser Rearrangement, Smiles Rearrangement and Von Richter Reactions

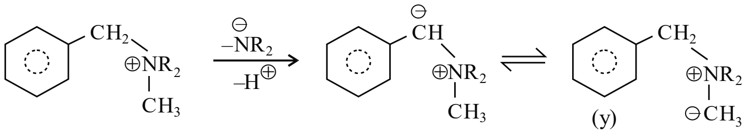
Benzylic quaternary ammonium salts on heating with alkali metal amides yield a benzylic testiory amine as a product. This conversion involve a rearrangement.

Product of rearrangement is benzylic tertiary amine, it can be further alkylated to obtained quaternary ammonium compound which is then subjected to rearrangement.

NOTES

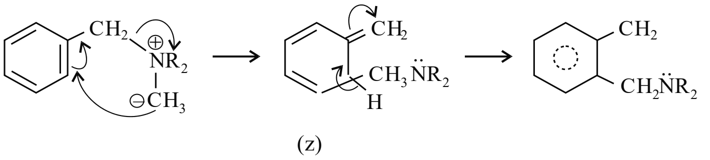
The proposed mechanism involves the following steps:

(a) Loss of bezylic hydrogen which is most acidic and formation of (Y).



(Y) is present in small amount but it is the species that undergoes rearrangement hence shift the equilibrium to wards itself.

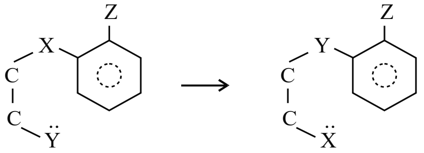
(b) Compound (Y) undergoes nucleolphilic attack at ortho position with a simultaneous bonde fission between benzylic carbon and nitrogen atom, yielding product (Z) undergoes [2, 3] sigmatropic rearrangement.



If the alkyl group attached to nitrogen contains β-hydrogen, Haffmann elimination always completes. Similarly if alkyl group attached to nitrogen contain electron with drawing group stevers rearrangement completes with sommlet Hauses rearrangement. When both rearrangement are possible, the strens rearrangement is favouored at high temperature and Sommlet-Hauses is preferred one at low temperatures.

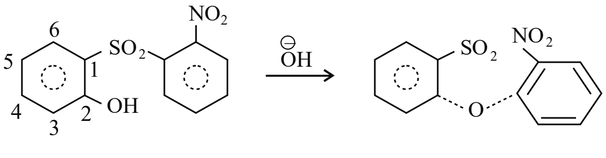
- **Smiles Rearrangement**

Smiles rearrangement is intermolecular nucleophilic substitution which is generally carried out on compounds containing two rings but it is not always true. In general this rearrangement is represented as



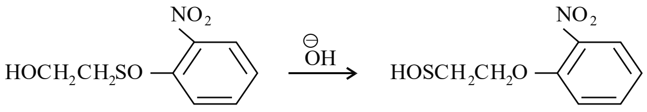
Some of the examples of similes rearrangement are:

In binuclear substrates:



(X)

In mononuclear substrates:



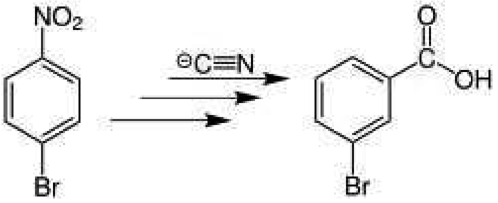
In compound (x) $-SO_2Ar$ group is acting as leaving group and ArO^-, the nucleophile. The nitrogroup present in the ring activates the ortho position for attack by ArO^- (nucleophile). The activation may be both at ortho as well as para positions.

In this rearrangement S, SO, SO_2 groups act as leaving group while the conjugate base of OH, NH_2, NHR, SH act as nucleophile. It has been observed that substitution of methyl, chloro or bromo group at ortho (C_8) to the leaving group enhances the rate of rearrangement by a factor 10^{15} as compared when present at para position (C_4) due to the steric effect, gives favourable conformation to the molecule.

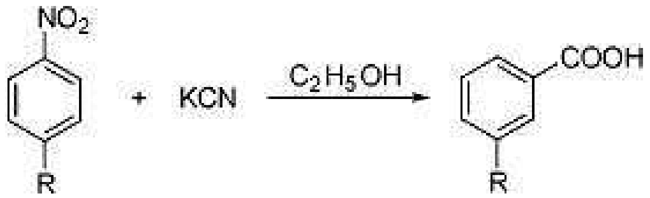
- **Von-Richter Reaction**

The Von-Richter reaction, also termed as the 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.

The reaction below shows the conversion of bromonitrobenzene into bromobenzoic acid.



The reaction is an aromatic nucleophilic substitution. Chlorine can be substituted instead of bromine. The following example shows the Von Richter rearrangement reaction.

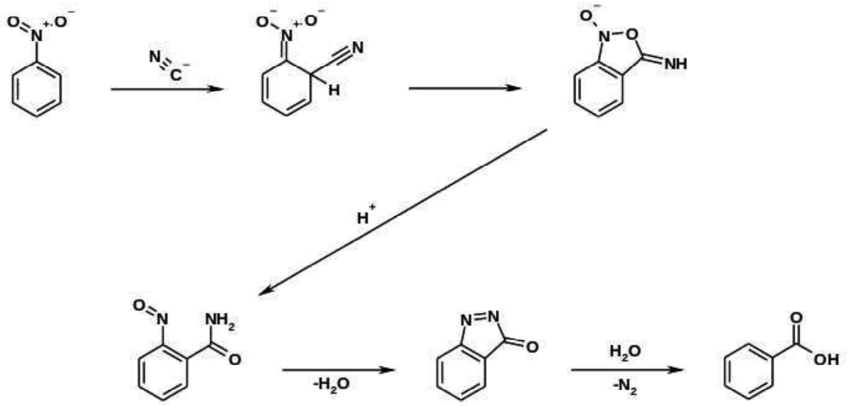


The above reaction shows the Carboxylation of para- or meta-substituted aromatic nitro compounds with cyanate which takes place at 120-270°. The carboxyl group enters with cine substitution in a position ortho to the eliminated nitro group.

Mechanism

The cyanide reacts with the carbon atom in ortho-position to the nitro group.

NOTES



The negative charged oxygen atom reacts with the neighbouring carbon atom to build a five-membered ring which on condensation forms a double bond between the two nitrogen atoms, as shown in the reaction. In the last step, the compound is protonated and the 3-halogenbenzoic acid is built.

Check Your Progress

18. Where is aromatic S_N1 mechanism seen?
19. What is an allylic rearrangement or allylic shift?
20. Write the difference between trans-additions and c is-additions.
21. Where is SNAR mechanism observed?

3.6 ANSWERS TO 'CHECK YOUR PROGRESS'

1. Reagents having an unshared pair of electrons are known as *nucleophilic reagents* or *nucleophiles* because they have a tendency to share this pair of electrons with electron deficient substrate.
2. A nucleofuge is the combination of two term, Nucleo, and Fugetake, (*nucleo*- nucleus means the positive charge part in an atom and fuge, *fugitive mean* to escape) is a leaving group which retains the lone pair from its previous bond with another species.
3. A Wagner–Meerwein rearrangement is a class of carbocation 1,2-rearrangement reactions in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon.
4. Ultrasound is a technique to increase the reaction rate. The use of ultrasound in chemical reactions in solution provides specific activation based on physical phenomenon.
5. Examples of the nucleophilic substitution reaction are hydrolysis of alkyl halides, acyl halides; cleavage of ethers with HI (Ziesel reaction and alkylation with alkyl halides (Williamson's synthesis).

6. The neighbouring group participation is defined as the interaction of the reaction centre either with a lone pair of electrons as adjacent atom or with electrons present in a sigma or pi-bonds (as in a double bond).
7. Substitution reactions initiated by electrophilic reagents are known as electrophilic substitution reactions.
8. Nitration is introduction of a nitro group (-NO_2) in place of hydrogen by electrophile (nitronium ion).
9. Saturated or aliphatic reaction and unsaturated or aromatic reaction are two types of electrophilic reactions.
10. If the reaction is unimolecular it is written as S_E1.
11. The carbocation formed as intermediate in an aromatic electrophilic substitution is an arenium ion, also known as Wheland intermediate or a sigma (s) complex.
12. Benzene undergoes chlorination and bromination forming monochloro or monobromobenzene. The reaction takes place in presence of $FeCl_3$ or $AlCl_3$ at room temperature.

    $$C_6H_6 + C_{12} \qquad C_6H_5Cl + HCl$$
13. Friedel-Crafts alkylation of benzene: Benzene on being treated with alkyl halide in presence of $AlCl_3$ form alkyl benzenes in which the alkyl group comes from alkyl halide.
14. Hammond's postulate states that the factors stabilizing the transition state should also operate in Wheland intermediate. Hence the stabler the intermediate faster is its formation.
15. When *o*-, *p*-directing and activating groups (for example., —NH_2, —OH etc.) are attached to benzene then the Wheland intermediate resulting from *o*- or *p*-attack is more stabilized by resonance.
16. Nitration of benzene is carried out with a mixture of conc. nitric and conc. sulphuric acid.
17. When a mixture of carbon monoxide and hydrogen chloride is passed in an ethereal solution of benzene in presence of anhydrous $AlCl_3$ and cuprous chloride, an aldehyde is obtained.
18. Aromatic SN_1 mechanism is observed in diazonium salts
19. 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 and is confronted in nucleophilic substitution.
20. If the two groups are added on opposite sides of the double bond—such additions are known as trans-additions. On the other hand if the two groups are added on the same side of the double bond such additions are known as cis-additions.
21. SNAR mechanism is observed when an electron withdrawing group like –NO_2 activate the ring towards nucleophilic attack.

3.7 SUMMARY

NOTES

- Reagents having an unshared pair of electrons are known as nucleophilic reagents or nucleophiles because they have a tendency to share this pair of electrons with electron deficient substrate.
- A nucleofuge - This term is the combination of two term Nucleo and Fugetake (*nucleo*- nucleus means the positive charge part in an atom and fuge, *fugitive mean* to escape) is a leaving group which retains the lone pair from its previous bond with another species.
- Substitution reactions by nucleophilic reagents are known as nucleophilic substitution (S_N) reactions.
- S_N1 reactions follow first order kinetics.
- S_N2 reactions follow second order kinetics.
- The various factors guiding the reaction to follow S_N1 or S_N2 mechanism are structure of the substrate, steric effect, rearrangement of carbocations, solvent effect and leaving group.
- If a covalent bond, in which carbon is attached to a more electronegative atom or group, breaks up by heterolytic fission, the more electronegative atom will take away the electron pair and become negatively charged while the carbon will lose its electron and thus acquire a positive charge. Such cationic species carrying a positive charge on carbon are known as carbocations.
- The carbocations like cycloheptatrienyl cation (tropylium cation) are so stable that they can be isolated and studied whereas methyl or ethyl cabocations are so unstable that it is normally not possible to detect them in a chemical reaction.
- Carbocations showing resonance are far more stable than those in which the resonance is not playing any part.
- Carbocations undergo three types of reactions: 1.Combination with a nucleophile or base to form a neutral molecule 2. Elimination of a proton. This results in the formation of an olefin 3. Rearrangement
- In classical carbocation, an electron deficient carbon bears a positive charge.
- In non-classical carbocation, the ground state has delocalized (bridged) bonding ð- or ó-electrons.
- The interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a sigma bond or pi bond contained within the parent molecule but not conjugated with the reaction centre. At the point when NGP is in activity it is typical for the response rate to be expanded.
- Substitution reactions initiated by electrophilic reagents are known as electrophilic substitution reactions.
- Electrophilic substitution reactions are designated as S_E reactions.

- If the reaction is unimolecular it is written as S_E1 and if it is bimolecular it is then written as S_E2 type of reaction.
- The reactivities in substitution at aromatic carbon atoms are strongly influenced by the nature of the substituents present in the ring.
- When methyl carbonyl compounds (CH_3CHO, $CH_3CO.CH_3$, etc.) react with halogens in presence of alkali, haloform (CHX_3) is formed. The reaction is known as haloform reaction.
- Substitution at aromatic or unsaturated carbon atoms. The most important reactions of the aromatic compounds are the electrophilic substitution reactions like nitration, halogenation, sulphonation etc. Nitration is introduction of a nitro group (—NO_2) in place of hydrogen by electrophile (nitronium ion). Sulphonation is the replacement of a hydrogen by —SO_3H group and takes place by electrophilic attack of SO_3 on aromatic carbon.
- The carbocation formed as intermediate in an aromatic electrophilic substitution is an arenium ion, also known as Wheland intermediate or a sigma (s) complex. The smallest arenium ion is a protonated benzene C_6H_7Å called benzenium ion which can be isolated as a stable compound when benzene is protonated by the carborane super acid.
- Electrophilic substitution of a monorsubstituted benzene derivative can give rise to three regioisomeric products in which the new substitutent is placed at C–2 (ortho), C–3 (meta) or C–4 (para) position. There are two ortho- and two meta positions available but a statistical distribution of products is not observed and the actual proportion is dependent upon whether the group present is activating or deactivating.
- A vast majority of electrophilic substitution reactions proceed under kinetic control where the rate- and product-determining step is the formation of a Wheland intermediate which is a highly endothemic process. Hammond's postulate states that the factors stabilizing the transition state should also operate in Wheland intermediate. Hence the stabler the intermediate faster is its formation.
- When o-, p-directing and activating groups (e.g., —NH_2, —OH, etc.) are attached to benzene then the wheland intermediate resulting from o- or p-attack is more stabilized by resonance.
- Nucleophilic aromatic substitution occur in several ways, including:

  (i) aromatic S_N1 mechanism, (ii) involving benzyne intermediate and

  (iii) S_NAR mechanism involving addition and elimination.
- In the S_N2 mechanism the nucleophile hydroxide ion approaches the alkyl halide molecule preferably from the side opposite to that occupied by the departing group.
- As the carbon atom involved in carbon to halogen bond is slightly deficient in electron density because of greater electronegativity of halogen (bromine in above example) the hydroxide ion offers a pair of electrons for the formation of bond with this carbon.

NOTES

- In the hydrolysis of t-butyl bromide which occurs by SN1 mechanism, the first step is the slow dissociation of alkyl halide to give a bromide ion and tertiary butyl carbocation, which is stabilised due to hyperconjugation. The tertiary butyl carbocation then combines with a hydroxide ion to form the tertiary butyl alcohol.
- The addition reactions are the reactions of the double or triple bonds. In a >C==C< or —C^{oo}C— the p electrons are most readily available. These electrons will shield the molecule from nucleophilic reagents and therefore such molecules will be readily attacked by electrophilic reagents.
- Additions at carbon to carbon multiple bonds. The electrophilic addition reactions are observed in alkenes, alkynes and conjugated systems and essentially mean the addition of a molecule to the double bond. Thus if a reagent breaks up to give a negative and a positive ion each one of these are added to double bond.

3.8 KEY TERMS

- **Rate of reaction:** It is the speed at which reactants are converted into products.
- **Substrate:** A substrate is typically the chemical species being observed in a chemical reaction, which reacts with a reagent to generate a product.
- **Leaving group:** A leaving group is a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage.
- **Nucleophile:** It is a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction.
- **Carbocation:** It is an ion that has a positively charged carbon atom.
- **Rearrangement reaction:** A rearrangement reaction is a broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule.
- **Aliphatic:** Relating to or denoting organic compounds in which carbon atoms form open chains (as in the alkanes), not aromatic rings.
- **Electrophilic:** It is a tendency of a molecule or group to attract or acquire electrons.
- **Substitution reaction:** Substitution reaction is a chemical reaction during which one functional group in a chemical com pound is replaced by another functional group.
- **Electrophilic Aromatic Substitution:**A reaction in which the hydrogen atom of an aromatic ring is replaced as a result of an electrophilic attack on the aromatic ring.
- **Gattermann Koch reaction:** When a mixture of carbon monoxide and hydrogen chloride is passed in an ethereal solution of benzene in presence of anhydrous $AlCl_3$ and cuprous chloride, an aldehyde is obtained.

- **Vilsmeier–Haack reaction:** The Vilsmeier–Haack reaction, also termed as the Vilsmeier reaction, is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone.
- **Vilsmeier Reagent:** The reaction of a substituted amide with phosphorus oxychloride gives a substituted chloroiminium ion (2), also termed as the Vilsmeier Reagent.
- **Nucleophilic aromatic substitution:** A nucleophilic aromatic substitution is a substitution reaction in organic chemistry in which the nucleophile displaces a good leaving group, such as a halide, on an aromatic ring.
- **Benzene nucleus:** The six carbon atoms of the benzene ring constitute what is known as benzene nucleus.
- **Side chain:** A carbon chain connected to one of the carbon atoms of the nucleus through a carbon atom, other than of the simple functional groups like —CHO, —COOH, >CO, is called a side chain.
- **Von-Richter reaction:** It is the chemical reaction of aromatic nitro compounds with potassium cyanide giving carboxylation ‘ortho’ to the position of the former nitro group.

3.9 SELF ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are the effects of reactivity on substate structure?
2. What is phase transfer catalysis?
3. Write some examples of typical electrophilic substitution reactions.
4. What are classical and non-classical carbocations?
5. How do carbocations undergo rearrangement reaction?
6. What is nucleophilic aromatic substitution?
7. What is addition reaction?
8. Write a short note on nucleophilic aromatic substitution and its application.
9. What is ozonolysis?
10. Write a short note on aldol condensation.

Long-Answer Questions

1. Explain the application of NMR spectroscopy in the detection of carbocations.
2. Describe the factors affecting S_N1 and S_n2 mechanisms.
3. Analyze the mechanism of haloform reaction.
4. Discuss the structure and stability of of carbocations.
5. Explain neighbouring group participation.

6. Describe Pinacol-Pinacolone rearrangement.
7. Analyze Semi-Pinacol rearrangement.
8. Discuss addition reaction along with its structure, reactivity and applications.

NOTES

3.10 FURTHER READING

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UNIT 4 ADDITION AND ELIMINATION REACTIONS

NOTES

Structure

4.0 INTRODUCTION

A carbon–carbon bond is a covalent bond between two carbon atoms. The most common form is the single bond: a bond composed of two electrons, one from each of the two atoms. The carbon–carbon single bond is a sigma bond and is formed between one hybridized orbital from each of the carbon atoms. In ethane, the orbitals are sp3-hybridized orbitals, but single bonds formed between carbon atoms with other hybridizations do occur (For example, sp2 to sp2). In fact, the carbon atoms in the single bond need not be of the same hybridization. Carbon atoms can also form double bonds in compounds called alkenes or triple bonds in compounds called alkynes. A double bond is formed with an sp2-hybridized orbital and a p-orbital that is not involved in the hybridization. A triple bond is formed with an sp-hybridized orbital and two p-orbitals from each atom. The use of the p-orbitals forms a pi bond.

Carbon–carbon bond-forming reactions are organic reactions in which a new carbon–carbon bond is formed. They are important in the production of many man-made chemicals such as pharmaceuticals and plastics. Some examples of reactions which form carbon–carbon bonds are aldol reactions, Diels–Alder reaction, and the addition of a Grignard reagent to a carbonyl group, a Heck reaction, a Michael reaction and a Wittig reaction.

Nucleophilic addition reactions of nucleophiles with electrophilic double or triple bond (p bonds) create a new carbon center with two additional single, or s, bonds. Addition of a nucleophile to carbon–heteroatom double or triple bonds such as >C=O or -C=N show great variety. These types of bonds are polar (have a large difference in electronegativity between the two atoms); consequently, their carbon atoms carries a partial positive charge. This makes the molecule an electrophile, and the carbon atom the electrophilic center; this atom is the primary target for the nucleophile. Chemists have developed a geometric system to describe the approach of the nucleophile to the electrophilic center, using two angles, the Bürgi–Dunitz and the Flippin–Lodge angles after scientists that first studied and described them.

In this unit you will study about addition to carbon-carbon multiple bonds, addition to carbon- hetro multiple bonds, mechanism of condensation reaction, elimination reactions, mechanism and orientation in pyrolytic elimination.

4.1 OBJECTIVES

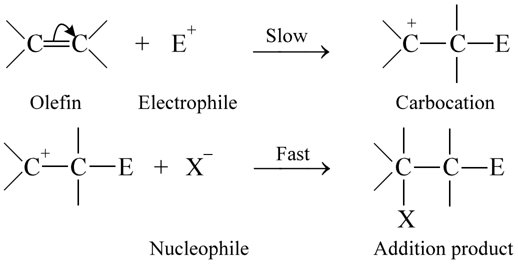
After going through this unit, you will be able to:

- Explain addition to carbon-carbon multiple bonds
- Understand addition to carbon- hetro multiple bonds
- Analyze mechanism of condensation reaction
- Discuss elimination reactions
- Explain mechanism and orientation in pyrolytic elimination

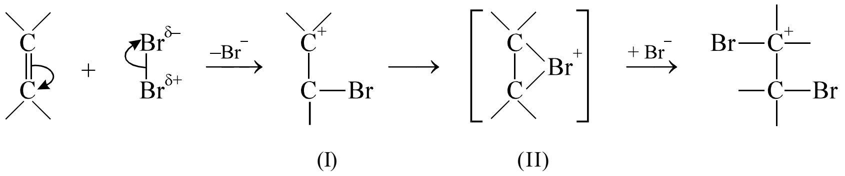
4.2 ADDITION TO CARBON-CARBON MULTIPLE BONDS

The electrophilic addition reactions are observed in alkenes, alkynes and conjugated systems and essentially mean the addition of a molecule to the double bond. Thus if a reagent breaks up to give a negative and a positive ion each one of these are added to double bond. Why the reaction is then known as an electrophilic addition although both the electrophile and the nucleophile are adding to the same double bond? The answer to this lies in the fact that the addition reaction is initiated by the attack of electrophile on the multiple bond which is slow and is the rate determining step and this is followed by the addition of nucleophile which is a fast reaction. In all addition reactions π bonds are converted to σ bonds or the hybridization state of carbon changes from sp^1 to sp^2 or sp^3 and from sp^2 to sp^3. The examples of such reactions are hydration and hydrogenation of olefins, additions of halogens and halogen acids to olefins and ozonolysis.

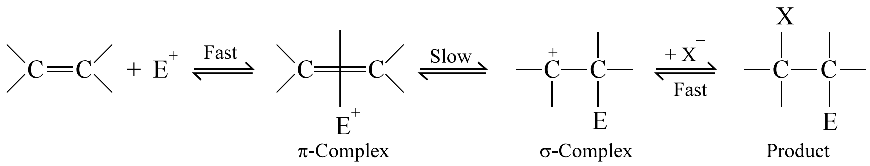
In electrophilic addition reactions an electrophile approaches the double or triple bond and in the first step forms a covalent bond with one of the carbon by converting π bond into a pair of σ bonds, resulting in the formation of a carbocation which then takes up a nucleophile to result in addition product. Thus:



Alternatively the E^+ can also be the positive end of a dipolar reagent. Thus for bromination following mechanism may be written:



A cation of the type II is possible because of the lone pairs of electrons at bromine which may be co-ordinated with electron deficient carbon. It has been suggested that electrophile first interacts with π electrons to form a π complex which later changes to a σ complex or carbocation, exemplified as follows:

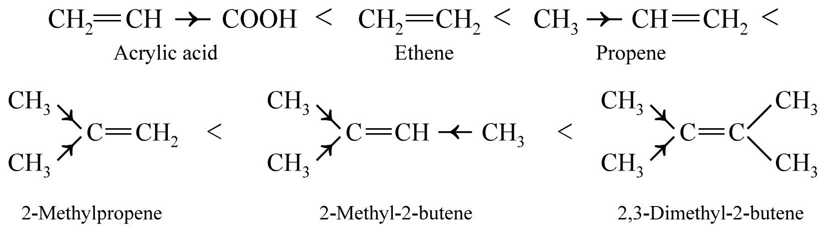


The π complex or the three membered ring cation is roughly on one side of the double bond and therefore the attack of nucleophile must occur from the other side of the double bond. Thus the two groups are added on opposite sides of the double bond—such additions are known as ***trans*-additions**. On the other hand if the two groups are added on the same side of the double bond such additions are known as ***cis*-additions.** Most electrophilic additions are trans additions. Thus stereochemistry of addition reactions yields useful information about the mechanism of these reactions.

Structure and Reactivity

Two carbon atoms are involved in double bond formation. Which one of these is chosen for electrophilic addition? In symmetrical olefins these two carbon atoms are identical in character and therefore addition of electrophile at either of these will yield the same product but in unsymmetrical olefins like propylene the two carbon atoms involved in double bond are not identical and hence the addition of electrophile to each one of these respectively should result in two isomeric products. Since the addition of electrophile to double or triple bond gives a carbocation it is logical to expect that carbocation having greater stability will predominate. *So the electromeric shift of electrons and addition of electrophile will take place in such a manner so as to form the more stable carbocation.*

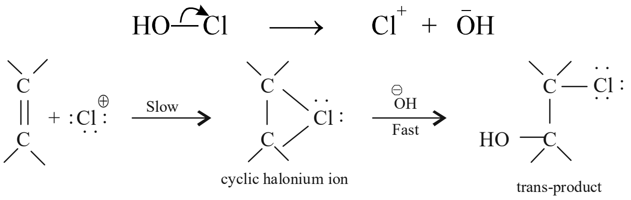
An electrophile attacks at the site rich in electrons so all the structural features which tend to increase electron density at the double or triple bond will increase the rate of reactions. *Thus electron donating substituents* (*+I effect*) *will increase the rate of reaction whereas electron withdrawing substituents* (*–I effect*) *will decrease it.* Structural features increasing the stability of carbocation tend to speed up the reaction. The polar solvents, likewise, markedly increase the reaction rate. The order of reactivity of double bonds to electrophilic additions in some of the common compounds is given below in increasing order which may be understood in terms of inductive effects.



Applications

Some of the applications are as follows:

(*i*) **Addition of Halogens and hypohalous acids to olefins:** When a halogen molecule or hypohalous acid reacts with olefin, the π bond is polarised by electromeric shift. The positively polarised halogen attacks and combines with the carbon carrying the pair of electrons after electromeric shift. A cyclic halonium ion is formed whihc prevents *cis*-addition of OH⁻. Then the completion of addition occurs by a trans combination of a bromide or hydroxide ion. The mechanism of addition of hypochlorous acid may briefly be illustrated as



In the reaction with bromine it is the bromonium ion (Br^+) which is the attacking species rather than bromide ion because the latter is more stable than former by virtue of its stable electronic configuration. As already mentioned the attack of Br^- or OH^- on the carbocation takes place from the side other than the one occupied by Br^+ or Cl^+ resulting in trans-addition. In simple aliphatic compounds the trans-addition has no significance because the product can easily change to *cis*-form by simple rotation along the carbon to carbon bond but it becomes important if the geometry of the molecule prevents this free rotation as in cyclic compounds.

This ionic mechanism is supported by the fact that the reaction rate is accelerated as the polarity of solvent is increased. If the reaction is carried out in presence of a number of anions like Cl^-, NO_2^-, RO^-, etc. then these are also incorporated in some of the substrate molecules. Thus:

$$CH_2{=}CH_2 + Br_2 \longrightarrow Br^- + Br{-}CH_2{-}\overset{+}{C}H_2 \xrightarrow{Br^-} Br.CH_2.CH_2.Br \qquad (4.1)$$

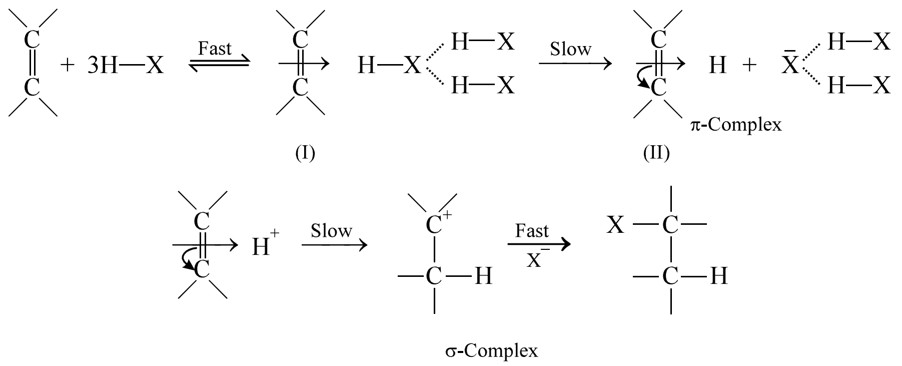
$$\xrightarrow{Cl^-} Br.CH_2.CH_2.Cl \qquad (4.2)$$

$$\xrightarrow{NO_2^-} Br.CH_2.CH_2.NO_2 \qquad (4.3)$$

$$\xrightarrow[ROH/Na]{RO^-} Br.CH_2.CH_2.OR \qquad (4.4)$$

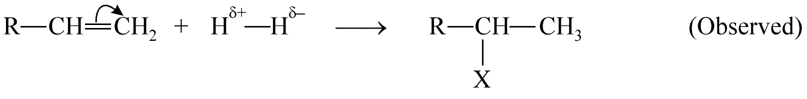
These products (4.2) to (4.4) are not the products of substitution of (4.1) but are formed as a result of competition between various anions for reaction with carbocation intermediate.

(*ii*) **Addition of halogen acids to olefins:** The addition of halogen acid (HX) to olefins may be shown as follows:



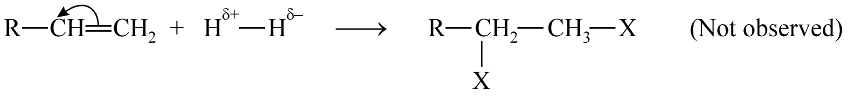
The addition of halogen acids to olefins is first order in olefin and indefinite (or third) order in halogen acid. The purpose of the other HX molecules is to polarise a HX molecule and to remove halide ion as shown in (I) and (II). Combination of a proton with π electrons gives a π complex which polarizes the π electrons pair by electromeric shift and combines with this pair to give a σ complex. The addition of halide ion then completes the addition.

When the olefin is asymmetric, the addition of halogen acid (HX) or hypohalous acid (HOX) can theoretically result in two possible products. Thus:



$$R—CH{=}CH_2 + \overset{\delta+}{H}—\overset{\delta-}{H} \longrightarrow R—\underset{\displaystyle X}{\underset{|}{CH}}—CH_3 \qquad \text{(Observed)}$$

(2-Substituted product)



$$R—CH{=}CH_2 + \overset{\delta+}{H}—\overset{\delta-}{H} \longrightarrow R—\underset{\displaystyle X}{\underset{|}{CH_2}}—CH_3—X \qquad \text{(Not observed)}$$

(1-Substituted product)

But in such reactions, it is the first type which predominates. To explain this, Markovnikov in 1869 gave a generalization which is known as **Markovnikov's rule. According to this rule** "*the negative part of the addendum (reagent which is adding) goes to the carbon atom, constituting the double bond, which is poorer in hydrogen*."

Obviously in such cases the direction of polarization of bond by electromeric shift is determined by the inductive effect (+I effect) of the alkyl group and thus it polarizes in such a manner that the electron pair shifts to carbon which is farthest from the alkyl substituent. Also the predominant direction will depend upon the formation of carbocation intermediate of greater stability. Thus out of the two

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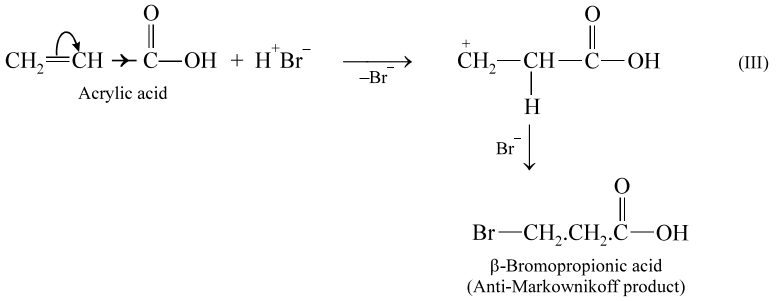
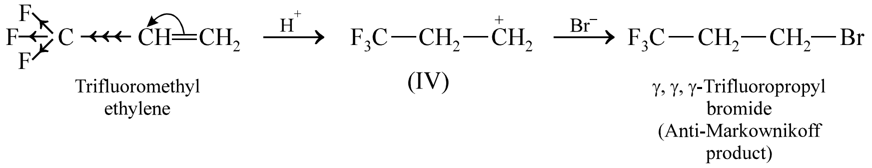
carbocations which may be formed in above reaction the (I) will be more stable as it is a secondary carbocation whereas (II) is a primary carbocation. Thus the stability of carbocation is the basis of familiar Markovnikov's rule. However, this rule is only applicable in ionic additions to hydrocarbons having only one multiple linkage. Exceptions to Markovnikov's rule are encountered in cases where factors other than hyperconjugation or inductive effect influence the relative stabilities of the two carbocations derived from one olefin. Thus addition of HBr to olefinic acids like acrylic acid proceeds as follows:

$$\underset{\text{(I)}}{\mathrm{R{-}\overset{+}{C}H{-}CH_3}} \qquad\qquad \underset{\text{(II)}}{\mathrm{R{-}CH_2{-}\overset{+}{C}H_2}}$$



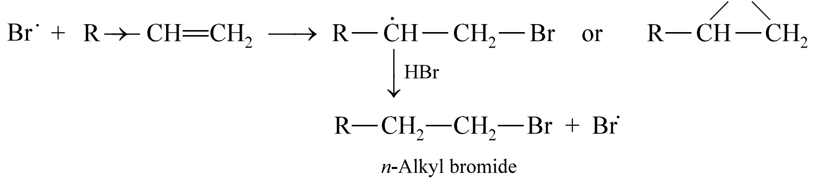
In acrylic acid both –I effect of — COOH group and –M effect (mesomeric effect) favours the formation of intermediate carbocation (III) and thus anti-Markovnikov addition takes place. Similarly in trifluoromethyl ethylene the –I effect of three fluorine atoms causes the formation of carbocation (IV) and again anti-Markovnikov addition occurs



Anti-Markovnikov addition of HBr to olefins is also observed if peroxides or elemental oxygen are present in the reaction mixture. This is known as **Kharasch effect** or **peroxide effect**. Kharasch and Mayo in 1933 found that the presence of peroxide results in the free radical addition reaction. The peroxides decompose to give free radicals which in turn abstracts hydrogen from halogen acids to give bromine free radicals. These radicals induce homolytic fission of electron pair and the bromine radical then combines with carbon atom of high electron availability. The intermediate free radical, so formed, is stabilised by the formation of bridged bromine radical, and this finally abstracts a hydrogen from HBr to give addition product.

$$\underset{\text{Dibenzoyl peroxide}}{\mathrm{C_6H_5CO.O.O.OC.C_6H_5}} \longrightarrow \underset{\text{Benzoyloxy radical}}{\mathrm{2C_6H_5CO.O^{\cdot}}}$$

$$\mathrm{C_6H_5CO.O^{\cdot} + H{-}Br \longrightarrow C_6H_5COOH + Br^{\cdot}}$$



That the reaction proceeds through a free radical mechanism can be shown by adding inhibitors, like hydroquinone which combines with free radicals, and thus decrease the rate of reaction. The free radical addition is favoured by non-polar solvents. However addition of hydrogen chloride and hydrogen iodide to olefins is not effected by peroxides.

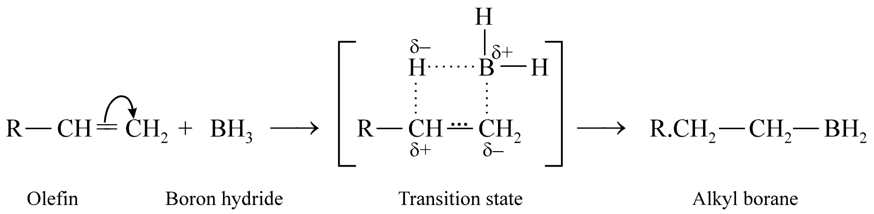
(*iii*) **Hydroboration of olefins:** Reaction of diborane (B_2H_6) with an olefinic double bond to produce alkylboranes is termed as *Hydroboration* (H.C. Brown). In the reaction diborane behaves as if it were its non-existent monomer borane (BH_3).

$$\underset{\text{Olefin}}{R—CH=CH_2} \xrightarrow{B_2H_6} \underset{\text{Alkylborane}}{R—CH_2—CH_2BH_2} \xrightarrow{R—CH=CH_2} \underset{\text{Dialkylborane}}{(R—CH_2—CH_2)_2BH}$$

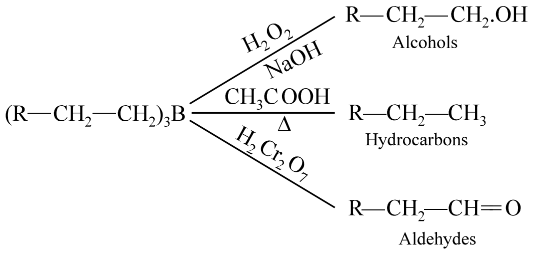
$$(R—CH_2—CH_2)BH \xrightarrow{R—CH=CH_2} \underset{\text{Trialkyl borane}}{(R—CH_2—CH_2)_3B}$$

The addition of diborane is an electrophilic attack by diborane on π electrons of olefins in accordance with Markownikoff's rule.

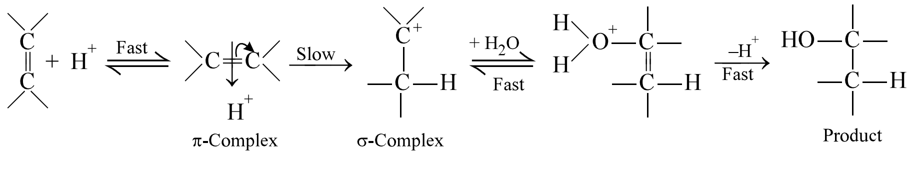
Due to the formation of a four centered transition state both hydrogen and boron become linked to the same side of the double bond leading to a *cis* addition.



Hydroboration is an important synthetic method because alkyl-boranes can be transformed into a number of useful products.

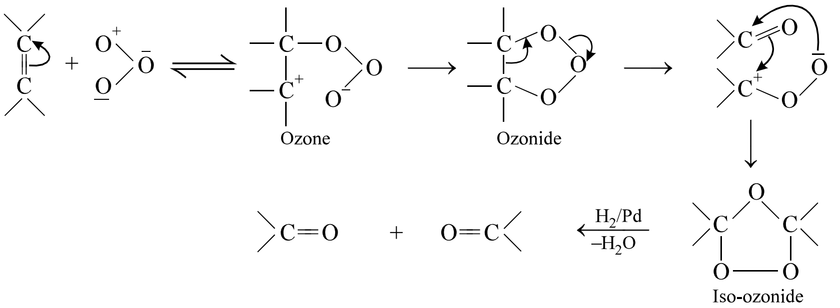


(*iv*) **Hydration of olefins:** Addition of a molecule of water to olefins is known as hydration reaction. Hydration of olefins in acidic media results in the formation of alcohols. The mechanism for hydration is the electrophilic addition at $>C=C<$.



Initially, a proton adds up at double bond to form a π complex which then changes to σ complex or intermediate carbocation. This then adds a molecule of water followed with the elimination of a proton to yield alcohols. Dilute acid used is the source of proton.

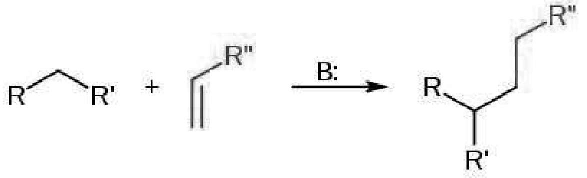
(*v*) **Ozonolysis:** Addition of ozone to olefinic linkage resulting in the formation of ozonide, which on subsequent hydrogenation gives carbonyl compounds, is known as ozonolysis. The reaction follows the electrophilic addition reaction mechanism.



Ozone may be represented as a resonance hybrid of structures $O{=}O^{+}{-}O^{-}$ and $O^{+}{-}O{-}O^{-}$. Such a polar molecule causes the electromeric shift of π electron pair and combines through its positive pole with carbon bearing the electron pair and later the negative pole also combines with the positive centre of resultant carbocation to yield the ozonide. The ozonide by a series of rearrangement steps yields iso-ozonide. The iso-ozonide is cleaved by hydrogenation or hydrolysis to >C=O compounds. Ozonolysis is used to locate the position of double bonds in olefins.

4.2.1 Michael Reaction

The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C–C bonds. Many asymmetric variants exist.



In this scheme the R and R′ substituents on the nucleophile (a Michael donor) are electron-withdrawing groups such as acyl and cyano making the methylene hydrogen acidic forming the carbanion on reaction with base ***B***:. The substituent on the activated alkene, also called a Michael acceptor, is usually a ketone making it an enone, but it can also be a nitro group.

As originally defined by Arthur Michael, the reaction is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon. A newer definition, proposed by Kohler, is the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. Some examples of nucleophiles include beta-ketoesters, malonates, and beta-cyanoesters. The resulting product contains a highly useful 1,5-dioxygenated pattern.

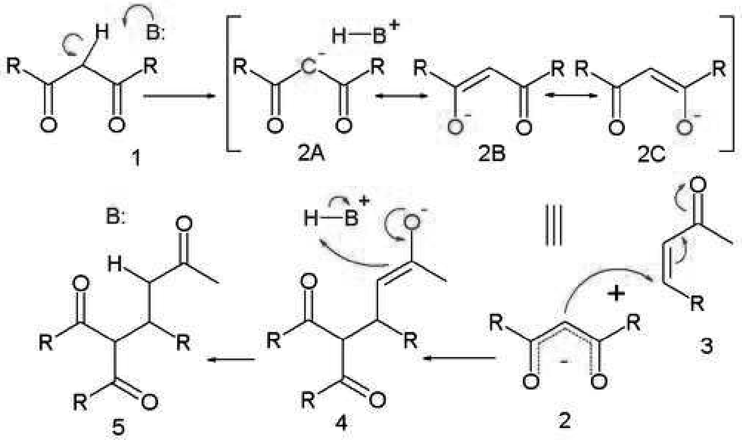
Classical examples of the Michael reaction are the reaction between diethyl malonate (Michael donor) and diethyl fumarate (Michael acceptor), that of mesityl oxide and diethyl malonate, that of diethyl malonate and methyl crotonate, that of

2-nitropropane and methyl acrylate, that of ethyl phenylcyanoacetate and acrylonitrile and that of nitropropane and methyl vinyl ketone.

The Michael addition is an important atom-economical method for diastereoselective and enantioselective C–C bond formation. A classical tandem sequence of Michael and aldol additions is the Robinson annulation.

Mechanism

In the reaction mechanism, there is 1 (with R an alkoxy group) as the nucleophile:



Deprotonation of 1 by base leads to carbanion 2 stabilized by its electron-withdrawing groups. Structures 2A to 2C are three resonance structures that can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic alkene 3 to form 4 in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate 4 to 5 is the final step.

The course of the reaction is dominated by orbital, rather than electrostatic, considerations. The HOMO of stabilized enolates has a large coefficient on the central carbon atom while the LUMO of many alpha, beta unsaturated carbonyl compounds has a large coefficient on the beta carbon. Thus, both reactants can be considered soft. These polarized frontier orbitals are of similar energy, and react efficiently to form a new carbon–carbon bond.

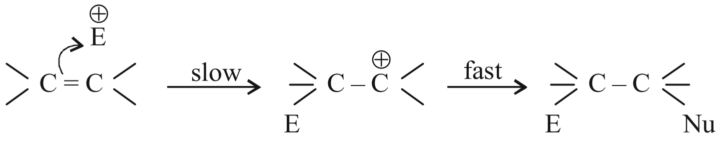
Like the aldol addition, the Michael reaction may proceed via an enol, silyl enol ether in the Mukaiyama-Michael addition, or more usually, enolate nucleophile. In the latter case, the stabilized carbonyl compound is deprotonated with a strong base (hard enolization) or with a Lewis acid and a weak base (soft enolization). The resulting enolate attacks the activated olefin with 1,4-regioselectivity, forming a carbon–carbon bond. This also transfers the enolate to the electrophile. Since the electrophile is much less acidic than the nucleophile, rapid proton transfer usually transfers the enolate back to the nucleophile if the product is enolizable; however, one may take advantage of the new locus of nucleophilicity if a suitable electrophile is pendant. Depending on the relative acidities of the nucleophile and product, the reaction may be catalytic in base. In most cases, the reaction is irreversible at low temperature.

4.2.2 Mechanistic and Stereochemical Aspects of addition Reactions Involving Electrophiles, Nucleophiles and Free Radicals

Addition to the double bond or triple bond may follow any of the following ways:

1. Electrophilic Addition Reactions

These reactions are termed as electrophilic because they are initiated by the interaction of π bond with an electrophile (electro poor species).



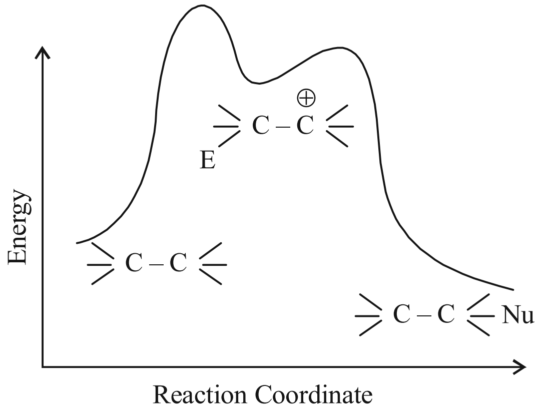
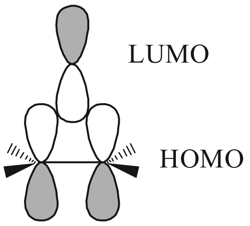


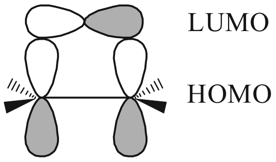
Fig. 4.1 *Energy Profile Diagram for Electrophilic Addition to Ethylenic Double Bond*

Formation of both the bonds in a concerted way required proper orientation of the HUMO/LUMO for effective mixing. In favorable cases two types of mixing is observed:

- Donation of π electrons of the alkene to the LUMO of the electrophile.

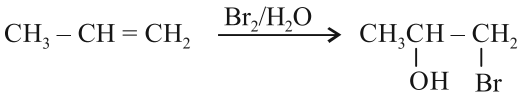


- Back donation from HOMO of electrophile to the LUMO (π*) of the alkene



Both these mixings decrease the bonding between both the carbons (i.e., changing of C=C to C-C) and create bonding between the electrophile (which here acting as a nuefeophile) and the alkene.

Addition reaction of halogens with alkene in presence of water (Holohydrin formation)

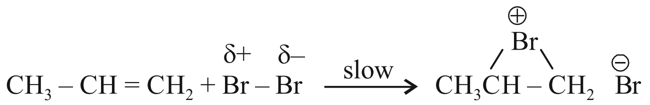


$$CH_3-CH=CH_2 \xrightarrow{Br_2/H_2O} \underset{OH}{CH_3CH}-\underset{Br}{CH_2}$$

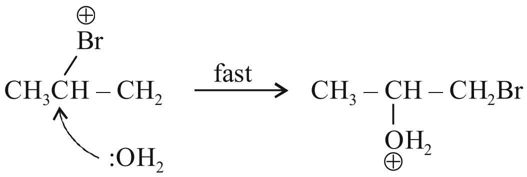
Mechanism

It includes the following process:

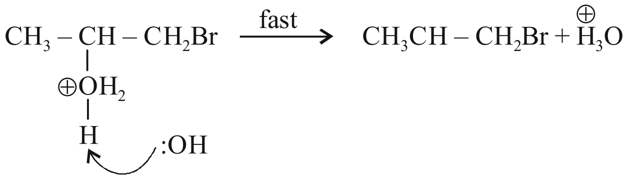
(i) Formation of bridge intermediate-Reaction of the pi bond with X to produce bridged promonium ion



(ii) Water is in excess. It acts as principle nucleophile and attacks bromonium ion formed in the first-step forming protonated halohydrin.



(iii) Protonated bromohydrin is a strong acid. It loses a proton and forms the final product, holohydrin.



2. Nucleophile Addition Reactions

An alkene is an electron-rich system so it will inherently appeal to electrophiles rather than nucleophiles. Although alkynes are less reactive than alkenes towards electrohiles, they are some-what more reactive than alkenes towards some nucleophiles.

Examples of nucleophilic addition to an alkyne is base catalysed reaction on diynes with hydrogen sulphide.

$$H_2S + :\overset{\ominus}{B} \longrightarrow \overset{\ominus}{H}S: + BB$$

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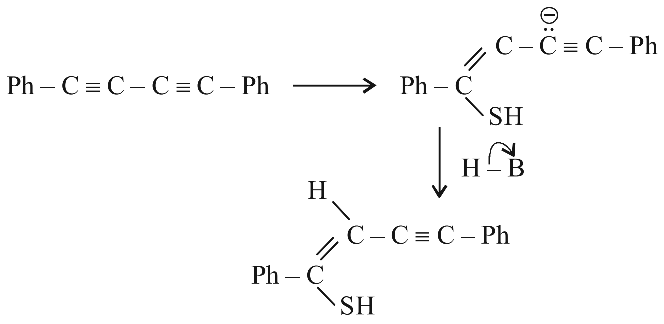
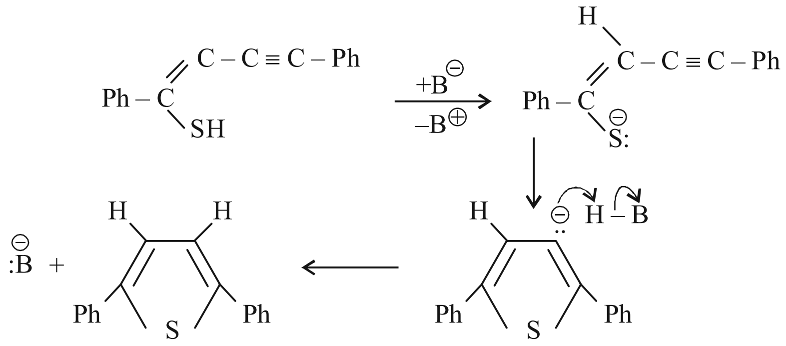


The second nucleophilic attack converts the product thiol to a thiophene drivative, the ultimate product.



Stereochemical Aspect of Addition Reaction

The attack of the reagent depending on the relative orientation of the atoms or groups that add to the carbons of the double bond.

(a) Both the reagents attacking some side-

Syn addition stereospecific

(b) Both the reagents attacking from the opposite side-

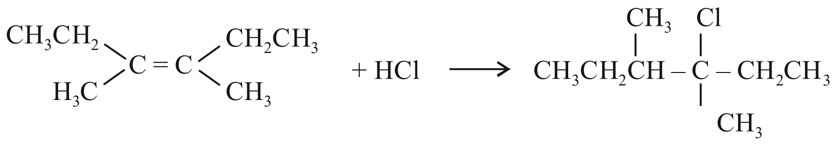
Anti addition stereospecific

(c) The reaction may be non-stereospecific is both (a) and (b) are possible.

An important principle be restated this time. The alkenes shown here are achiral but the addition products (a) and (b) have chiral centers and in many cases may exist as enantiomer stereoisomer.

In many cases the addition of bromine to the alkene is highly steneoselective reaction.

It two chirality centers are created as a result of an addition reaction that forms a carbocation intermediate, four stereoisomers can be obtained as products.

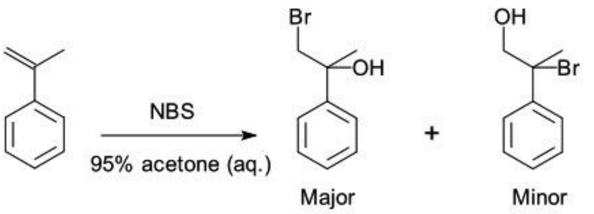


cis-3,4 -dimethyl-3-hexene 3-chloro 3,4, dimethyl hexane

4.2.3 Regioselectivity and Chemoselectivity

In chemistry, regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions. It can often apply to which of many possible positions a reagent will affect, such as which proton with a strong base will abstract from an organic molecule, or where on a substituted benzene ring a further substituent will add.

A specific example is a halohydrin formation reaction with 2-propenylbenzene.



Because of the preference for the formation of one product over another, the reaction is selective. This reaction is regioselective because it selectively generates one constitutional isomer rather than the other.

Various examples of regioselectivity have been formulated as rules for certain classes of compounds under certain conditions, many of which are named. Among the first introduced to chemistry students are Markovnikov's rule for the addition of protic acids to alkenes, and the Fürst-Plattner rule for the addition of nucleophiles to derivatives of cyclohexene, especially epoxide derivatives.

Regioselectivity in ring-closure reactions is subject to Baldwin's rules. If there are two or more orientations that can be generated during a reaction, one of them is dominant (for example, Markovnikov/anti-Markovnikov addition across a double bond) Regioselectivity can also be applied to specific reactions such as addition to pi ligands.

Regioselectivity also occurs in carbene insertions, for example in the Baeyer-Villiger reaction. In this reaction, an oxygen is regioselectively inserted near an adjacent carbonyl group. In ketones, this insertion is directed toward the carbon which is more highly substituted (i.e. according to Markovnikov's rule). For example, in a study involving acetophenones, this oxygen was preferentially inserted between the carbonyl and the aromatic ring to give acetyl aromatic esters instead of methyl benzoates.

Addition of non-symmetrical reagent (i.e. A-B where A is not equal to B) to a non-symmetrical alkene (i.e. where the groups at each end of the double bond are different), then two isomeric products that are constitutional isomers can be obtained. For example, the reaction of HCl with propene gives 1-chloropropane and 2-chloropropane.

$$CH_3\text{-}CH=CH_2 \xrightarrow{HCl} \underset{\text{major}}{CH_3\overset{\overset{Cl}{|}}{C}HCH_3} \qquad CH_3CH_2CH_2-Cl$$

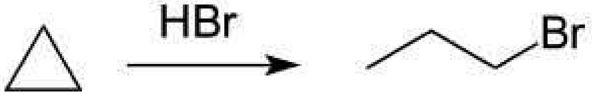
Normally, 2-chloropropane is the major product. Since one product is favoured over the other, the reaction is said to be regioselective. If 2-chloropropane were the only product then the reaction is said to be regiospecific.

Chemoselectivity is the preferential outcome of a chemical reaction over a set of possible alternative reactions. In another definition, chemoselectivity refers to the selective reactivity of one functional group in the presence of others; often this process in convoluted and protecting groups are on the molecular connectivity alone. Such predictions based on connectivity are generally considered plausible, but the physical outcome of the actual reaction is ultimately dependent on a number of factors that are practically impossible to predict to any useful accuracy (solvent, atomic orbitals, etc.).

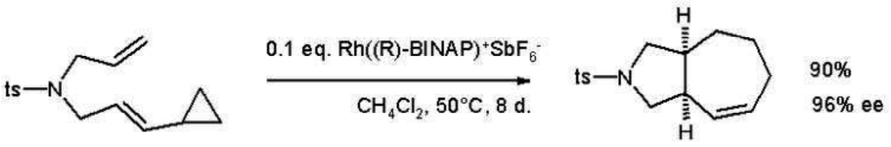
Chemoselectivity can be difficult to predict, but observing selective outcomes in cases where many reactions are plausible, is common. Examples include the selective organic reduction of the greater relative chemoselectivity of sodium borohydride reduction versus lithium aluminium hydride reduction. In another example, the compound 4-methoxyacetophenone is oxidized by bleach at the ketone group at high pH (forming the carboxylic acid) and oxidized by EAS (to the aryl chloride) at low pH.

4.2.4 Addition to Cyclopropane Ring

Cyclopropane is the cycloalkane with the molecular formula $(CH_2)_3$, consisting of three methylene groups (CH_2) linked to each other to form a ring. The small size of the ring creates substantial ring strain in the structure. The characteristic reaction equations of the cyclopropane rings are similar to that of double bonds, hence the reactivity of the cyclopropane rings can be defined with reference to C-C multiple bonds. Because of the increased p-character of its C-C bonds, cyclopropane can react like an alkene in certain cases. For instance, it undergoes hydrohalogenation with mineral acids to give linear alkyl halides. Substituted cyclopropanes also react, following Markovnikov's rule. Substituted cyclopropanes can oxidatively add to transition metals, in a process referred to as C–C activation.



Cyclopropyl groups adjacent to vinyl groups can undergo ring expansion reactions. Examples include the vinylcyclopropane rearrangement and the divinylcyclopropane-cycloheptadiene rearrangement. This reactivity can be exploited to generate unusual cyclic compounds, such as cyclobutenes, or bicyclic species, such as the cycloheptene shown below.



Actually, the cyclopropane ring system, although an alkane, shows reactivity akin to an alkene towards various electrophiles, nucleophiles or free radicals.

Cyclopropane has a triangular planar structure due to which the bond angles between carbon-carbon bonds are expected to be 60°. This is considerably less than the thermodynamically stable angle of 109.5° as per the sp^3 hybridisation of the carbon atoms. Due to this there is a considerable amount of ring strain in the cyclopropane molecule.

Activation of Cyclopropanes by Transition Metals

The first example of cyclopropane being activated by a metal complex involved the reaction of cyclopropane and hexachloroplatinic acid. This reaction produced the polymeric platinacyclobutane complex $Pt(C_3H_6)Cl_2$. The bis(pyridine) adduct of this complex was characterized by X-ray crystallography.

The electrophile $Cp^*Ir(PMe_3)(Me)OTf$ reacts with cyclopropane to give the allyl complex of the form:

$$Cp^*Ir(PMe_3)(Me)OTf + C_3H_6 \rightarrow [Cp^*Ir(PMe_3)(\eta^3\text{-}C_3H_5)]OTf + CH_4$$

4.2.5 Hydrogenation of Double and Triple Bonds and Aromatic Rings

Hydrogenation is a chemical reaction between molecular hydrogen (H_2) and another compound or element, usually in the presence of a catalyst, such as nickel, palladium or platinum. The process is commonly used to reduce or saturate organic compounds. Hydrogenation typically constitutes the addition of pairs of hydrogen atoms to a molecule, often an alkene. Catalysts are required for the reaction to be usable; non-catalytic hydrogenation takes place only at very high temperatures. **Hydrogenation** reduces **double** and **triple bonds** in **hydrocarbons**.

Hydrogenation has three key components, namely the unsaturated substrate, the hydrogen (or hydrogen source) and, invariably, a catalyst. The reduction reaction is carried out at different temperatures and pressures depending upon the substrate and the activity of the catalyst.

Steps in the Hydrogenation

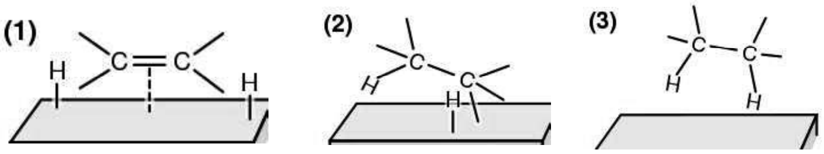
Steps in the hydrogenation of a C=C double bond at a catalyst surface, for example Ni or Pt include the following:

Step 1: The reactants are adsorbed on the catalyst surface and H_2 dissociates.

Step 2: An H atom bonds to one C atom. The other C atom is still attached to the surface.

Step 3: A second C atom bonds to an H atom. The molecule leaves the surface.

Following figures illustrate the various steps in the hydrogenation:

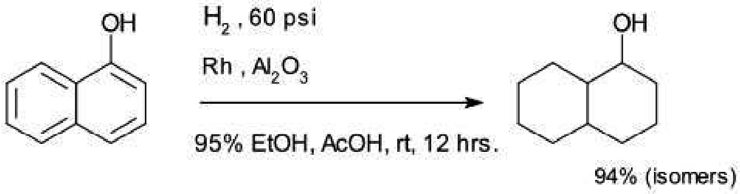


The same catalysts and conditions that are used for hydrogenation reactions can also lead to isomerization of the alkenes from cis to trans. This process of hydrogenation technology generates most of the trans-fat in foods. A reaction where bonds are broken while hydrogen is added is called hydrogenolysis, a reaction that may occur to carbon-carbon and carbon-heteroatom (oxygen, nitrogen or halogen) bonds. Some hydrogenations of polar bonds are accompanied by hydrogenolysis.

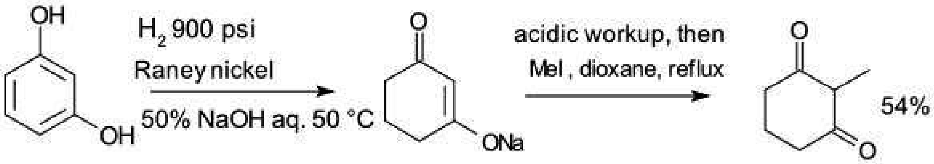
Aromatic compounds are those chemical compounds that contain one or more rings with Pi (π) electrons delocalized all the way around them. In contrast to compounds that exhibit aromaticity, aliphatic compounds lack this delocalization. The term 'Aromatic' was assigned before the physical mechanism determining aromaticity was discovered. Aromatic hydrocarbons, or arenes, are aromatic organic compounds containing solely carbon and hydrogen atoms. The configuration of six carbon atoms in aromatic compounds is called a 'Benzene Ring', after the simple aromatic compound benzene, or a phenyl group when part of a larger compound.

Benzene, C_6H_6, is the least complex aromatic hydrocarbon, and it was the first one named as such. The nature of its bonding was first recognized by August Kekulé in the 19th century. Each carbon atom in the hexagonal cycle has four electrons to share. One goes to the hydrogen atom, and one to each of the two neighbouring carbons. This leaves one electron to share with one of the two neighbouring carbon atoms, thus creating a double bond with one carbon and leaving a single bond with the other, which is why some representations of the benzene molecule portray it as a hexagon with alternating single and double bonds.

Hydrogenation of arenes create saturated rings. The compound 1-naphthol is completely reduced to a mixture of decalin-ol isomers.



The compound resorcinol, hydrogenated with Raney nickel in presence of aqueous sodium hydroxide forms an enolate which is alkylated with methyl iodide to 2-methyl-1,3-cyclohexandione.



4.2.6 Hydroboration

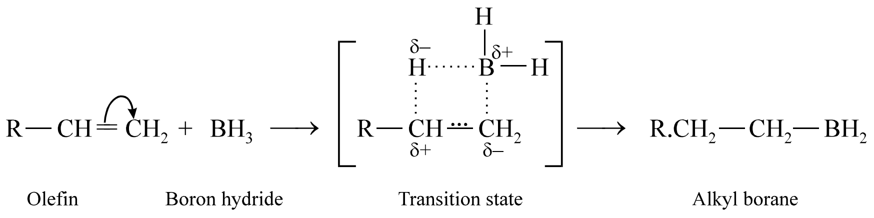
Reaction of diborane (B_2H_6) with an olefinic double bond to produce alkylboranes is termed as *Hydroboration* (H.C. Brown). In the reaction diborane behaves as if it were its non-existent monomer borane (BH_3).

$$\underset{\text{Olefin}}{R—CH=CH_2} \xrightarrow{B_2H_6} \underset{\text{Alkylborane}}{R—CH_2—CH_2BH_2} \xrightarrow{R—CH=CH_2} \underset{\text{Dialkylborane}}{(R—CH_2—CH_2)_2BH}$$

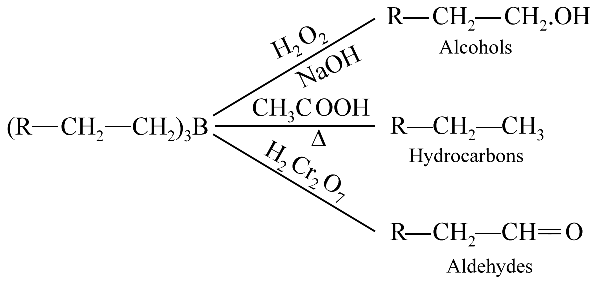
$$(R—CH_2—CH_2)BH \xrightarrow{R—CH=CH_2} \underset{\text{Trialkyl borane}}{(R—CH_2—CH_2)_3B}$$

The addition of diborane is an electrophilic attack by diborane on π electrons of olefins in accordance with Markownikoff's rule.

Due to the formation of a four centered transition state both hydrogen and boron become linked to the same side of the double bond leading to a *cis* addition.



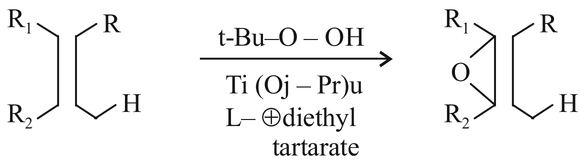
Hydroboration is an important synthetic method because alkyl-boranes can be transformed into a number of useful products.



4.2.7 Sharpless Asymmetric Epoxidation

It is one of the most important reactions discovered in last 30 years and for this reaction Prof. Barry Sharpless received Noble Prize in 2001.

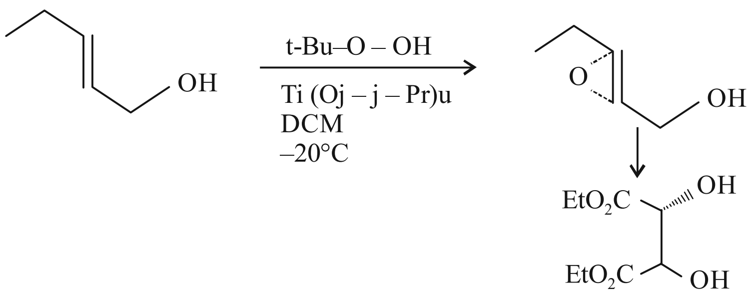
The Sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2, 3 epoxy alcohol from primary and secondary allyl alcohol.



Sharpless's asymmetric epoxidation converts a double bond of allelic alcohol into epoxide using a transition metal catalyst, Titanium tetra isopropoxide and enantiometrically pure diethyl tartrate.

Mechanism of Sharpless Asymmetric Eposidation

Reagents from an asymmetric complex in which allylic alcohol exposes one side of its double bond towards the oxygen to be transfered.

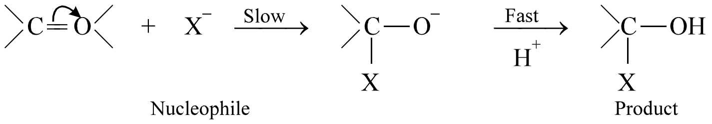


Check Your Progress

1. Write the examples of electrophilic addition reactions.
2. What is the effect of electron donating substituents on the rate of reactions?
3. Define the peroxide effect.
4. What is used to locate the position of double bonds in olefins?
5. What is regioselectivity?
6. Define chemoselectivity.
7. What is Sharpless asymmetric epoxidation?

4.3 ADDITION TO CARBON-HETERO MULTIPLE BOND

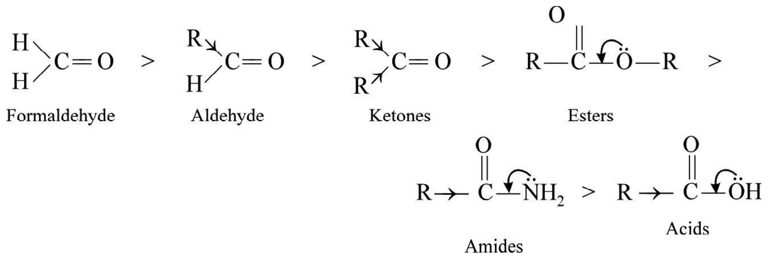
Unlike the carbon to carbon multiple bonds, the carbon to oxygen double bonds are highly polarized because of greater electronegativity of oxygen atom. The π electrons are shifted towards oxygen atom by simple electromeric effect at the requirement of the attacking reagent. The carbon thus acquires a positive charge and becomes more susceptible to attack by electron rich nucleophiles. On the other hand oxygen is attacked by electron deficient electrophiles completing the addition reaction. The product wherever possible undergoes elimination of water molecules to result in the double bond (see condensation reactions) formation.



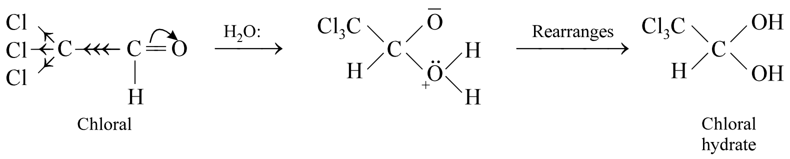
The above scheme shows a simple nucleophilic addition of a nucleophile X^- to $> C{=}O$ groups. At the approach of X^- the π electrons are shifted towards oxygen by electromeric shift. The nucleophile combines with the positively charged carbon to yield anion which then takes up a proton or electrophile at oxygen to give the end product.

Structure and reactivity

Since the nucleophilic addition involves the addition of nucleophile to positively charged carbon, the reactivity of this carbon depends on the magnitude of this charge. The order of reactivity of some carbonyl compounds decreases in the order given below:



The electron donating groups (with +I effect) reduce the reactivity of the positively charged carbon in the above examples which is reflected in the order shown above. The resonance effect due to lone pair at adjacent hetero atoms as in amide etc., also contribute to decreased reactivity. The presence of bulky groups also decrease the reactivity of the positively charged carbon due to crowding around the carbon. On the other hand electron withdrawing group (with –I effect) tend to increase its reactivity. Thus chloral ($CCl_3.CHO$) because of the –I effect due to three chlorine atoms is highly susceptible to nucleophilic additions—so much so that it can react with a very weak nucleophile like water to form a stable compound chloral hydrate.



Thus percentage hydration gives a complete idea regarding the reactivity of the >C═O group. The percentage hydration of some compounds is as follows:

Hydration %

$HCHO$	CH_3CHO	CH_3COCH_3
99	58	0

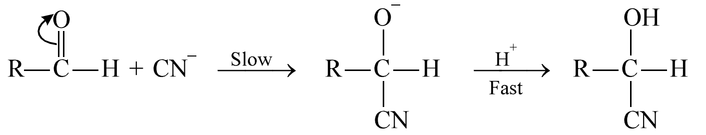
Polar solvents, acids and bases catalyze nucleophilic addition reactions.

Applications

Some of the applications are as follows:

(1) **Addition of HCN and $NaHSO_3$ (sodium bisulphite) to carbonyl group:** The addition of HCN and $NaHSO_3$ to >C═O group is a simple nucleophilic addition. HCN combines with >C═O group in the presence of basic catalysts to give corresponding cyanohydrin. The base helps in dissociating HCN to H^+ and CN^- ions. At the approach of CN^- the π electrons undergo electromeric shift towards oxygen. The cyanide ion then combines with carbon of the > C═O group to give an anion (I) which then combines with an electrophile H^+ to give cyanohydrin.

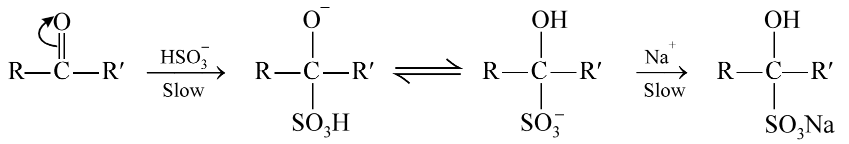
$$HCN \rightleftharpoons H^+ + CN^-$$



Aldehyde Anion II Cyanohydrin

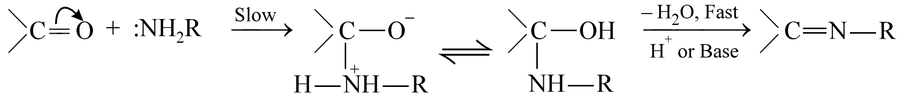
Addition of sodium bisulphite to carbonyl group occurs in the absence of acids or bases because sodium bisulphite readily ionises to give bisulphite anion nucleophile which then adds to carbon of carbonyl group resulting in anion (I). The (I) then rearranges by migration of a hydrogen from —SO_3H group to negatively charged oxygen to give anion (II) which then combines with sodium ion to give bisulphite addition product.

$$NaHSO_3 \rightleftharpoons Na^+ + HSO_3^-$$



I II Bisulphite adduct

(2) **Addition of ammonia and amine derivatives to carbonyl group:** Ammonia and its derivatives like R—NH_2 (amines), NH_2OH (hydroxylamine), $NH_2.CO.NH.NH_2$ (semicarbazide), and $NH_2.NH_2$ (hydrazine) etc., add to carbonyl group by a nucleophilic addition mechanism. The addition is catalyzed by acids and also by bases. The following general mechanism may be written for these reactions.



Amine derivative Intermediate Product

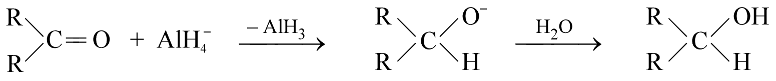
Amine derivatives act as nucleophiles because of the presence of the lone pair of electrons at nitrogen. At the approach of these reagents, π electron pair is shifted to oxygen by electromeric effect and the lone pair of nitrogen co-ordinates with electron deficient carbon to give a dipolar intermediate. This then rearranges by migration of proton from nitrogen to oxygen carrying the negative charge. Finally the addition is followed by elimination of a molecule of water to result in a carbon to nitrogen double bond.

The reaction of ammonia is different with different carbonyl compounds. Thus formaldehyde with ammonia gives hexamethylene tetramine $(CH_2)_6N_4$; acetaldehyde and other aldehydes give aldehyde ammonia $RCH(OH)NH_2$; whereas ketones usually undergo condensation reaction to give complex products.

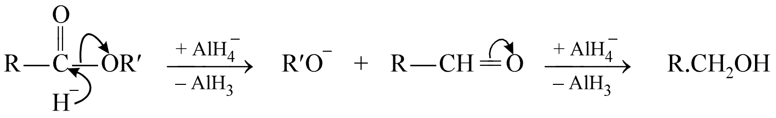
Products of some of these reactions like oximes, phenyl hydrazones, semicarbazides etc., are useful derivatives of carbonyl compounds helpful in their identifications.

(3) **Hydride transfer reaction:** Reductions of carbonyl compounds by $LiAlH_4$ (lithium aluminium hydride) or $NaBH_4$ (sodium borohydride) are in essence

nucleophilic additions of a hydride ion to the carbon atom. $LiAlH_4$ dissociates to give AlH_4^- which acts as a carrier of hydride ion. The reduction of ketones and esters may be represented as given below:



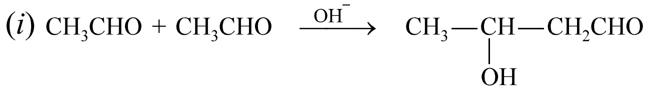
Ketone Secondary alcohol



Ester Aldehyde Primary alcohol

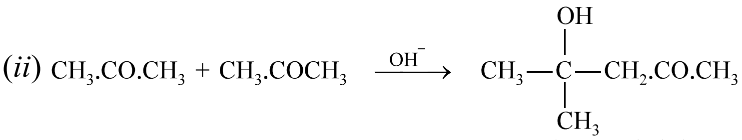
These reagents react with hydroxylic solvents so the reduction is carried out in either ether or tetrahydrofuran (THF). The reaction is specific for the reduction of aldehydes, ketones, acids and esters to alcohols.

(4) **Aldol condensation:** When aldehydes and ketones having α-hydrogen atoms are treated with alkali, they undergo self-addition between two molecules to form a β-hydroxy aldehyde or β-hydroxy ketone (known as aldols). This addition is usually followed by elimination of a water molecule resulting in overall condensation reaction. The reaction is therefore known *as Aldol condensation reaction.* Essentially this is a nucleophilic addition of a carbanion, generated by the abstraction of a proton from α-position of an aldehyde or ketone by a base, to the carbonyl group. The reaction can occur between two or more molecules of same or different aldehyde or ketone, and between one or more molecules each of an aldehyde and a ketone. Also an aldehyde or ketone having no α-hydrogen atom may condense with another aldehyde or ketone having α-hydrogen atoms. Some examples are given below to illustrate this point.



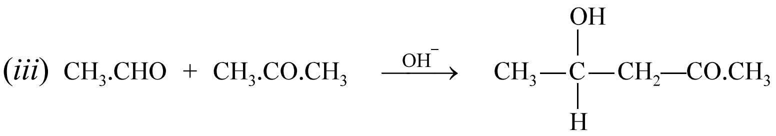
$$(i)\ CH_3CHO + CH_3CHO \xrightarrow{OH^-} CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2CHO$$

Acetaldehyde (2 moles) β-Hydroxy butyraldehyde (Aldol)



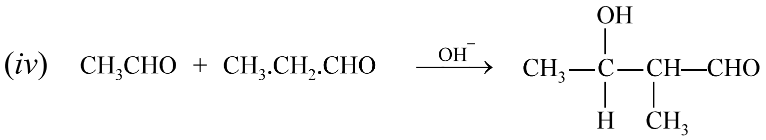
$$(ii)\ CH_3.CO.CH_3 + CH_3.COCH_3 \xrightarrow{OH^-} CH_3-\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}-CH_2.CO.CH_3$$

Diacetone alcohol
(4-Hydroxy-4-methyl-2-pentanone)



$$(iii)\ CH_3.CHO + CH_3.CO.CH_3 \xrightarrow{OH^-} CH_3-\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle H}{\underset{|}{C}}}}-CH_2-CO.CH_3$$

Acetaldehyde Acetone 4-Hydroxyl-2-pentanone



$$(iv)\quad CH_3CHO + CH_3.CH_2.CHO \xrightarrow{OH^-} CH_3—\overset{OH}{\underset{H}{C}}—\underset{CH_3}{CH}—CHO$$

Acetaldehyde Propionaldehyde α-Methyl β-hydroxy butyraldehyde

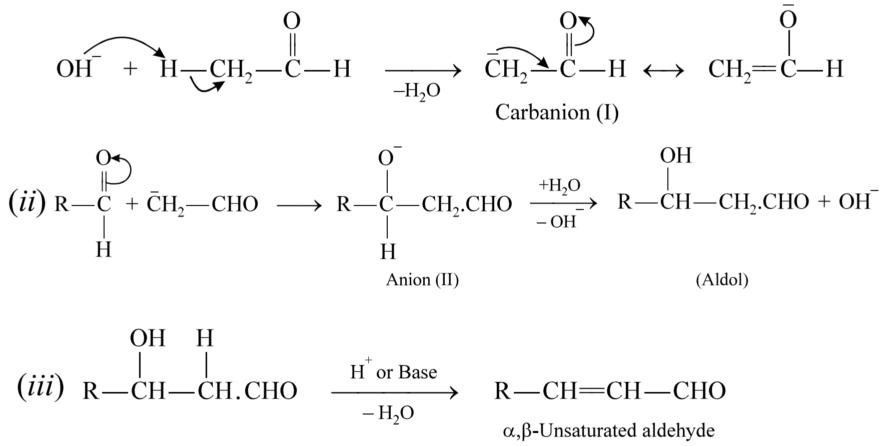
NOTES

As seen in the above examples, in crossed aldol condensations the carbonyl group of aldehydes is more reactive than carbonyl group of ketones. Thus the aldol formation involves carbonyl group of aldehyde and α-hydrogen of ketone. Similarly when condensation is between two aldehydes the α-hydrogen comes from aldehyde having bigger alkyl group.

Reaction between two molecules of an aldehyde, not having α-hydrogen atoms, in presence of alkali, results in Cannizzaro's reaction. Thus formaldehyde reacts with NaOH to form a mixture of methyl alcohol and sodium formate.

Generally accepted mechanism for aldol condensation may be written as below:

$$(i)\quad NaOH \rightleftharpoons Na^+ + OH^-$$



$$OH^- + H—CH_2—\overset{O}{\overset{\|}{C}}—H \xrightarrow[-H_2O]{} \bar{C}H_2—\overset{O}{\overset{\|}{C}}—H \longleftrightarrow CH_2{=}\overset{\bar{O}}{\overset{|}{C}}—H$$

Carbanion (I)

$$(ii)\quad R—\overset{O}{\overset{\|}{\underset{H}{C}}} + \bar{C}H_2—CHO \longrightarrow R—\overset{O^-}{\underset{H}{C}}—CH_2.CHO \xrightarrow[-OH^-]{+H_2O} R—\overset{OH}{CH}—CH_2.CHO + OH^-$$

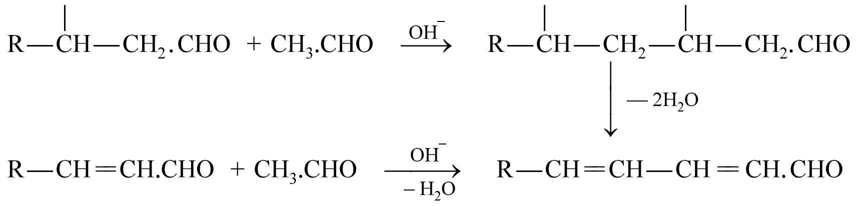
Anion (II) (Aldol)

$$(iii)\quad R—\overset{OH}{CH}—\overset{H}{CH}.CHO \xrightarrow[-H_2O]{H^+ \text{ or Base}} R—CH{=}CH—CHO$$

α,β-Unsaturated aldehyde

In the first step the alkali gives OH^- ions which abstracts a proton from the π-position of the carbony1 group to form a carbanion (I). This carbanion attacks the carbony1 group of other molecule causing electromeric shift of π electrons and adds to the electron deficient carbon of the carbony1 group giving anion (II). This anion then takes up a proton from water to form aldol. Usually the aldol undergoes dehydration reaction (elimination of a molecule of water) to form α,β-unsaturated aldehyde or ketone in presence of acids and bases.

However the reaction does not stop here because the aldol is still having a free carbony1 group. It can add another molecule of aldehyde or ketone having α-hydrogen atoms to give a more complex aldol. Thus:



$$R—\overset{OH}{CH}—CH_2.CHO + CH_3.CHO \xrightarrow{OH^-} R—\overset{OH}{CH}—CH_2—\overset{OH}{CH}—CH_2.CHO$$

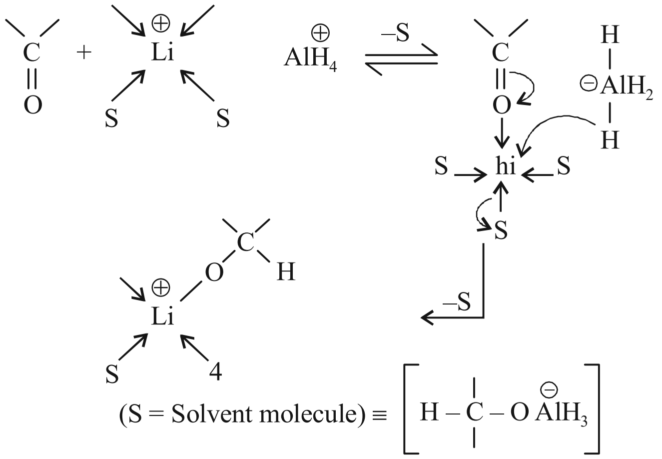
$$\downarrow —2H_2O$$

$$R—CH{=}CH.CHO + CH_3.CHO \xrightarrow[-H_2O]{OH^-} R—CH{=}CH—CH{=}CH.CHO$$

4.3.1 Mechanism of Metal Hybrid Reduction of Saturated and Unsaturated Carbonyl Compounds, Acids, Esters and Nitriles

Most reductions of carbonyl compounds one done with regents that transfer hydride ions. The advantage of there metal hydrides over other reducing reagents is that they contain of hydrogen in small amount of regent.

Isolated and conjugated double bonds are not generally affected by metal hydrides. Functional group is selectively attacked in the presence of a different functional group the reaction is said to be chemioselective.



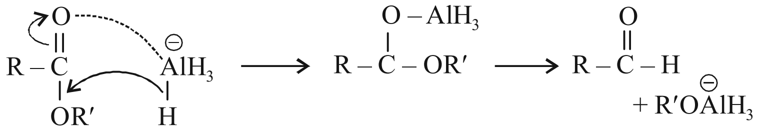
Activation of carbonyl group by co-ordination with a metal cation is probably involved in most condition.

Evidence: The above mechanism suggests that cation plays an essential role which was proved by the fact that when Li was effectively removed from Li AlHy by addition of crown ether the reaction did not take place.

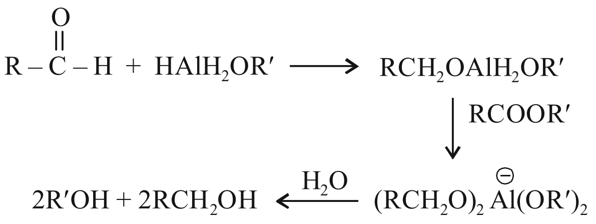
Reduction of Carboxylic Acids and Esters

In the reduction of carboxylic acid, the first reduction product is an alkoxide from which the alcohol is liberated by hydrolysis.

(a) Ist phase step – Conversion of an ester into aldehyde which is an elimination reaction



(b) IInd phase step – Conversion of aldehyde to primary alcohol which involves hydrides transfer



$$R-\overset{\overset{O}{\|}}{C}-H + HAlH_2OR' \longrightarrow RCH_2OAlH_2OR'$$

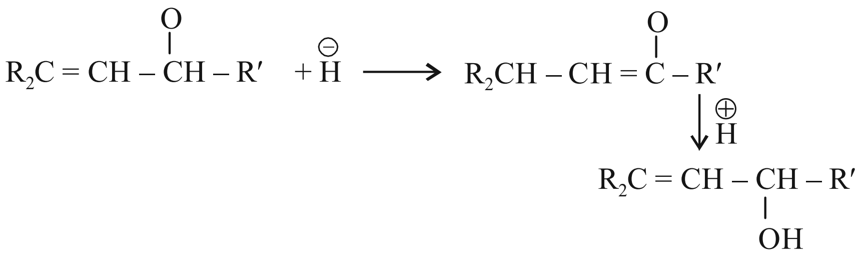
$$\downarrow RCOOR'$$

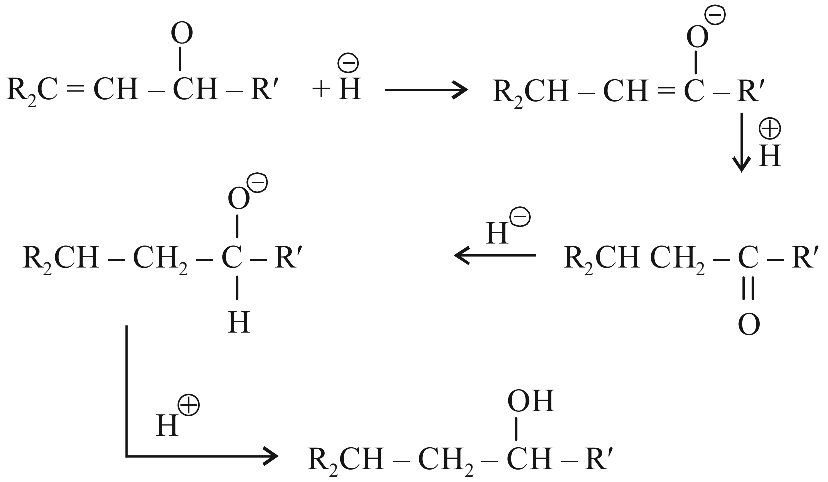
$$2R'OH + 2RCH_2OH \xleftarrow{H_2O} (RCH_2O)_2\overset{\ominus}{Al}(OR')_2$$

Reduction of α-β Unsaturated Carbonyl Compounds

The reduction of α-β Unsaturated carbonyl compounds has selectivity as it can occur at the carbonyl group giving ally's alcohol or at the double bond giving a saturated ketone which by a second reduction can be converted into saturated alcohol.

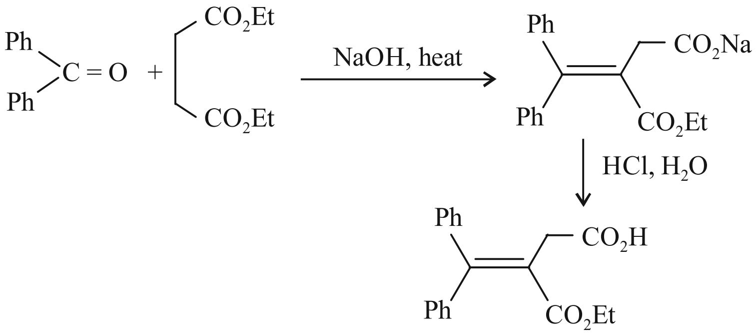
If hydride is added to carbonyl group, allyle alcohol is obtained which is not susceptible for further reduction.



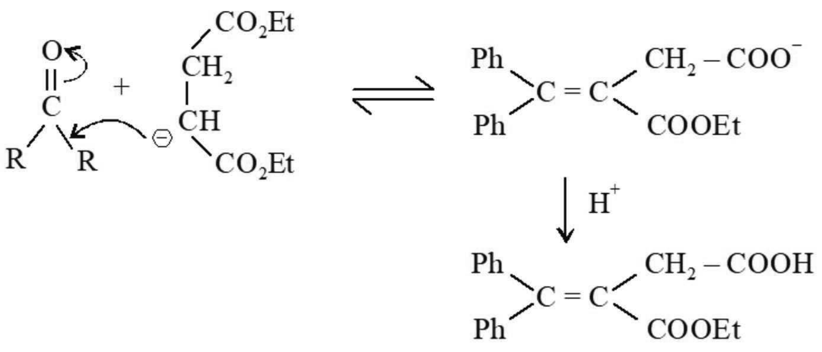


Stobbe condensation: The condensation reaction of aldehyde or ketone with succinic ester in the presence of basic catalyst like NaOH to form alkylidene succinic acid is known as stable condensation.

Mixture of ketone, diethyl succinate and ether solution of sodium ethoxids is allowed to stand at room temperature for several days and then the product is recovered by acidification.



Mechanism

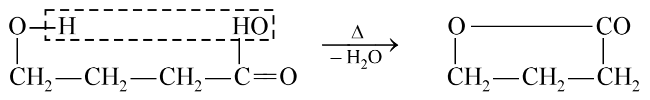


4.4 MECHANISM OF CONDENSATION REACTION

The term condensation has been used to describe a wide variety of organic reactions resulting in the lengthening of the carbon skeleton of the molecule. However it may be defined as *a reaction (through functional groups) between two or more molecules of the same or different compounds resulting in the formation of new carbon to carbon bonds with or without the elimination of simple molecules like water, alcohol, metallic halides etc.* However, the term condensation has been used rather loosely in organic chemistry and often includes the formation of other bonds besides carbon to carbon.

There can be two types of condensation reactions:

(1) **Intramolecular Condensation:** When the two functional groups of the *same molecule* react to eliminate a simple molecule the reaction is known as Intramolecular condensation for example, formation of a γ-lactone from γ-hydroxybutyric acid.



γ-Hydroxybutyric acid γ-Butyrolactone

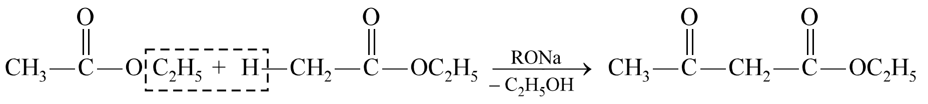
(2) **Intermolecular Condensation:** The condensation reaction between two molecules of the *same* or *different compounds* is known as Intermolecular condensation. Thus two molecules of acetaldehyde condense in presence of sodium hydroxide to give aldol.

$$CH_3CHO + H.CH_2CHO \xrightarrow{NaOH} \underset{\text{Aldol}}{CH_3CH(OH)CH_2CHO}$$

The reaction is called aldol condensation.

A large number of intermolecular condensation reactions are obseverd between similar or different carbonyl compounds. Important reactions of this class are Aldol condensation, Claisen condensation, Benzoin condensation and Perkin reaction.

(*i*) Claisen Condensation



$$CH_3-\overset{\overset{O}{\|}}{C}-O\boxed{C_2H_5 + H}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5 \xrightarrow[-C_2H_5OH]{RONa} CH_3-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-OC_2H_5$$

Ethyl acetate (2 moles) Ethyl acetoacetate (Acetoacetic ester or β-Keto ester)

NOTES

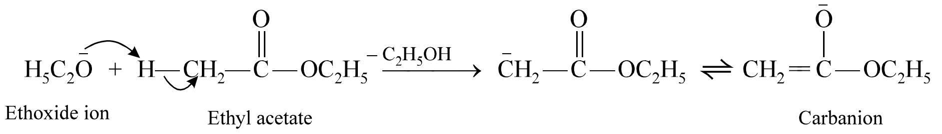
Claisen (1887) observed that when esters having hydrogens at α-carbon atoms are treated with sodium alkoxides, they are transformed to β-keto esters. Such condensations between two molecules of esters having α-hydrogen atoms in the presence of a base, resulting in the formation of a compound having reactive methylene group[1], are known as Claisen condensation reactions. The following mechanism has been suggested for the reaction:

(*a*) Reaction of sodium with ethyl alcohol gives ethoxide ion which acts as a base:

$$2C_2H_5OH + 2Na \longrightarrow 2C_2H_5ONa + H_2$$

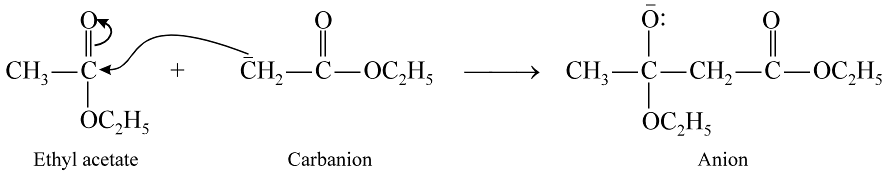
$$\underset{}{C_2H_5ONa} \rightleftharpoons \underset{\text{Ethoxide ion}}{C_2H_5O^-} + Na^+$$

(*b*) The ethoxide ion, so formed, abstracts a proton form the α-carbon of the esters like ethyl acetate to give a carbanion



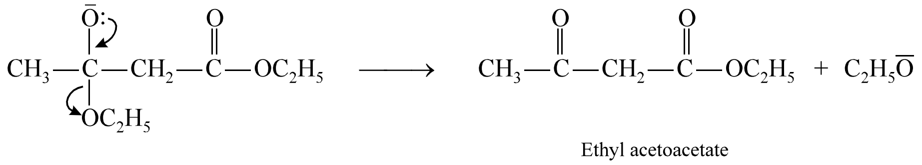
$$\underset{\text{Ethoxide ion}}{H_5C_2\bar{O}} + \underset{\text{Ethyl acetate}}{H-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5} \xrightarrow{-C_2H_5OH} \bar{C}H_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \rightleftharpoons \underset{\text{Carbanion}}{CH_2=\overset{\bar{O}}{\overset{|}{C}}-OC_2H_5}$$

(*c*) This carbanion induces the electromeric shift in the carbonyl group of the other ester molecule. As a result of this shift, the carbon atom of carbonyl group acquires a positive charge and the carbanion combines with it to give an anion.



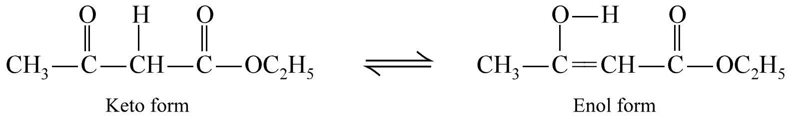
$$\underset{\text{Ethyl acetate}}{CH_3-\overset{O}{\overset{\|}{\underset{OC_2H_5}{\underset{|}{C}}}}} + \underset{\text{Carbanion}}{\bar{C}H_2-\overset{O}{\overset{\|}{C}}-OC_2H_5} \longrightarrow \underset{\text{Anion}}{CH_3-\overset{\bar{O}:}{\overset{|}{\underset{OC_2H_5}{\underset{|}{C}}}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5}$$

(*d*) As the attacking reagent, i.e., carbanion is removed by addition, the electron pair which has shifted to oxygen because of electromeric effect, reverts back to form a double bond and the ethoxide ion is expelled with its pair of the electrons.



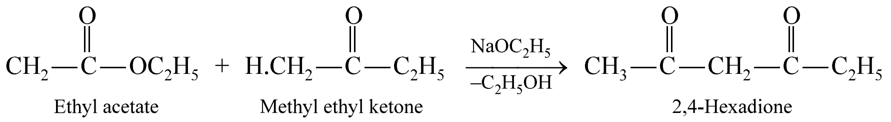
$$CH_3-\overset{\bar{O}:}{\overset{|}{\underset{OC_2H_5}{\underset{|}{C}}}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5 \longrightarrow \underset{\text{Ethyl acetoacetate}}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5} + C_2H_5\overline{O}$$

On acidification with acetic acid it is converted to a tautomeric mixture of the two forms of ethyl acetoacetate.



$$\underset{\text{Keto form}}{CH_3-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5} \rightleftharpoons \underset{\text{Enol form}}{CH_3-\overset{O-H}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OC_2H_5}$$

Claisen condensation can be carried out between different esters also when a mixture of different products is obtained. The reaction may also be extended to the condensations between esters and carbonyl compounds like ketones. Thus:

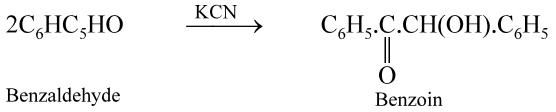


$$\underset{\text{Ethyl acetate}}{CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5} + \underset{\text{Methyl ethyl ketone}}{H.CH_2-\overset{O}{\overset{\|}{C}}-C_2H_5} \xrightarrow[-C_2H_5OH]{NaOC_2H_5} \underset{\text{2,4-Hexadione}}{CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-C_2H_5}$$

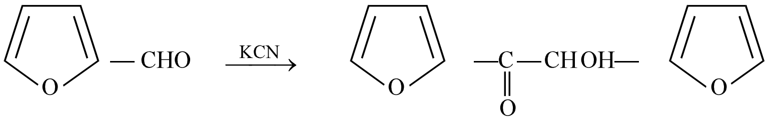
NOTES

(*ii*) Benzoin condensation

Aromatic aldehydes like benzaldhyde, furfural, etc., when treated with ethanolic potassium cyanide and refluxed, undergo dimerization to form keto-alcohols. Since benzaldehyde forms benzoin by condensation of its two melecules, the reaction is known as benzoin condensation. Furfural, on benzoin condensation, forms furoin.

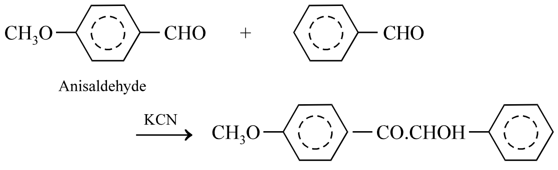


$$\underset{\text{Benzaldehyde}}{2C_6HC_5HO} \xrightarrow{KCN} \underset{\text{Benzoin}}{C_6H_5.\underset{\underset{O}{\|}}{C}.CH(OH).C_6H_5}$$



Furfural Furoin

Nitro and hydroxy benzaldehydes and cinnamaldehyde do not undergo benzoin condensation, while halo- and *p*-dimethylamino benzaldehydes give only poor yields of benzoins. Though anisaldehyde is unreactive towards self-condensation, it, however, forms 4-methoxy benzoin in 70 per cent yield, when condensed with benzaldehyde:

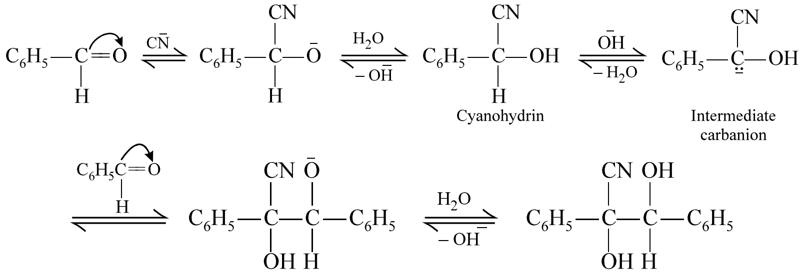


4-Methoxy benzoin

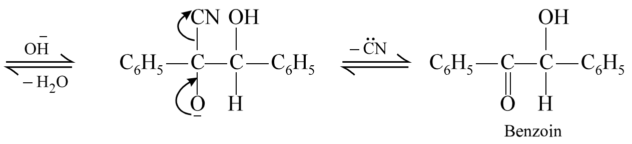
Relatively only a few examples of benzoin type of condensation are known in aliphatic compounds. When there are α-hydrogen atoms, the aldol condensation proceeds in the presence of basic cyanide in forming analogous compounds, R.CO.CHOH.R, known as *acyloins*, which are usually prepared by the condensation of esters in an inert medium in the presence of metallic sodium. Sodium salts of enediols on subsequent hydrolysis form acyloins.

Mechanism

Lapworth was the first to point out that the reaction is not a simple aldol type condensation, as it is not catalysed by ordinary bases but rather specifically by alkali cyanides. He proposed that the first step in the benzoin condensation is the addition of cyanide ion to the aldehyde, followed by proton transfer to form cyanohydrin. Since the cyanohydrin contains hydrogen at-α carbon to the cyanide group, it can undergo base catalysed addition to the carbony1 group of a second aldehyde molecule. Cyanohydrin of benzoin thus formed then loses a molecule of HCN to form benzoin.

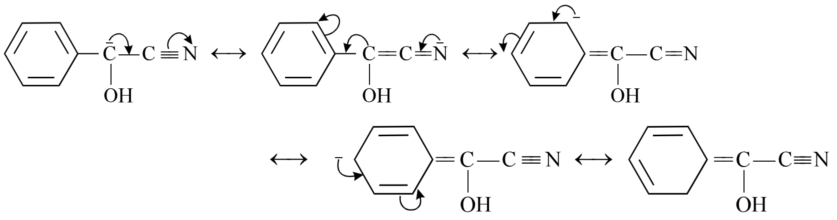


Cyanohydrin of benzoin



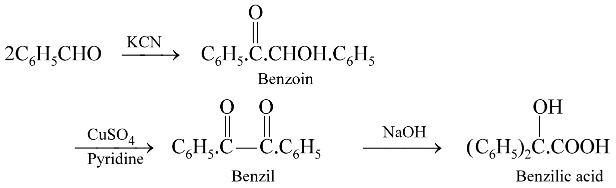
Benzoin

The carbanion intermediate is resonance stabilised and is formed preferentially from the cyanohydrin.



Applications

Benzoin condensation is used for the preparation of keto-alcohols of the aromatic series of the type of benzoin. It is also used as the first step in the preparation of benzil and benzilic acid from benzaldehyde.



$$2C_6H_5CHO \xrightarrow{KCN} \underset{\text{Benzoin}}{C_6H_5.\overset{O}{\overset{\|}{C}}.CHOH.C_6H_5}$$

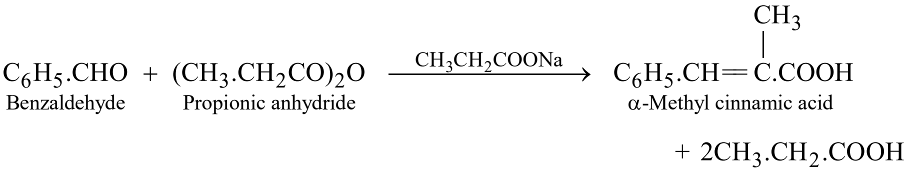
$$\xrightarrow[\text{Pyridine}]{CuSO_4} \underset{\text{Benzil}}{C_6H_5.\overset{O}{\overset{\|}{C}}—\overset{O}{\overset{\|}{C}}.C_6H_5} \xrightarrow{NaOH} \underset{\text{Benzilic acid}}{(C_6H_5)_2\overset{OH}{\overset{|}{C}}.COOH}$$

(*iii*) Perkin Reaction

In 1867 W.H. Perkin observed that when aromatic aldehydes are heated with the anhydride of an aliphatic acid in the presence of the sodium salt of the same acid, an α, β, unsaturated acid is formed. The reaction is known as *Perkin reaction* and is shown mainly by aromatic aldehydes. For example benzaldehyde, when heated with acetic anhydride in the presence of sodium acetate, forms cinnamic acid.

$$\underset{\text{Benzaldehyde}}{C_6H_5CHO} + \underset{\text{Acetic anhydride}}{(CH_3CO)_2O} \xrightarrow[170–175°C]{CH_3COONa} \underset{\text{Cinnamic acid}}{C_6H_5.CH{=}CH.COOH} + \underset{\text{Acetic acid}}{2CH_3COOH}$$

Similarly



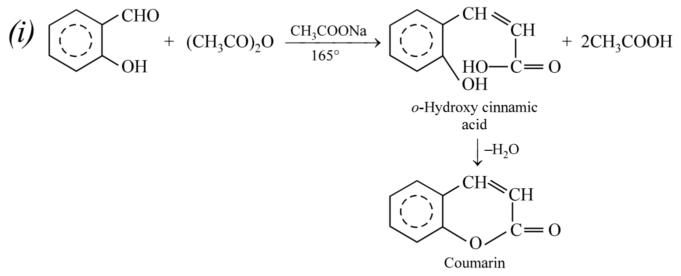
$$\underset{\text{Benzaldehyde}}{C_6H_5.CHO} + \underset{\text{Propionic anhydride}}{(CH_3.CH_2CO)_2O} \xrightarrow{CH_3CH_2COONa} \underset{\alpha\text{-Methyl cinnamic acid}}{C_6H_5.CH{=}\overset{CH_3}{\overset{|}{C}}.COOH} + 2CH_3.CH_2.COOH$$

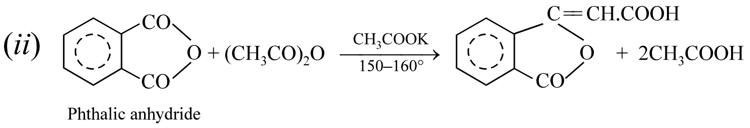
Substituted benzaldehydes also undergo Perkin reaction and it has been noticed that substituents affect the yields of substituted cinnamic acids. The electron-withdrawing substituents increase the yield of the substituted cinnamic acids, while electron-releasing groups decrease it. Table 4.1 illustrates the point.

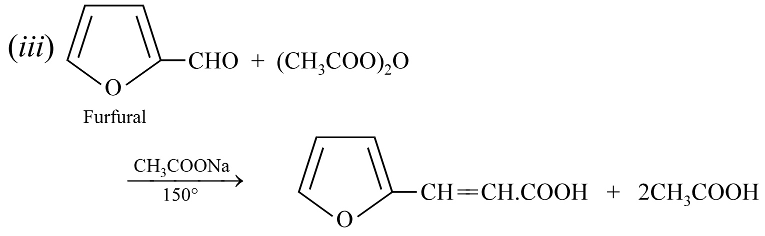
Table 4.1 *Yield of the Substituted Cinnamic Acids*

Substituent	*Yield %*	*Substituent*	*Yield %*
H	45–50		
2-Chloro	71	4-Nitro	82
3-Chloro	63	2-Methyl	15
4-Chloro	52	3-Methyl	23
2-Nitro	75	4-Methyl	33
3-Nitro	75	2,6-Dimethyl	0

Salicylaldehyde, phthalic anhydride and furfural also undergo Perkin reaction.



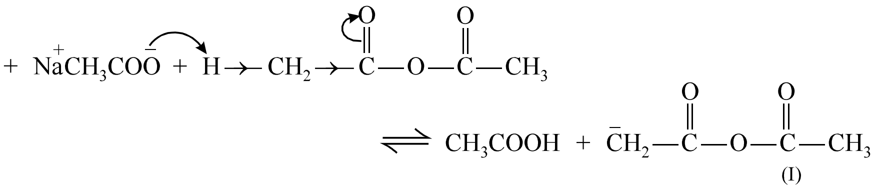




Mechanism

Perkin believed that it is an aldol type addition of anhydride to aromatic aldehydes, whereas Fittig argued that it is the carboxylate anion that adds to aldehydes. However, the present view is that carboxylate anion abstracts a proton from the α-carbon of the anhydride forming a carbanion I. This carbanion undergoes nucleophilic addition at carbonyl carbon of the aldehyde. The anion (II) so formed takes up a proton to form a hydroxy compound (III), which first undergoes dehydration in the presence of anhydride and then in the presence of acid, hydrolyses to form an α, β-unsaturated acid.

(*i*) $CH_3COONa \rightleftharpoons CH_3CO\bar{O}$

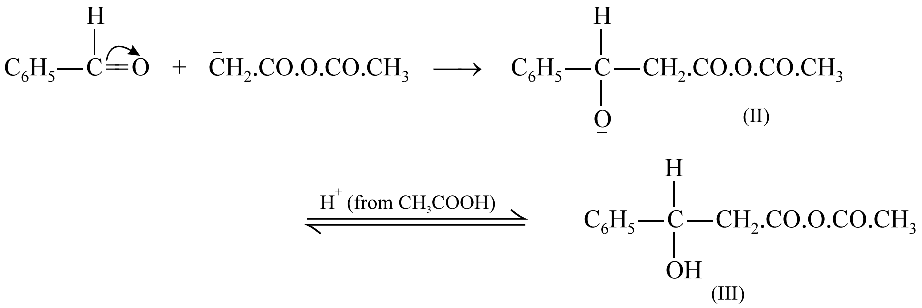


$$+\ \overset{+}{Na}CH_3CO\bar{O} + H \rightarrow CH_2 \rightarrow \overset{\overset{O}{\|}}{C} - O - \overset{\overset{O}{\|}}{C} - CH_3$$

$$\rightleftharpoons CH_3COOH + \bar{C}H_2 - \overset{\overset{O}{\|}}{C} - O - \overset{\overset{O}{\|}}{C} - CH_3$$

(I)

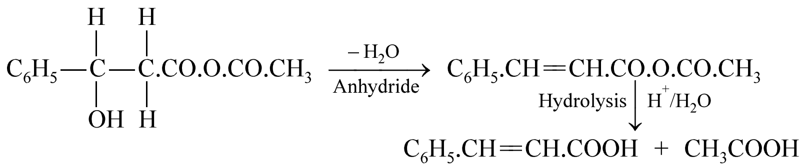
(ii)



$$C_6H_5-\overset{H}{C}=O + \bar{C}H_2.CO.O.CO.CH_3 \longrightarrow C_6H_5-\overset{H}{\underset{\underline{O}}{C}}-CH_2.CO.O.CO.CH_3 \quad \text{(II)}$$

$$\xrightleftharpoons{H^+ \text{ (from } CH_3COOH)} C_6H_5-\overset{H}{\underset{OH}{C}}-CH_2.CO.O.CO.CH_3 \quad \text{(III)}$$

(iii)



$$C_6H_5-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{H}{C}}.CO.O.CO.CH_3 \xrightarrow[\text{Anhydride}]{-H_2O} C_6H_5.CH=CH.CO.O.CO.CH_3 \xrightarrow[\text{Hydrolysis}]{H^+/H_2O} C_6H_5.CH=CH.COOH + CH_3COOH$$

(III)

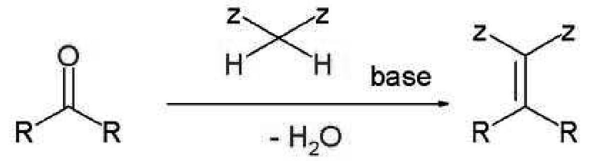
Cinnamic acid
(α,β-Unsaturated acid)

Applications

Perkin reaction is not only useful in the synthesis of α,β-unsaturated acids like cinnamic acid, but is also employed for the synthesis of coumarin used in perfumery. Some other condensation reactions are as follows:

(i) Knoevenagel Condensation

The Knoevenagel condensation reaction is an organic reaction named after Emil Knoevenagel. It is a modification of the aldol condensation. A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated (hence condensation). The product is often an α,β-unsaturated ketone (a conjugated enone).



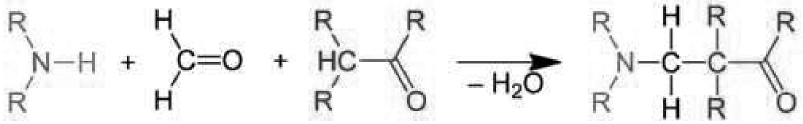
In this reaction the carbonyl group is an aldehyde or a ketone. The catalyst is usually a weakly basic amine. The active hydrogen component has the form

- Z–CH_2-Z or Z–CHR–Z for instance diethyl malonate, Meldrum's acid, ethyl acetoacetate or malonic acid, or cyanoacetic acid.
- Z–CHR_1R_2 for instance nitromethane.

where Z is an electron withdrawing functional group. Z must be powerful enough to facilitate deprotonation to the enolate ion even with a mild base. Using a strong base in this reaction would induce self-condensation of the aldehyde or ketone. The Hantzsch pyridine synthesis, the Gewald reaction and the Feist–Benary furan synthesis all contain a Knoevenagel reaction step. The reaction also led to the discovery of CS gas.

(ii) Mannich Reaction

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.

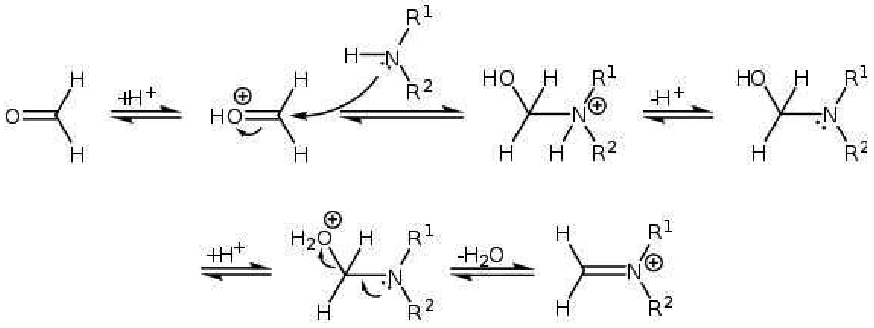


The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol). The Mannich reaction is also considered a condensation reaction.

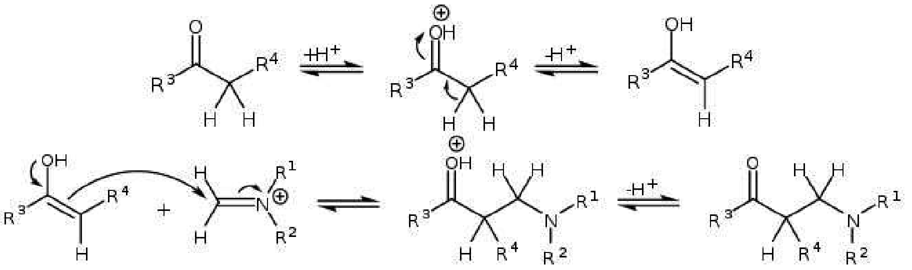
In the Mannich reaction, primary or secondary amines or ammonia, are employed for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α-CH-acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives.

Mechanism

The mechanism of the Mannich reaction starts with the formation of an iminium ion from the amine and the formaldehyde**.**

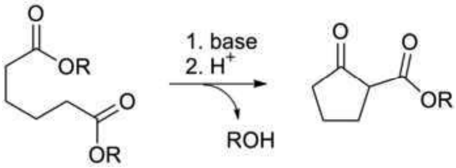


The compound with the carbonyl functional group (in this case a ketone) can tautomerize to the enol form, after which it can attack the iminium ion.



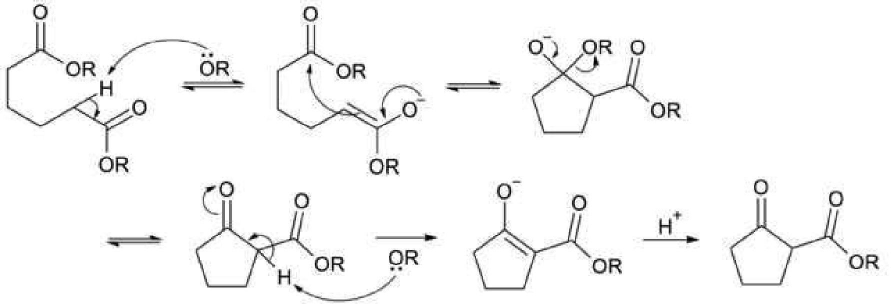
(iii) Dieckmann Condensation

Dieckmann condensation is the intramolecular chemical reaction of diesters with base to give β-keto esters. It is named after the German chemist Walter Dieckmann (1869–1925). The equivalent intermolecular reaction is the Claisen condensation.



Mechanism

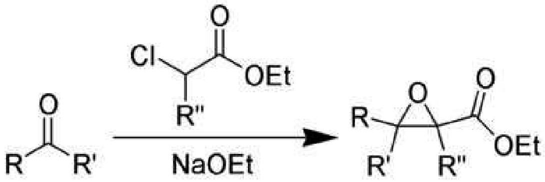
Deprotonation of an ester at the α-position generates an enolate ion which then undergoes a 5-exo-trig nucleophilic attack to give a cyclic enol. Protonation with a Brønsted-Lowry acid (H_3O+ for example) re-forms the β-keto ester.



Due to the steric stability of five- and six-membered rings, these structures will preferentially be formed. 1,6 diesters will form five-membered cyclic β-keto esters, while 1,7 diesters will form six-membered β-keto esters.

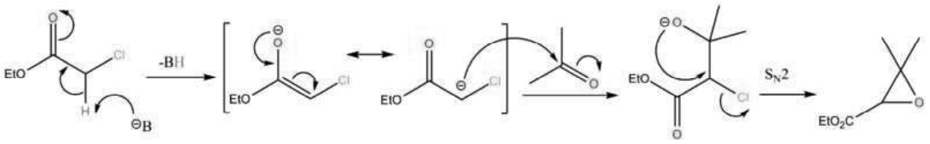
(iv) Darzens Reaction

The Darzens reaction (also known as the Darzens condensation or glycidic ester condensation) is the chemical reaction of a ketone or aldehyde with an α-haloester in the presence of a base to form an α,β-epoxy ester, also called a "glycidic ester". This reaction was discovered by the organic chemist Auguste George Darzens in 1904.



Mechanism

The reaction process begins when a strong base is used to form a carbanion at the halogenated position. Because of the ester, this carbanion is a resonance-stabilized enolate, which makes it relatively easy to form. This nucleophilic structure attacks another carbonyl component, forming a new carbon–carbon bond. These first two steps are similar to a base-catalyzed aldol reaction. The oxygen anion in this aldol-like product then does an intramolecular S_N2 attack on the formerly-nucleophilic halide-bearing position, displacing the halide to form an epoxide. This reaction sequence is thus a condensation reaction since there is a net loss of HCl when the two reactant molecules join.



The primary role of the ester is to enable the initial deprotonation to occur, and other carbonyl functional groups can be used instead. If the starting material is an α-halo amide, the product is an α,β-epoxy amide. If an α-halo ketone is used, the product is an α,β-epoxy ketone. Any sufficiently strong base can be used for the initial deprotonation. However, if the starting material is an ester, the alkoxide corresponding to the ester side-chain is commonly chosen in order to prevent complications due to potential acyl exchange side reactions.

(v) Wittig Reaction

The Wittig reaction or Wittig olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a Wittig reagent) to give an alkene and triphenylphosphine oxide.

The Wittig reaction was discovered in 1954 by Georg Wittig, for which he was awarded the Nobel Prize in Chemistry in 1979. It is widely used in organic synthesis for the preparation of alkenes. It should not be confused with the Wittig rearrangement.

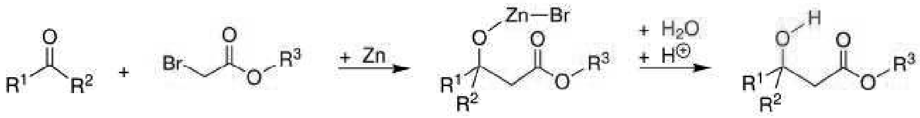
NOTES

Wittig reactions are most commonly used to couple aldehydes and ketones to singly-substituted triphenylphosphonium ylides. For the reaction with aldehydes, the double bond geometry is readily predicted based on the nature of the ylide. With unstabilised ylides (R^3 = alkyl) this results in (Z)-alkene product with moderate to high selectivity. With stabilized ylides (R^3 = ester or ketone), the (E)-alkene is formed with high selectivity. The (E)/(Z) selectivity is often poor with semistabilized ylides (R^3 = aryl).

To obtain the (E)-alkene for unstabilized ylides, the Schlosser modification of the Wittig reaction can be used. Alternatively, the Julia olefination and its variants also provide the (E)-alkene selectively. Ordinarily, the Horner-Wadsworth-Emmons reaction provides the (E)-enoate (α,β-unsaturated ester), just as the Wittig reaction does. To obtain the (Z)-enoate, the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction can be used.

(vi) Reformatsky Reaction

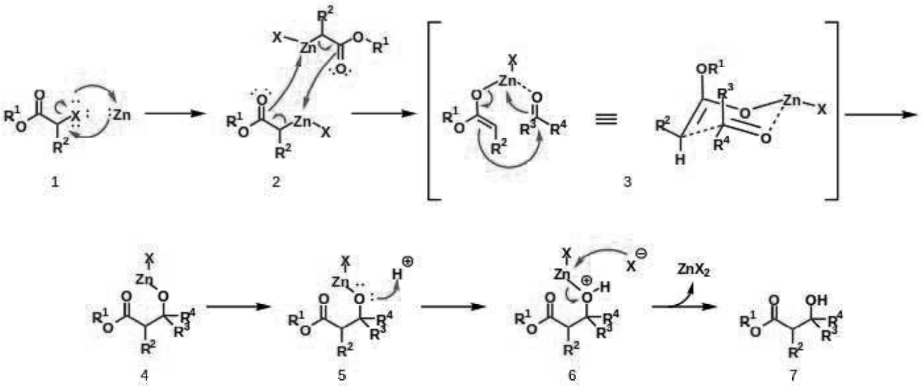
The Reformatsky reaction (sometimes spelled Reformatskii reaction) is an organic reaction which condenses aldehydes or ketones, with α-halo esters, using a metallic zinc to form β-hydroxy-esters.



The organozinc reagent, also called a 'Reformatsky enolate', is prepared by treating an alpha-halo ester with zinc dust. Reformatsky enolates are less reactive than lithium enolates or Grignard reagents and hence nucleophilic addition to the ester group does not occur. The reaction was discovered by Sergey Nikolaevich Reformatsky.

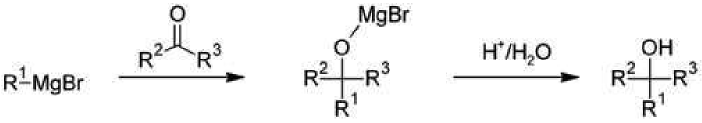
Mechanism

Zinc metal is inserted into the carbon-halogen bond of the α-haloester by oxidative addition 1. This compound dimerizes and rearranges to form two zinc enolates 2. The oxygen on an aldehyde or ketone coordinates to the zinc to form the six-member chair like transition state 3. A rearrangement occurs in which zinc switches to the aldehyde or ketone oxygen and a carbon-carbon bond is formed 4. Acid workup 5,6 removes zinc to yield zinc(II) salts and a β-hydroxy-ester 7.



(vii) Grignard Reaction

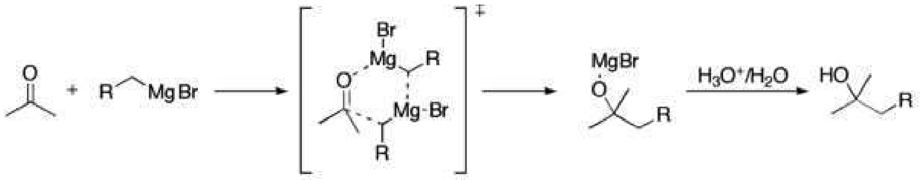
The Grignard reaction is an organometallic chemical reaction in which alkyl, vinyl, or aryl-magnesium halides (Grignard reagents) add to a carbonyl group in an aldehyde or ketone. This reaction is an important tool for the formation of carbon–carbon bonds. The reaction of an organic halide with magnesium is not a Grignard reaction, but provides a Grignard reagent.



Grignard reactions and reagents were discovered by and are named after the French chemist François Auguste Victor Grignard (University of Nancy, France), who published it in 1900 and was awarded the 1912 Nobel Prize in Chemistry for this work. Grignard reagents are similar to organolithium reagents because both are strong nucleophiles that can form new carbon–carbon bonds. The nucleophilicity increases if the alkyl substituent is replaced by an amido group. These amido magnesium halides are called Hauser bases.

Mechanism

The Grignard reagent functions as a nucleophile, attacking the electrophilic carbon atom that is present within the polar bond of a carbonyl group. The addition of the Grignard reagent to the carbonyl typically proceeds through a six-membered ring transition state.



However, with hindered Grignard reagents, the reaction may proceed by single-electron transfer. Similar pathways are assumed for other reactions of Grignard reagents, for example, in the formation of carbon–phosphorus, carbon–tin, carbon–silicon, carbon–boron and other carbon–heteroatom bonds.

Hydrolysis of Ester and Amids

Esters' most essential reaction is hydrolysis. When an ester is hydrolyzed in acid, it produces a carboxylic acid and an alcohol. A carboxylate salt and an alcohol are produced by basic hydrolysis of an ester.

When an amide is hydrolyzed, the carbonâ€“nitrogen link is broken, resulting in a carboxylic acid and either ammonia or an amine. Although the reaction is similar to ester hydrolysis, there are some key distinctions. Although ester hydrolysis is very simple, amide hydrolysis is more difficult.

Ammonylsis of Esters

The reaction of esters with ammonia to produce acid amide and alcohol is known as ammonolysis. Ammonolysis is when ammonia acts as the nucleophile and reacts with an organic compound.

Check Your Progress

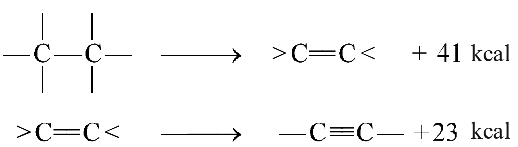
8. What is aldol condensation?
9. What is a condensation reaction?
10. What are the types of condensation reaction?
11. Define Perkin reaction.
12. Define Mannich reaction.

4.5 ELIMINATION REACTIONS

In elimination reactions, two substituents, from a pair of adjacent atoms in a molecule, are removed. As a consequence of the removal of atoms or groups from the adjacent atoms of molecule, unsaturation is introduced. The most common multiple bonds formed as a result of such reaction are

$$>C=C<,\ —C\equiv C—,\ —C\equiv N,\ >C=N—,\ >C=O,\quad \text{etc.}$$

Commonly one of the two groups removed from the substrate in elimination reaction is an electrophile, usually a proton. The other group is generally a nucleophile which may be X^- (halide), OH^-, $RCOO^-$ etc. The adjacent atoms of substrate molecule from which these groups are removed, are designated as α- and β-atoms and the type of elimination is referred to as β-elimination. The elimination reactions in which two groups leave from the same atoms are less frequent and result in a highly reactive species having only six electrons in outer shell (*cf.* carbenes). In elimination reactions energy is released and this acts as the driving force for elimination reactions. For a conversion of sp^3 hybridized carbon to sp^2 carbon approx. 41 kcal/mole are released. Similarly conversion of sp^2 to sp^1 hybridized carbon results in a release of 23 kcal/mole.

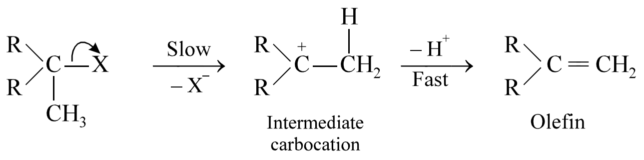


$$—\overset{|}{\underset{|}{C}}—\overset{|}{\underset{|}{C}}— \longrightarrow >C=C< \quad + 41 \text{ kcal}$$

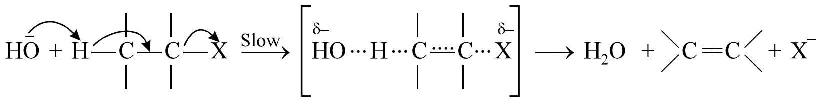
$$>C=C< \longrightarrow —C\equiv C— \ +23 \text{ kcal}$$

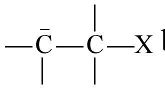
Elimination reactions usually compete with nucleophilic substitution reactions at saturated carbon atoms (S_N reactions). By analogy to S_N reactions, in elimination also there are two extreme types of reactions. With nucleophile which are strong bases a concerted reaction involving a transition state results in bimolecular elimination designated as E_2. Another type involving ionization and formation of a carbocation which then loses a proton to result in elimination is designated as E_1 or unimolecular elimination. E_1 reactions follow first order kinetics whereas E_2 reactions follow second order kinetics. The two mechanisms are:

E_1 mechanism



E_2 mechanism

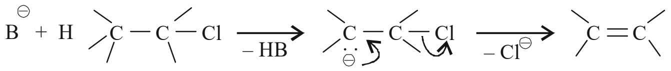


The E_2 reaction theoretically can involve the formation of a carbanion of the type  $-\bar{C}-C-X$ but evidence has been obtained that such an intermediate is not formed in elimination reaction.

In E_1 reactions a carbocation is formed and the factors stabilizing carbocation will favour this type of elimination. In E_2 reactions a state has been suggested in which all the five atoms or groups involved must be in the same plane and the groups to be eliminated (H and X) must be trans with respect to each other. Hence it is also known as **trans-elimination**.

A special type of elimination reaction for explaining the formation of alkenes from alkyl halides through carbanion intermediate is known as $E_{1C}B$ (Elimination 1st order conjugate base).

The reaction take place around sp^3–sp^3 covalent bond with an α-acidic hydrogen and a β-leaving group (like halide or tosyl etc.). A strong base abstracts the α-proton forming carbanion. The electron pair of carbanion expels the leaving group forming a double bond.



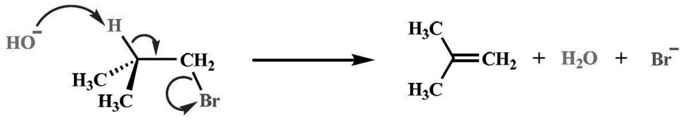
When the carbanion-forming step is fast and deprotonation is reversible, the reaction is called $(E_1cB)_r$ but when the first step is forming carbanium is slow and second step fast then the reaction is irreversible and is called $E_1(cB)_i$.

Some examples of elimination reactions are dehydration of alcohols, dehydrohalogenation of alkyl halides and dehydrogenation of alcohols etc.

Structure and reactivity

The nature of the substrate, solvent and the catalyst (usually a nucleophile) determine whether the reaction will proceed by E_1 or E_2 mechanism. It has also been observed that conditions favouring S_N1 reactions will lead to E_1 reactions as well. Similarly conditions favourable to S_N2 reactions also lead to E_2 reactions. The ratios of E_1 to S_N1 and E_2 to S_N2 reactions have been shown to be fairly constant for a given alkyl group, no matter what the departing group is. Unsymmetrical substrates generally give a mixture of olefins.

4.5.1 The E_2 Mechanism



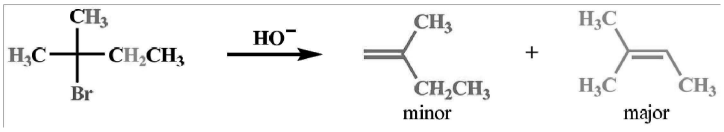
The most common mechanism for dehydrohalogenation is the E_2 mechanism.

It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation.

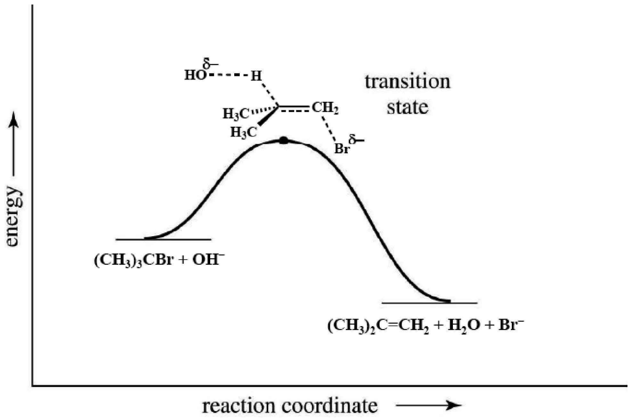
$$\mathbf{rate = k[(CH_3)_3CBr][HO^-]}$$

The reaction is concerted—all bonds are broken and formed in a single step.

E_2 reactions are **regioselective** and favor the formation of Zaitsev products.



Energy Profile for an E_2 Reaction



Factors Affecting the Rate of an E_2 Reaction

Some of the factors that affect the rate of an E_2 reaction are as follows:

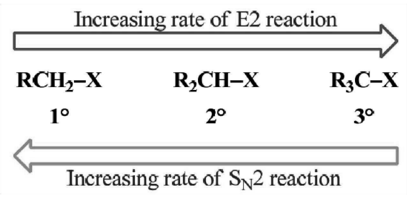
- There are close parallels between E_2 and S_N2 mechanisms in how the identity of the base, the leaving group and the solvent affect the rate.
- The base appears in the rate equation, so the rate of the E_2 reaction increases as the strength of the base increases.
- E_2 reactions are generally run with strong, negatively charged bases like OH^- and OR^-.
- Polar aprotic solvents increase the rate of E_2 reactions.
- There is a partial breaking of the bond to the leaving group in the transition state. So, the better the leaving group the faster the E_2 reaction.

Rate of reaction follows the order,

$$R–I > R–Br > R–Cl > R–F$$

The S_N2 and E_2 mechanisms differ in how the R group affects the reaction rate.

As the number of R groups on the carbon with the leaving group increases, the rate of the E_2 reaction increases.



The increase in E_2 reaction rate with increasing alkyl substitution can be rationalized in terms of transition state stability.

In the transition state, the double bond is partially formed. Thus, the transition state for a more substituted alkene is lower in energy, reducing the activation energy for the reaction and making the reaction faster.

Characteristics of an E_2 Reaction

Kinetics – Second order

Mechanism – Single step

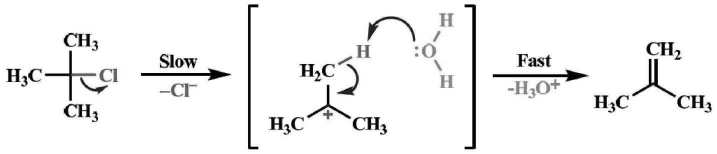
Identity of R group – More substituted halides react faster
Rate: $R_3CX > R_2CHX > RCH_2X$

Strength of the base – Stronger bases favor the reaction

Leaving group – Better leaving group leads to faster reaction rates

Type of solvent – Favored by polar aprotic solvents

E_2 reactions are stereoselective, resulting in the formation of trans-double bonds preferably.



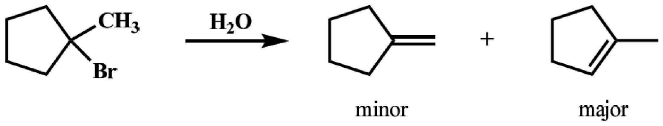
4.5.2 E_1 Reaction

The E_1 reaction proceeds via a two-step mechanism: the bond to the leaving group breaks first before the π bond is formed. The slow step is unimolecular, involving only the alkyl halide.

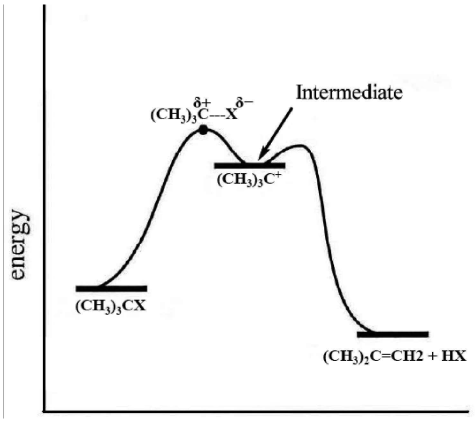
It exhibits first-order kinetics,

$$\textbf{rate} = \mathbf{k[(CH_3)_3CCl]}$$

E_1 reactions also are regioselective and follow Zaitsev rule

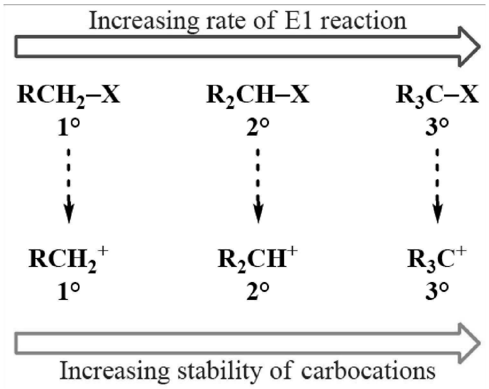


Energy Profile for an E_1 Reaction



Factors Affecting the Rate of an E_1 Reaction

The rate of an E_1 reaction increases as the number of R groups on the carbon with the leaving group increases.



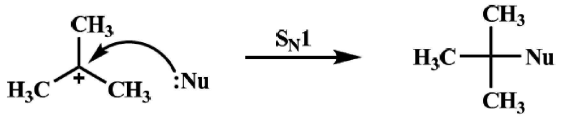
The strength of the base usually determines whether a reaction follows the E_1 or E_2 mechanism. Strong bases like OH^- and OR^- favor E_2 reactions, whereas weaker bases like H_2O and ROH favor E_1 reactions.

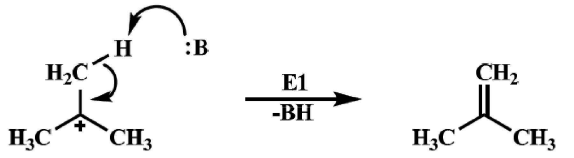
Characteristics of an E_1 Reaction

Kinetics	– First order
Mechanism	– Two steps
Identity of R group	– More substituted halides react faster Rate: $R_3CX > R_2CHX > RCH_2X$
Strength of the base	– Favored by weaker bases such as H_2O and ROH
Leaving group	– Better leaving group leads to faster reaction rates. Just as in S_N1 reactions, the rate determining step involves the C—X bond cleavage
Type of solvent	– Favored by polar protic solvents, which can stabilize the ionic intermediates

S_N1 and E_1 Reactions

S_N1 and E_1 reactions have exactly the same first step—formation of a carbocation. They differ in what happens to the carbocation.





Since in both the reactions, the rate determining steps are the same, they cannot be individually controlled.

Because E_1 reactions often occur with a competing S_N1 reaction, E_1 reactions of alkyl halides are much less useful than E_2 reactions.

S_N1, S_N2, E_1 or E_2

3° Alkyl Halides

With strong bases: E_2 elimination occurs

With weak nucleophiles or bases: A mixture of products from S_N1 and E_1 reactions

1° Alkyl Halides

With strong nucleophiles: Substitution occurs by an S_N2 mechanism

With strong sterically hindered bases: Elimination occurs by an E_2 mechanism

2° Alkyl Halides

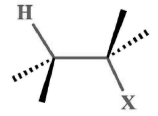
With strong bases and nucleophiles: A mixture of S_N2 and E_2 reaction products are formed

With strong sterically hindered bases: Elimination occurs by an E_2 mechanism

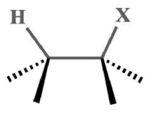
With weak nucleophiles or bases: A mixture of S_N1 and E_1 products results

4.5.3 Stereochemistry of the E_2 Reaction

The transition state of an E_2 reaction consists of four atoms from the substrate (one hydrogen atom, two carbon atoms, and the leaving group, X) aligned in a plane. There are two ways for the C—H and C—X bonds to be coplanar.



anti periplanar
H and X are on the opposite side



syn periplanar
H and X are on the same side

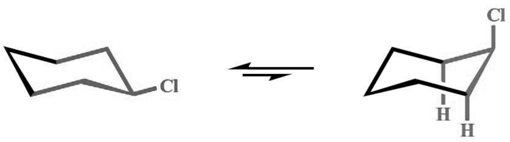
E_2 elimination occurs most often in the anti periplanar geometry. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.

The anti periplanar geometry also allows direct interaction between the bonding electrons of C—H bond and the anti-bonding orbital of the C—X bond.

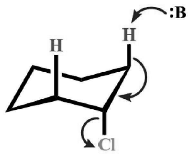
E_2 Reactions in 6-Membered Rings

The stereochemical requirement of an anti periplanar geometry in an E_2 reaction has important consequences for compounds containing six-membered rings.

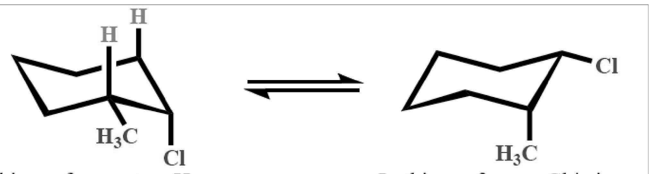
- **Chlorocyclohexane**



For E_2 elimination, the C—Cl bond must be anti periplanar to the C—H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position. The requirement for trans-diaxial geometry means that elimination must occur from the less stable conformer.



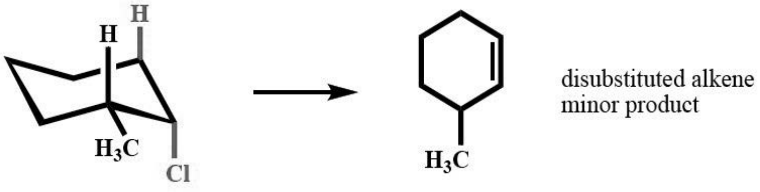
- **Dehydrohalogenation of cis-1-Chloro-2-methylcyclohexane**

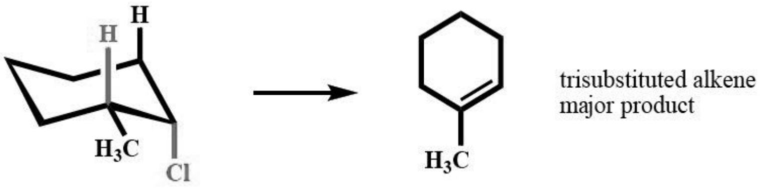


In this conformer two Hs are anti periplanar to the Cl.

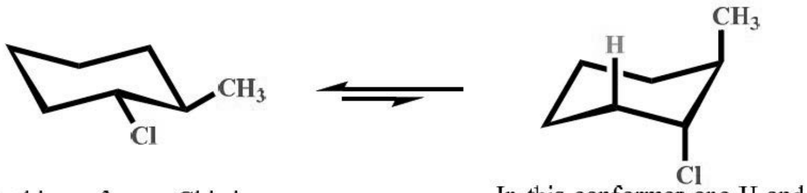
In this conformer Cl is in an equatorial psition and has no Hs periplanar to it.

The conformer with Cl in an axial orientation reacts to give two alkenes. The alkene that is more substituted is the major product.





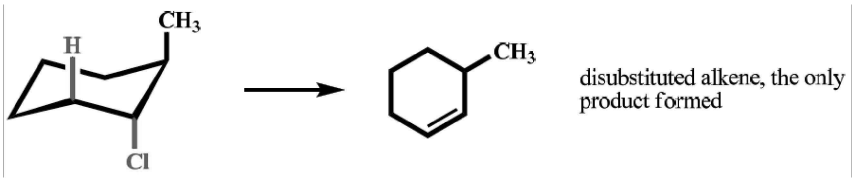
- **Dehydrohalogenation of trans-1-Chloro-2-methylcyclohexane**



In this conformer Cl is in an equatorial psition and has no Hs periplanar to it.

In this conformer one H and one CH_3 are anti periplanar to the Cl.

The conformer with Cl in an axial orientation has just one β-H atom. Only one product is formed, which is not what is predicted by the Zaitsev rule.

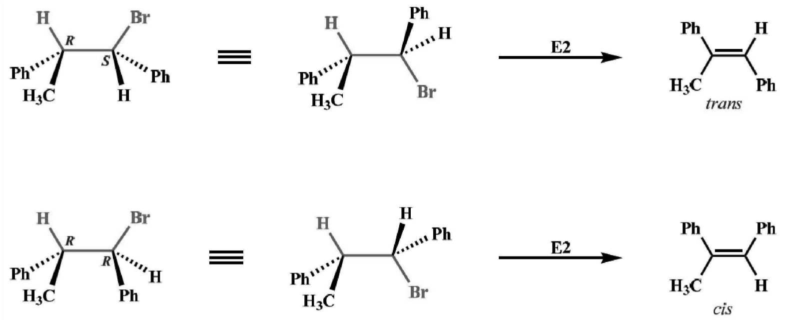


disubstituted alkene, the only product formed

In conclusion with substituted cyclohexanes E_2 elimination should conclusion, cyclohexanes, occur with a trans diaxial arrangement of the leaving group and the β-H, and as a result of this requirement, the more substituted alkene is not necessarily the major product.

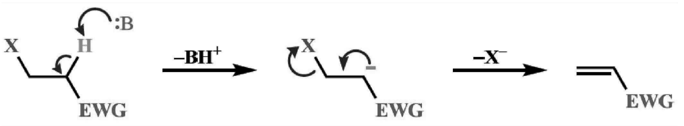
Stereospecificity in E_2 reactions

Diastereomeric starting compounds yield diastereomeric products after an E_2 reaction.



E_1cB Reaction

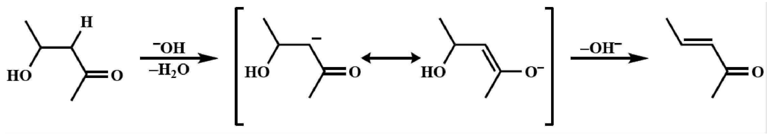
An elimination reaction that happens when a compoundbearing a poorleaving group and an acidic hydrogen is treated with a base.



E_1cB stands for Elimination Unimolecular conjugate Base. The reaction is unimolecular from the conjugate base of the starting compound, which in turn is formed by deprotonation of the starting compound by a suitable base.

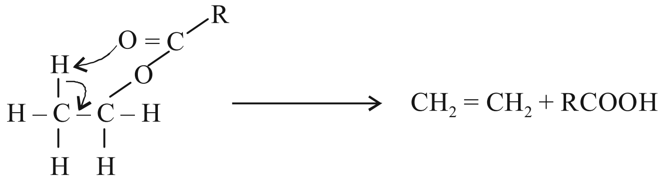
The electron withdrawing group (EWG) can be a carbonyl group (keto, aldehyde, ester), a nitro group, an electron deficient aromatic group etc. Dehydration of aldol is the most common E_1cB reaction.

NOTES



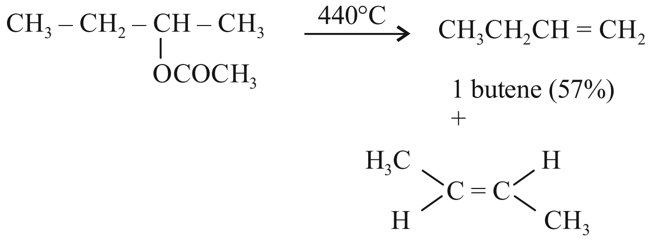
4.6 PYROLYTIC ELIMINATION

A number of reactions are known which proceed through a molecular process with no base or solvent. Such reactions take place in gas phase and simply on heating. These reactions are called pyrolytic or thermolytic reactions.



Pyrolytic Elimination in Acyclic System

Similar to elimination reactions in solution, the pyrolytic eliminations are required to be eliminated from the same side of the molecular in the transition state, if they are not eclipsed in the starting material. It the substrate of two are more syn-periplaner managements are available, the one with least crowding is preferred.



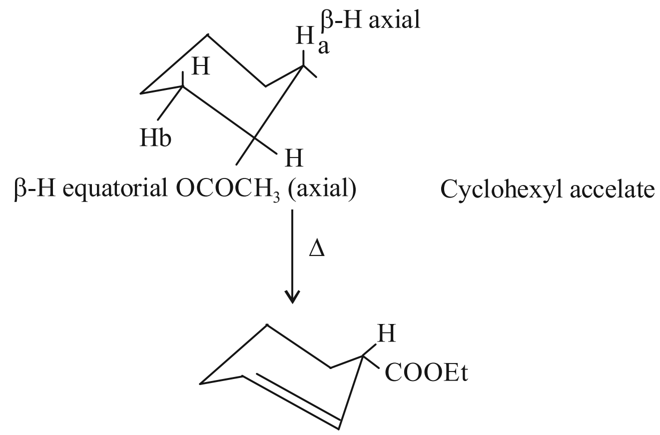
1 butene (57%)

trans-2 butene 28%

Pyrolytic Elimination in Cyclic System

In these systems some restrictions are imposed by the conformations of the leaving group and the necessity to form the cyclic intermediate.

In cyclohexane system, if the leaving group is axial then the hydrogen on the adjacent carbon must be equatorial, i.e., C has the relationship with the leaving group.



Exclusive product

Check Your Progress

13. What is dehydrohalogenation?
14. How is reaction rate determined in E1 reactions?
15. What does E1cB stand for?
16. Give some examples of elimination reactions.

4.7 ANSWERS TO 'CHECK YOUR PROGRESS'

1. The examples of electrophilic addition reactions are hydration and hydrogenation of olefins, additions of halogens and halogen acids to olefins and ozonolysis.
2. Electron donating substituents will increase the rate of reaction whereas electron withdrawing substituents will decrease it.
3. Anti-Markovnikov addition of HBr to olefins is also observed if peroxides or elemental oxygen are present in the reaction mixture. This is known as kharasch effect or peroxide effect.
4. Ozonolysis is used to locate the position of double bonds in olefins.
5. In chemistry, regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions.
6. Chemoselectivity is the preferential outcome of a chemical reaction over a set of possible alternative reactions.
7. The sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2, 3 epoxy alcohol from primary and secondary allyl alcohol.
8. When aldehydes and ketones having a-hydrogen atoms are treated with alkali, they undergo self-addition between two molecules to form a b-hydroxy aldehyde or b-hydroxy ketone (known as aldols). This addition is usually followed by elimination of a water molecule resulting in overall condensation reaction. The reaction is therefore known as Aldol condensation reaction.

9. A reaction (through functional groups) between two or more molecules of the same or different compounds resulting in the formation of new carbon to carbon bonds with or without the elimination of simple molecules like water, alcohol, metallic halides etc. is known as condensation reaction.
10. There can be two types of condensation reactions: Intramolecular Condensation and Intermolecular Condensation.
11. In 1867 W.H. Perkin observed that when aromatic aldehydes are heated with the anhydride of an aliphatic acid in the presence of the sodium salt of the same acid, an a, b, unsaturated acid is formed. The reaction is known as Perkin reaction and is shown mainly by aromatic aldehydes.
12. The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia.
13. The elimination of a hydrogen atom and a halogen atom, for example, is known as dehydrohalogenation.
14. In an E1 reaction, the reaction rate is proportional to the concentration of the substance to be transformed.
15. Elimination Unimolecular Conjugate Base.
16. Some examples of elimination reactions are dehydration of alcohols, dehydrohalogenation of alkyl halides and dehydrogenation of alcohols etc.

4.8 SUMMARY

- The electrophilic addition reactions are observed in alkenes, alkynes and conjugated systems and essentially mean the addition of a molecule to the double bond. Thus if a reagent breaks up to give a negative and a positive ion each one of these are added to double bond.
- When a halogen molecule or hypohalous acid reacts with olefin the bond is polarised by electromeric shift.
- The positively polarised halogen attacks and combines with the carbon carrying the pair of electrons after electromeric shift.
- A cyclic halonium ion is formed which prevents cis-addition of OH–. Then the completion of addition occurs by a trans combination of a bromide or hydroxide ion.
- Markovnikov in 1869 gave a generalization which is known as Markovnikov's rule. According to this rule "the negative part of the addendum (reagent which is adding) goes to the carbon atom, constituting the double bond, which is poorer in hydrogen."
- Anti-Markovnikov addition of HBr to olefins is also observed if peroxides or elemental oxygen are present in the reaction mixture. This is known as kharasch effect or peroxide effect.

NOTES

- Reaction of diborane (B_2H_6) with an olefinic double bond to produce alkylboranes is termed as Hydroboration (H.C. Brown). In the reaction diborane behaves as if it were its non-existent monomer borane (BH_3).
- Addition of a molecule of water to olefins is known as hydration reaction. Hydration of olefins in acidic media results in the formation of alcohols.
- Addition of ozone to olefinic linkage resulting in the formation of ozonide, which on subsequent hydrogenation gives carbonyl compounds, is known as ozonolysis.
- The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an a,b-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C–C bonds.
- A Gilman reagent is a lithium and copper (diorganocopper) reagent compound, R2CuLi, where R is an alkyl or aryl. These reagents are useful because, unlike related Grignard reagents and organolithium reagents, they react with organic halides to replace the halide group with an R group (the Corey-House reaction).
- The Diels-Alder reaction is a conjugate addition reaction of a conjugated diene to an alkene (the dienophile) to produce a cyclohexene.
- Unlike the carbon to carbon multiple bonds, the carbon to oxygen double bonds are highly polarized because of greater electronegativity of oxygen atom.
- Polar solvents, acids and bases catalyze nucleophilic addition reactions.
- Amine derivatives act as nucleophiles because of the presence of the lone pair of electrons at nitrogen.
- The reaction of ammonia is different with different carbonyl compounds.
- Products of some of these reactions like oximes, phenyl hydrazones, semicarbazides etc. are useful derivatives of carbonyl compounds helpful in their identifications.
- When aldehydes and ketones having a-hydrogen atoms are treated with alkali, they undergo self-addition between two molecules to form a b-hydroxy aldehyde or b-hydroxy ketone (known as aldols). This addition is usually followed by elimination of a water molecule resulting in overall condensation reaction. The reaction is therefore known as Aldol condensation reaction.
- Reaction between two molecules of an aldehyde, not having a-hydrogen atoms, in presence of alkali, results in Cannizzaro's reaction. Thus formaldehyde reacts with NaOH to form a mixture of methyl alcohol and sodium formate.
- A reaction (through functional groups) between two or more molecules of the same or different compounds resulting in the formation of new carbon to carbon bonds with or without the elimination of simple molecules like water, alcohol, metallic halides etc. is known as condensation reaction.

- There can be two types of condensation reactions: Intramolecular Condensation and Intermolecular Condensation.
- In elimination reactions two substituents, from a pair of adjacent atoms in a molecule, are removed. As a consequence of the removal of atoms or groups from the adjacent atoms of molecule, unsaturation is introduced.
- E1 reactions follow first order kinetics whereas E2 reactions follow second order kinetics.
- In E1 reactions a carbocation is formed and the factors stabilizing carbocation will favour this type of elimination. In E2 reactions a state has been suggested in which all the five atoms or groups involved must be in the same plane and the groups to be eliminated (H and X) must be trans with respect to each other. Hence it is also known as trans-elimination.
- A special type of elimination reaction for explaining the formation of alkenes from alkyl halides through carbanion intermediate is known as E1CB (Elimination 1st order conjugate base).
- Some examples of elimination reactions are dehydration of alcohols, dehydrohalogenation of alkyl halides and dehydrogenation of alcohols etc.

4.9 KEY TERMS

- **Carbon–carbon bond:** A carbon–carbon bond is a covalent bond between two carbon atoms.
- **Electrophilic addition:** The electrophilic addition reactions are observed in alkenes, alkynes and conjugated systems and essentially mean the addition of a molecule to the double bond.
- **Regioselectivity**: In chemistry, regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions.
- **Chemoselectivity:** Chemoselectivity is the preferential outcome of a chemical reaction over a set of possible alternative reactions.
- **Hydroboration**: Reaction of diborane (B_2H_6) with an olefinic double bond to produce alkylboranes is termed as Hydroboration (H.C. Brown). In the reaction diborane behaves as if it were its non-existent monomer borane (BH_3).
- **Michael reaction:** Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an a ,b-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions.
- **Elimination reaction**: Elimination reaction is a type of organic chemical reactions in which a pair of atoms or groups of atoms are eliminated from a molecule, usually through the action of acids, bases, or metals and, in some cases, by heating to a high temperature.
- **Saturated Compound**: Organic compounds containing only single carbon-carbon bondsare called saturated compounds.

- **Unsaturated compound**: Organic compounds containing double or triple carbon-carbon bonds are called unsaturated compounds.
- **Reformatsky Reaction**: The Reformatsky reaction is an organic reaction which condenses aldehydes or ketones, with a-halo esters, using a metallic zinc to form b-hydroxy-esters.

4.10 SELF ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. Why is the reaction known as an electrophilic addition when both the electrophile and the nucleophile are adding to the same double bond?
2. What is the difference between trans-additions and cis-additions?
3. Write the mechanism of Sharpness asymmetric epoxidation.
4. What do you understand by Michael reaction.
5. What do you understand by conjugate addition of Gilman reagents?
6. Write the mechanism of Aldol condensation.
7. What is a condensation reaction? Describe its types.
8. Give the mechanism of Claisen condensation.
9. What is the mechanism of benzoin condensation?
10. Write the the mechanism of Perkin reaction.
11. What do you understand by Knoevenagel condensation?
12. Define elimination reaction.
13. Write is the mechanism of E1 reactions.

Long-Answer Questions

1. Discuss the mechanism of addition of (a) HI (b) Br_2 and (c) HOCl to propene.
2. Discuss the mechanism and predict the products from the reaction of bromine with propene dissolved in methanol containing lithium chloride.
3. State and illustrate 'Markownikoff's rule' and 'peroxide effect' taking example of the addition of HBr to propene.
4. Describe the mechanism of metal hybrid reduction of saturated and unsaturated carbonyl compounds.
5. Analyze the mechanism of Michael reaction.
6. Explain the formation of alkenes from alkyl halides through carbanion intermediate.
7. Analyze the Characteristics of an E1 reaction.
8. Discuss the factors affecting the rate of an E2 reaction.
9. Explain E1cB Reaction.
10. Explain pyrolytic elimination or thermal elimination.

4.11 FURTHER READING

NOTES

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UNIT 5 PERICYCLIC REACTIONS

NOTES

Structure

5.0 INTRODUCTION

In organic chemistry, a pericyclic reaction is a type of organic reaction wherein the transition state of the molecule has a cyclic geometry, the reaction progresses in a concerted fashion, and the bond orbitals involved in the reaction overlap in a continuous cycle at the transition state. Pericyclic reactions are usually rearrangement or addition reactions. The major classes of pericyclic reactions are electrocyclic reaction, cycloaddition (and cycloreversion), sigmatropic reaction, group transfer reaction, ene reaction, cheletropic reaction, and dyotropic reaction. Cheletropic reactions also known as chelotropic reactions are a type of pericyclic reaction. A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals. A reorganization of s and p bonds occurs in this cyclic array.

A sigmatropic reaction in organic chemistry is a pericyclic reaction wherein the net result is one s-bond is changed to another p-bond in an uncatalyzed intramolecular process. The name sigmatropic is the result of a compounding of the long-established sigma designation from single carbon–carbon bonds and the Greek word tropos, meaning turn. In this type of rearrangement reaction, a substituent moves from one part of a p-bonded system to another part in an intramolecular reaction with simultaneous rearrangement of the p system.

In this unit you will study about pericyclic reaction, molecular orbital symmetry, cheleotropic reactions, suprafacial and antarafacial shifts, sigmatropic rearrangements, chlaisen, cope and aza-cope rearrangements, fluxional tautomerism and ene reaction.

5.1 OBJECTIVES

After going through this unit, you will be able to:

- Explain pericyclic reaction
- Discuss molecular orbital symmetry
- Understand cheleotropic reactions
- Discuss suprafacial and antarafacial shifts
- Analyze sigmatropic rearrangements
- Explain chlaisen, cope and aza-cope rearrangements
- Analyze fluxional tautomerism and ene reaction

5.2 PERICYCLIC REACTIONS: INTRODUCTION AND CLASSIFICATION

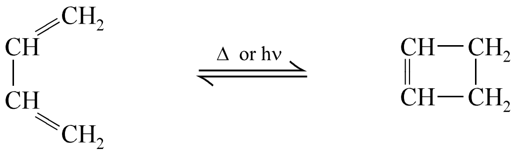
A large number of reactions of olefinic compounds are known which do not involve ionic or free radical intermediates and are initiated by heat or light. Apparently solvents and catalysts do not affect these reactions. Such reactions in which bonds are broken and made in a single concerted step through a cyclic transition state were termed as *pericyclic reactions* by Woodward and Hofmann in 1965. Most of these reactions are highly stereospecific, so much so that initiation of reaction by heat or light gives products with different sterochemical nature.

Pericyclic reactions include some of the most important reactions in organic chemistry which were poorly understood till recently and were called '*no-mechanism reactions*'. Diels-Alder reaction and Claisen reaction can be cited here as examples of pericyclic reactions. These reactions are divided into following four classes:

(*i*) Electrocyclic Reactions

In organic chemistry, an electrocyclic reaction is a type of pericyclic rearrangement where the net result is one pi bond being converted into one sigma bond or vice versa. These reactions are usually categorized by the following criteria:

- Reactions can be either photochemical or thermal.
- Reactions can be either ring-opening or ring-closing (electrocyclization).
- Depending on the type of reaction (photochemical or thermal) and the number of pi electrons, the reaction can happen through either a conrotatory or disrotatory mechanism.
- The type of rotation determines whether the cis or trans isomer of the product will be formed.

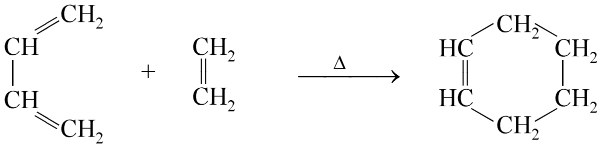


Butadiene Cyclobutene

(*ii*) Cycloaddition Reactions: Diels-Alder Reaction

A cycloaddition is a chemical reaction, in which "two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity." The resulting reaction is a cyclization reaction. Many but not all cycloadditions are concerted and thus pericyclic. Nonconcerted cycloadditions are not pericyclic. As a class of addition reaction, cycloadditions permit carbon–carbon bond formation without the use of a nucleophile or electrophile.

The Diels-Alder reaction is perhaps the most important and commonly taught cycloaddition reaction. Formally it is a [4+2] cycloaddition reaction and exists in a huge range of forms, including the inverse electron-demand Diels–Alder reaction, Hexadehydro Diels-Alder reaction and the related alkyne trimerisation. The reaction can also be run in reverse in the retro-Diels–Alder reaction.

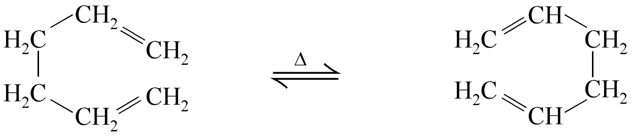


Butadiene Ethylene Cyclohexene

(*iii*) Sigmatropic Reactions

A sigmatropic reaction in organic chemistry is a pericyclic reaction wherein the net result is one σ-bond is changed to another σ-bond in an uncatalyzed intramolecular process. The name sigmatropic is the result of a compounding of the long-established sigma designation from single carbon–carbon bonds and the Greek word tropos, meaning turn. In this type of rearrangement reaction, a substituent moves from one part of a π-bonded system to another part in an intramolecular reaction with simultaneous rearrangement of the π system. True sigmatropic reactions are usually uncatalyzed, although Lewis acid catalysis is possible. Sigmatropic reactions often have transition-metal catalysts that form intermediates in analogous reactions. The most well-known of the sigmatropic rearrangements are the [3,3] Cope rearrangement, Claisen rearrangement, Carroll rearrangement and the Fischer indole synthesis.

(*a*) *Cope reaction*



1,5-Hexadiene 1,5-Hexadiene (rearranged)

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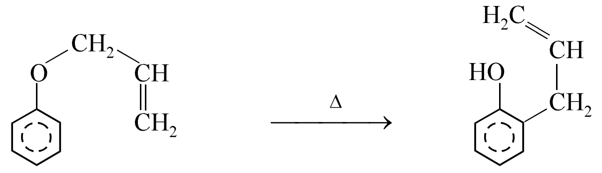
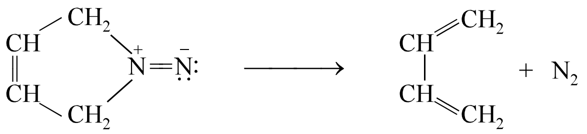
(*b*) *Claisen reaction*



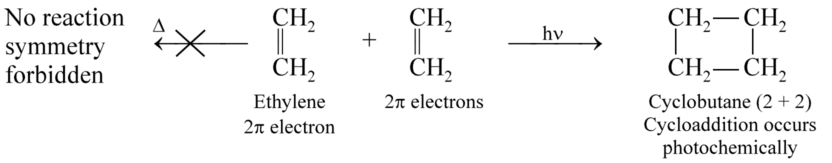
Allyl-phenyl ether   *o*-Allyl phenol

(*c*) *Cheletropic reaction*



(*iv*) Cycloaddition Reactions

In contrast to electrocyclic reactions where two double bonds of the same molecule changed to one σ and one π bond, the *cycloaddition* reactions are basically additions of two separate molecules combining through two π bonds to form two σ bonds



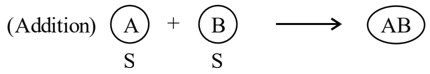
5.2.1 Molecular Orbital Symmetry

Linear Combination of Atomic Orbitals (LCAO) gives two molecular orbitals.

(i) Bonding orbitals

$\psi_1 + \phi_A + \phi_B$ (φ = Atomic orbital)

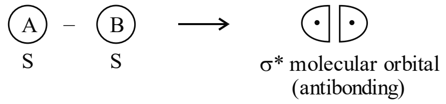
(ψ = Molecular orbital)



(S – S overlapping)   σ molecular orbital (bonding)

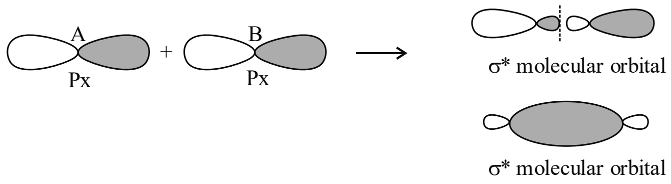
(ii) Antibonding orbitals

(subtraction) $\psi_2 + \phi_A + \phi_B$

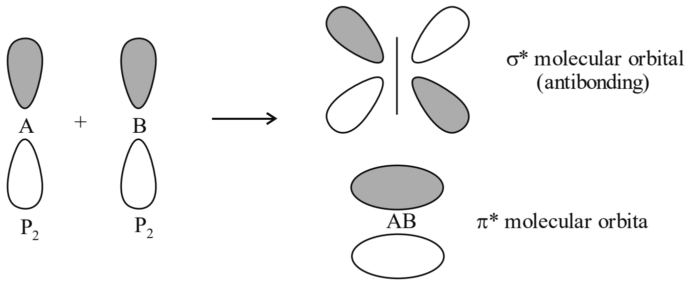


p-orbital being directional can overlap co-axial or side wise. Each overlap may be represented as:

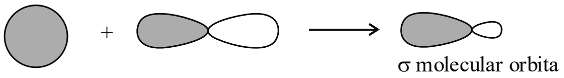
Co-axial overlap



Side wise overlap



s-p overlapping



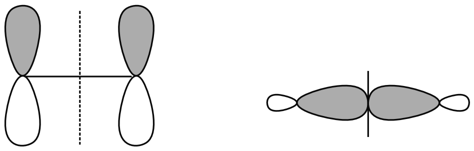
Bonding orbital's electrons are concentrated in the region between the two nuclei. They are attracted by both the nuclei. The increase in electrostatic attraction lowers the energy of the system and makes it more stable.

Thereby increase in repulsion between the nuclei makes the system more energetic than the isolated atom.

Symmetry

Mainly two molecular orbitals symmetry properties concern for pericyclic reactions- (i) mirror plane symmetry, (ii) C_2-axis of symmetry.

Some molecular orbitals have the symmerty about a mirror plane symmetry that bisects the molecular orbitals and perpendicular to the plane of atoms.



π-bonding σ-(bonding)

m-plane symmetry

π^* and σ^* are antisymmetric to m-plane symmetry.

Another type of symmetry, C_2-axis of symmetry is said to be present if the rotation of molecular around the axis by 180°(360/2) result in a molecular orbital identical with the original, σ bonding, orbitals have mirror plane symmetry and a rotation of 180° through its mid-point regenerates the same σ orbitals and thus has C_2-axis of symmetry also. Similarly π^* orbital possesses C_2-axis of symmetry while π does not.

Methods of analysis of pericyclic reactions

The three methods are as follows:

(i) Correlation Diagram Method

The passing of one orbital to another is referred as a correlation of these orbitals and an orbital energy diagram showing the correlation of reactant orbitals with product orbitals is a correlation diagram.

(ii) Frontier Molecular Orbital Method (FMO)

Woodward and Haffman and Fukui discussed the steric career of pericycle reaction by consdering highest occupied molecular orbitals (HOMO) and lowest occupied molecular orbitals (LUMO) and termed them as frontier molecular orbitals.

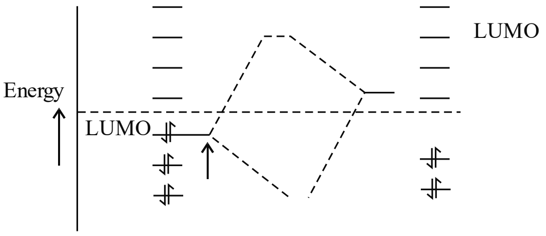
This theory explains whether a pericyclic reaction is allowed or not under given sets of reaction conditions which is based on intractions between the frontier molecular orbitals (FMO) i.e., HOMO, LUMO and SOMO. The interaction between one FMO of one molecule with one FMO of another molecule results in the formation of two new molecular orbitals, one bonding of lower energy and the other antibonding of higher energy.

If both the resulting molecular orbitals filled with electrons, the bonding interaction is cancelled by the antibonding interaction; the net result is no-bonding between molecules.

Table 5.1 *Interaction between Frontier Molecular Orbitals*

Interacting Frontier Molecular Orbitals	Types of Interaction
HOMO + HOMO	No bonding
HOMO + LUMO	Attraction-Bonding
LUMO + LUMO	No electron-null interaction- no bonding
SOMO + HOMO	
SOMO + LUMO	Attraction-bonding
SOMO + SOMO	

The interaction of occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) results in the stabilization of transition state.



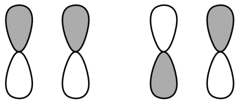
HOMO-LUMO Interaction

In photochemical reactions HOMO will be SOMO (singly unoccupied molecular orbital) due to transfer of electron from lower energy level to higher one due to abserption of light radiation of proper wavelength.

(iii) Perturbational Molecular Orbital Method PMO

The PMO approach developed by MJS Dewar, aims at calculating the π energy differences between closely related system, using perturbational theory and the assumptions of Huckel's molecules orbital method for the treatment of delocalized system.

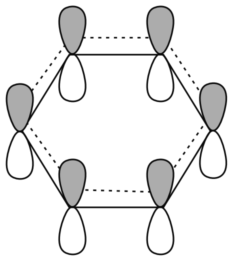
Huckel's rule is applicable to the molecules in the ground state while in dealing wood Ward and Haffman rule we are mainly concerned with the transition state. A transition state may be aromatic or antiaromatic.



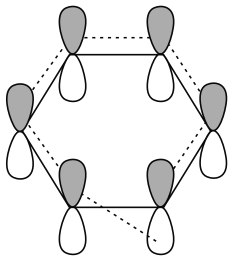
Two Basis Set for an Isolated Double Bond

Two Basis Set for Conjugated Diene

A system with zero or even number of sign inversion is called Huckel system while a system with odd number of sign inversion is called Mobius system or anti Huckel system.



Huckel System (with Zero Node)



Anti Huckel System (with One Node)

5.2.2 Frontier Orbitals of Ethylene, 1, 3 - Butadiene 1, 3, 5 - Hexatriene and Allyl System

In the case of ethylene one of the electrons in the HOMO can be promoted to the LUMO orbital having the same spin (Refer Figure 5.1). This process occurs with electromagnetic energy just to the high energy side of the ultraviolet range (UV, ~200 - 400 nm). This excited state LUMO (a singlet, paired electrons) involves the absorption of energy. When the electron returns to the ground state (HOMO) energy is emitted. Higher homologs of ethylene such as 1,3-butadiene, 1,3,5-hexatriene, 1,3,5,7-octatatraene, etc. can be treated in a similar way.

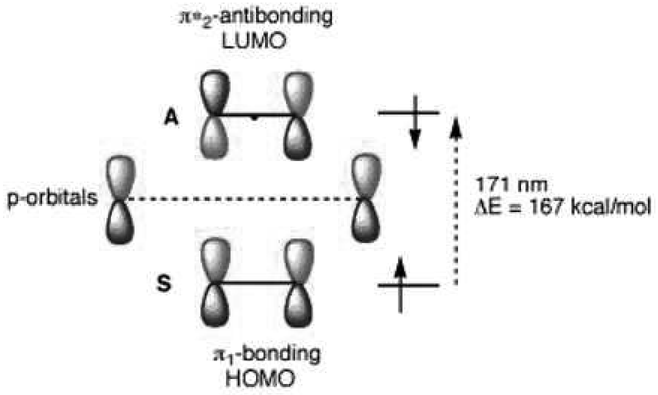


Fig. 5.1 *Ethylene Electrons in the HOMO*

When the wave functions of two bonding MOs of ethylene are combined, two new MOs are formed. One of these will be lower in energy than the ethylene MOs, the other higher. The lower one will have S symmetry while the higher one will have A symmetry, hence the single node. Likewise, the two non-bonding MOs of ethylene (A), can be brought together to form a LUMO having constructive overlap between C_2 and C_3 and lower energy than either of the LUMOs of ethylene. Non-constructive overlap gives the non-bonding A MO of butadiene having three nodes. The HOMO-LUMO energy gap in 1,3-butadiene is therefore lower in energy than it is ethylene. This method of building MOs is called Perturbational Theory. It can be used to construct the MOs of higher polyenes.

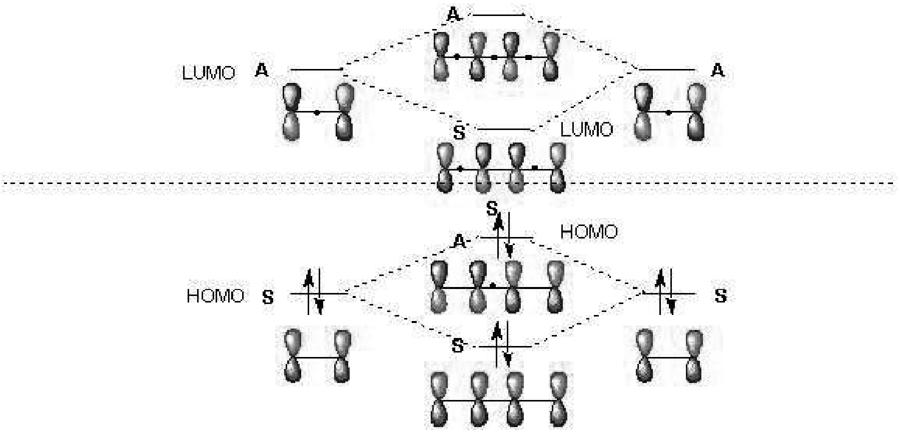


Fig. 5.2 *MOs are Formed*

For 1,3-butadiene there are four MOs, two bonding and two antibonding. Each successive, higher energy MO has an additional node. The HOMO is π_2 while the LUMO is π_3^*. The energy gap between the HOMO and the LUMO is 131 kcal/mol (214 nm), less than that for ethylene. Promotion of a bonding HOMO electron to the LUMO is effected by UV light. It is called a $\pi \rightarrow \pi^*$ transition. The 16 orbitals in are all shown as the same size. In fact, they are of different sizes. The terminal orbitals in the HOMO and LUMO are larger than their respective internal orbitals. Nonetheless, treating all of these orbitals as the same size will suffice for our needs.

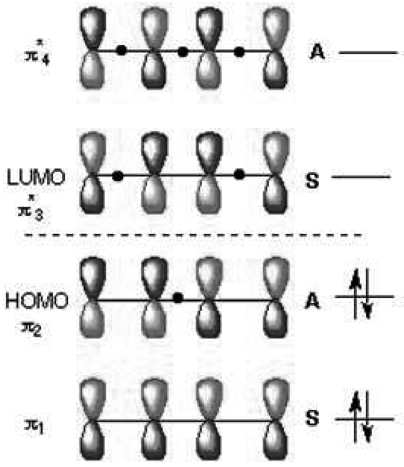


Fig. 5.3 *1,3-Butadiene showing Four Mos (Two Bonding and Two Antibonding)*

One last example is 1,3,5-hexatriene (Refer Figure 5.3). There are three bonding and three antibonding MOs.

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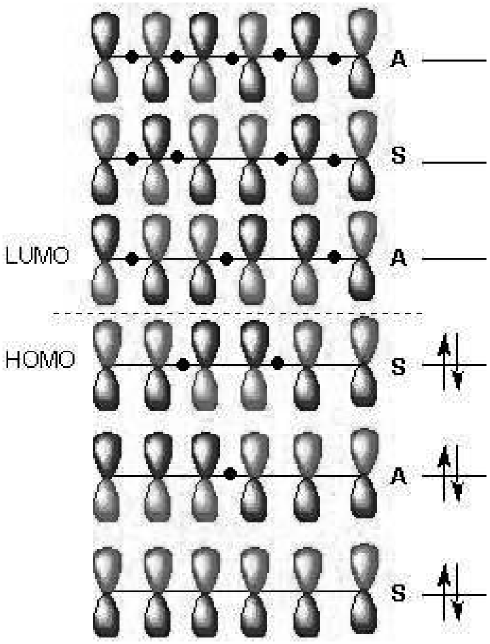


Fig. 5.4 *1,3,5-Hexatriene*

The HOMO-LUMO gap ($\pi \rightarrow \pi^*$ transition) in the hexatriene has dropped to 109 kcal/mol (258 nm) and the wavelength of absorption has increased. Note that the symmetry of the FMOs for each successive longer polyene alternates S|A, SA|SA, and SAS|ASA, etc. The HOMO of ethylene and the HOMO of 1,3,5-hexatriene are both **S** while their LUMOs are **A**. This situation is the opposite of that observed for 1,4-butadiene where the HOMO is **A** and the LUMO is **S**. What about 1,3,5,7-octatatraene? It is the same as 1,3-butadiene. Thus, every other polyene has the same HOMO-LUMO phasing. One group obeys the 4n + 2 rule while the other one satisfies 4n, where n = 0, 1, 2, 3, etc.

n = 0, 1, 2,3, etc.	**HOMO**	**LUMO**
4n + 2	**S**	**A**
4n	**A**	**S**

It also follows that the terminal orbitals of any **S**-MO must mirror one another because the whole MO as a whole does so. Likewise, an **A**-MO has terminal orbitals that do not match. Pericyclic reactions require the proper matching of the symmetry of the HOMO and LUMO of reacting components.

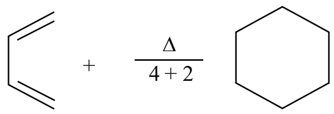
Check Your Progress

1. What happens when a reaction is highly stereospecific?
2. What does FMO stand for?
3. What is the basic principle involved in pericyclic reactions?

5.3 CYCLOADDITIONS

When two or more mulecules containing unsaturated functional groups condense and form cyclic molecules transfering electrons from π bond to new σ bond, the reaction is termed as cyclo as cycloaddition.

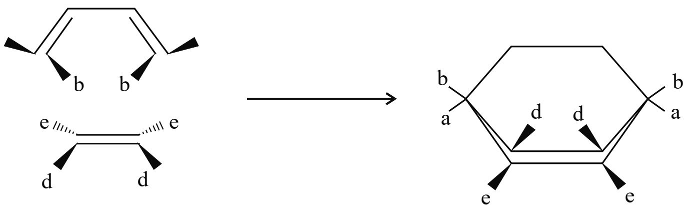
Example: Diels-Alder reaction, in which a conjugated diene reacts with substituted alkene, to form cyclohexene.



Depending upon number of π electrons of the reaction molecules the addition is termed as 2 + 2, 2 + 4, 4 + 4, etc. In general, a system of *m* π electrons add to a system of *n* π electrons giving a product with (m–2 + n–2) π electrons and two newly formed σ bonds.

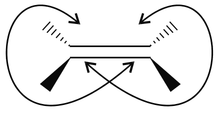
Modes of Addition: Two modes of additions.

Suprafacial: When both the π frame works add to the same phase or broken from the same phase, it is termed as suprafacial.

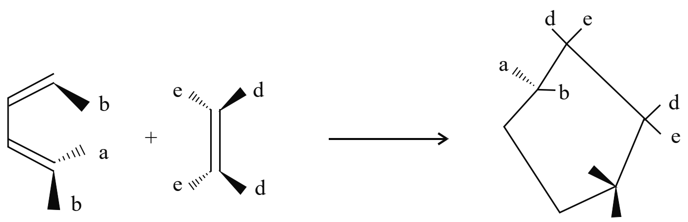


($\pi_4 s + \pi_2 s$)

Antarafacial: In another approach the newly formed bonds lie on opposite faces of the π system. This type of orientation is termed as antarafacial addition and subscript "*a*" is used to denote it.

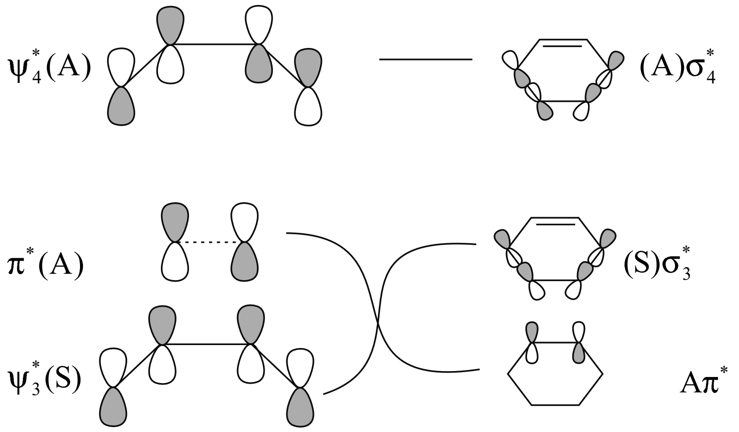


Antarafacial at Both End



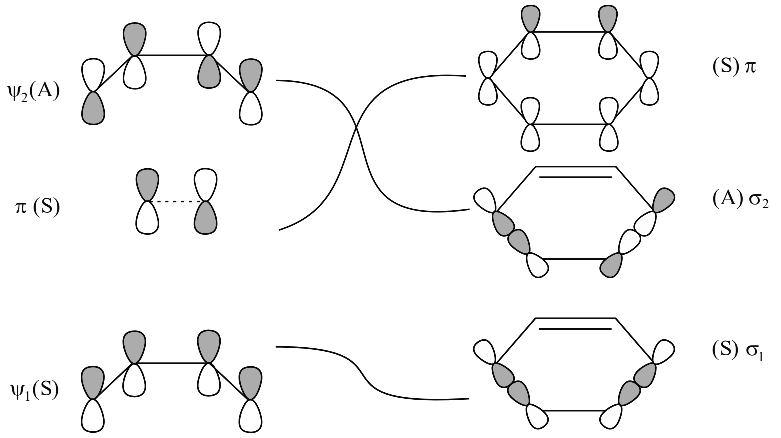
Analysis of cycloaddition reaction by correlation diagra method

The correlation diagram for this reaction may be drawn as:



Butadine and Ethylene
π Orbitals with Symmetry Properties

Cyclohexene σ and π Orbitals
with Symmetry Properties



Butadine and Ethylene

Cyclohexene

Symmetry properties of obtials for Diels-Alder reaction

$\psi_1, \pi, \psi_2 \rightarrow$ ground state of Butadiene and Ethylene

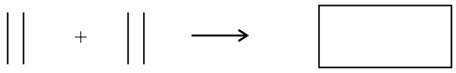
σ_1, σ_2, and $\pi \rightarrow$ ground state of Cyclohexene

$\psi_3^*\pi^*, \psi_4^* \rightarrow$ excited state of Butadiene and Ethylene

$\pi^*, \sigma_3^*\pi^*, \sigma_4^* \rightarrow$ Excited state of Cyclohexene

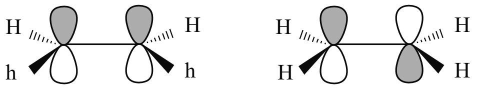
Anslysis of Cycloaddition by FMO Method

2 + 2 Addition is dimeisation of ethylene molecule



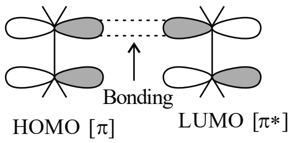
Ethylene ***Cyclobutane***

According to FMO method σ-bond formation must involve interaction of HOMO of one ethylene molecule with LUMO of other ethylene molecule. The symmetry properties of these orbitals may be given as



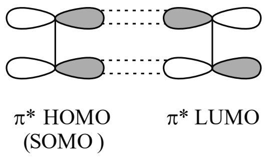
HOMO [π] ***LUMO [π*]***

Bonding effect of overlap between similar phases is cancelled out by antibonding effect resulting to net bonding



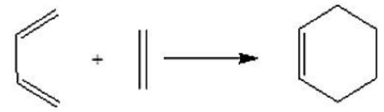
Overlap between HOMO and LUMO

Interaction produces a net bonding effect and photochemical dimerisation of ethylene is symmetry allowed.



Overlap of SOMO and LUMO

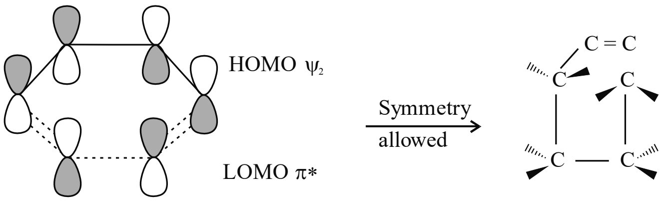
(4 + 2) Cycloaddition

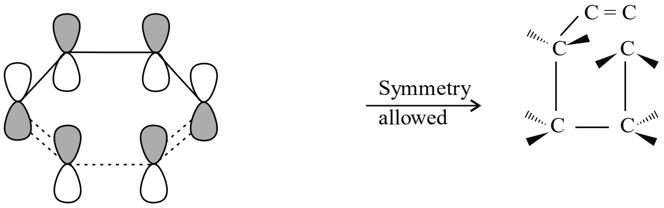


There will be two combination of HOMO-LUMO of reactants.

(a) ψ_2 HOMO of butadiene, π LUMO of ethylene

(b) π HOMO ethylene and ψ_3^* LUMO of butadiene

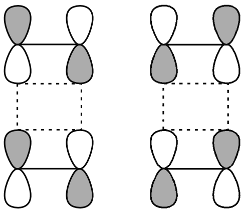




3. Analysis by PMO Method

Transition state for each patterns of cycloaddition is constructed.

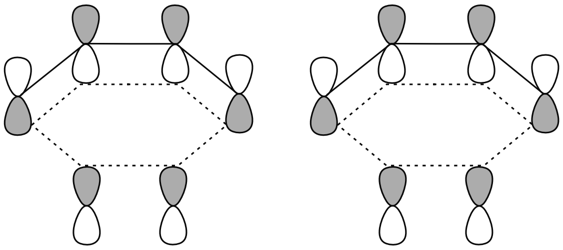
(a) 2s + 2s Cycloaddition



Transition State 4π Electrons, O Node Therefore Antiaromatic

Hence thermally forbidden and photochemically allowed.

(b) 4s + 2s Cycloaddition



Transition State 6π Electrons, O Node Therefore Aromatic

Hence thermally allowed and photochemically forbidden.

Table 5.2 *Selection Rules for Cycloaddition and Cycloreversion by PMO Method*

($m+n$) electron	**Number of node**	**Type of aromaticity**	**Nature of reaction**	
			Δ allowed	***nν* allowed**
4*n*	O or even	Antiaromatic	–	Supra-supra Antara-antara
4*n*	Odd	Aromatic	Supra-supra Antara-supra	–
4*n* + 2	O or even	Aromatic	Supra-supra Antara-antara	–
4*n* + 2	Odd	Antiaromatic	–	Supra-antara Antara-supra

2+2 Addition of ene-Ketenes

Intramolecular [2+2] cycloaddition of ene-ketenes produces either fused-ring (via normal [2+2] cycloaddition) or bridged-ring (via cross-[2+2] cycloaddition) cyclobutanones. For example, the fused-ring cycloadducts are produced by terminal ene-ketenes and on the other hand, dimethyl-substituted ene-ketenes furnish bridged-ring cycloadducts. Both [2+2] cycloadducts are generated for monomethyl-substituted ene-ketenes.

5.4 CHELEOTROPIC REACTIONS

Cheletropic reactions also known as chelotropic reactions are a type of pericyclic reaction. A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals. A reorganization of σ and π bonds occurs in this cyclic array.

Specifically, cheletropic reactions are a subclass of cycloadditions. The key distinguishing feature of cheletropic reactions is that on one of the reagents, both new bonds are being made to the same atom. A few examples are below. In the first case, the single atom is the carbonyl carbon that ends up in carbon monoxide. The end result is making two new bonds to one atom. The first two examples are known as cheletropic extrusions because a small stable molecule is given off in the reaction. The driving force for these reactions is often the entropic benefit of gaseous evolution (For example, CO or N_2).

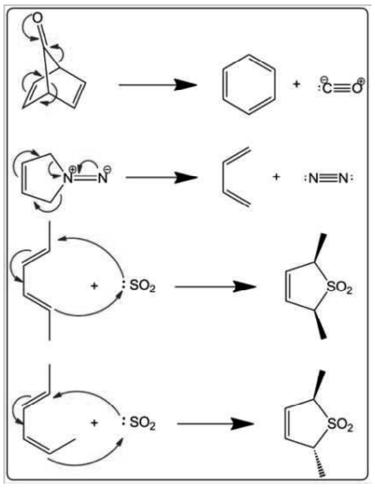


Fig. 5.5 *Cheletropic Reactions*

Theoretical Analysis

In the pericyclic transition state, a small molecule donates two electrons to the ring. The reaction process can be shown using two different geometries. The small molecule can approach in a linear or non-linear fashion. In the linear approach, the electrons in the orbital of the small molecule are pointed directly at the π-system. In the non-linear approach, the orbital approaches at a skew angle. The π-system's ability to rotate as the small molecule approaches is crucial in forming new bonds. The direction of rotation will be different depending on how many π-electrons are in the system. Shown below is a diagram of a two-electron fragment approaching a four-electron π-system using frontier molecular orbitals. The rotation will be disrotatory if the small molecule approaches linearly and conrotatory if the molecule approaches non-linearly. Disrotatory and conrotatory are sophisticated terms expressing how the bonds in the π-system are rotating. Disrotatory means opposite directions while conrotatory means the same direction.

Using Hückel's Rule, one can tell if the π-system is aromatic or anti-aromatic. If aromatic, linear approaches use disrotatory motion while non-linear approaches use conrotatory motion. The opposite goes with an anti-aromatic system. Linear approaches will have conrotatory motion while non-linear approaches will have disrotatory motion.

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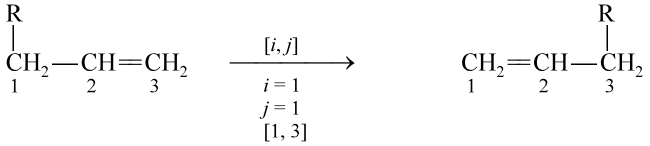
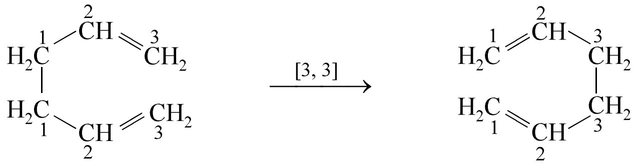
5.4.1 Sigmatropic Rearrangement

Rearrangements involving migration of a σ (sigma) bond to a new position within the system on heating (or by photolysis) are known as *Sigmatropic rearrangements* which proceed in a concerted manner with conservation of orbital symmetry. The general reaction may be written as follows:

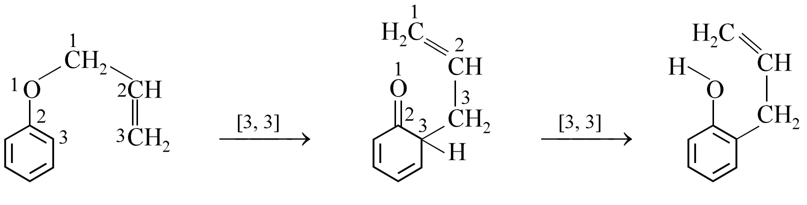


$$\underset{1}{\overset{\overset{R}{|}}{CH_2}}-\underset{2}{CH}=\underset{3}{CH_2} \xrightarrow[\substack{i=1\\ j=1\\ [1,3]}]{[i,j]} \underset{1}{CH_2}=\underset{2}{CH}-\underset{3}{\overset{\overset{R}{|}}{CH_2}}$$

The reactions are designated by [*i, j*] order where *i* and *j* refer to the number of atoms to which the migrating bond joins. The above reaction is a [1, 3] shift and the Cope rearangement and Claisen rearangement are [3, 3] shift.



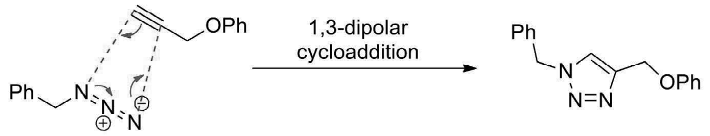
Cope rearrangement [3, 3] shift



Claisen rearrangement

5.4.2 1,3-Dipolar Cycloaddition

The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring. The earliest 1,3-dipolar cycloadditions were described in the late 19th century to the early 20th century, following the discovery of 1,3-dipoles. Mechanistic investigation and synthetic application were established in the 1960s, primarily through the work of Rolf Huisgen. Hence, the reaction is sometimes referred to as the Huisgen cycloaddition (this term is often used to specifically describe the 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate 1,2,3-triazole). 1,3-dipolar cycloaddition is an important route to the regio- and stereoselective synthesis of five-membered heterocycles and their ring-opened acyclic derivatives.



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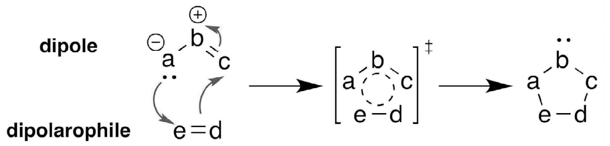
Mechanistic Overview

Originally two proposed mechanisms describe the 1,3-dipolar cycloaddition: first, the concerted pericyclic cycloaddition mechanism, proposed by Rolf Huisgen; and second, the stepwise mechanism involving a diradical intermediate, proposed by Firestone. After much debate, the former proposal is now generally accepted— the 1,3-dipole reacts with the dipolarophile in a concerted, often asynchronous, and symmetry-allowed $\pi 4_s + \pi 2_s$ fashion through a thermal six-electron Huckel aromatic transition state. Although, few examples exist of stepwise mechanism of the catalyst free 1,3-dipolar cycloaddition reactions for thiocarbonyl ylides, and nitrile oxides.



Pericyclic Mechanism

Huisgen investigated a series of cycloadditions between the 1,3-dipolar diazo compounds and various dipolarophilic alkenes. The following observations support the concerted pericyclic mechanism, and refute the stepwise diradical or the stepwise polar pathway.

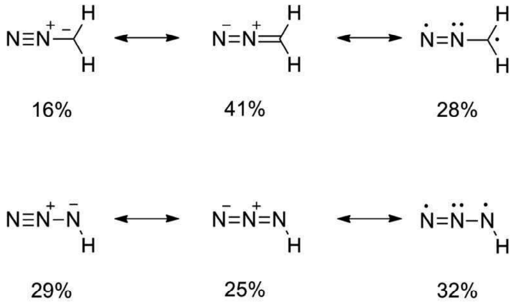
- **Substituent effects:** Different substituents on the dipole do not exhibit a large effect on the cycloaddition rate, suggesting that the reaction does not involve a charge-separated intermediate.
- **Solvent effects:** Solvent polarity has little effect on the cycloaddition rate, in line with the pericyclic mechanism where polarity does not change much in going from the reactants to the transition state.
- **Stereochemistry:** 1,3-dipolar cycloadditions are always stereospecific with respect to the dipolarophile (i.e., *cis*-alkenes giving *syn*-products), supporting the concerted pericyclic mechanism in which two sigma bonds are formed simultaneously.
- **Thermodynamic parameters:** 1,3-dipolar cycloadditions have an unusually large negative entropy of activation similar to that of the Diels-Alder reaction, suggesting that the transition state is highly ordered, which is a signature of concerted pericyclic reactions.

- **1,3-Dipole**

A 1,3-dipole is an organic molecule that can be represented as either an allyl-type or a propargyl/allenyl-type zwitterionic octet/sextet structures. Both types of 1,3-dipoles share four electrons in the π-system over three atoms. The allyl-type is bent whereas the propargyl/allenyl-type is linear in geometry. 1,3-Dipoles containing higher-row elements such as sulfur or phosphorus are also known, but are utilized less routinely.

Resonance structures can be drawn to delocalize both negative and positive charges onto any terminus of a 1,3-dipole. A more accurate method to describe the electronic distribution on a 1,3-dipole is to assign the major resonance contributor based on experimental or theoretical data, such as dipole moment measurements or computations. For example, diazomethane bears the largest negative character at the terminal nitrogen atom, while hydrazoic acid bears the largest negative character at the internal nitrogen atom.

Major resonance structures



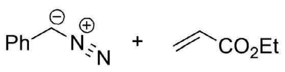
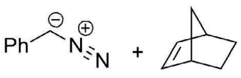
Consequently, this ambivalence means that the ends of a 1,3-dipole can be treated as both nucleophilic and electrophilic at the same time. The extent of nucleophilicity and electrophilicity at each end can be evaluated using the frontier molecular orbitals, which can be obtained computationally. In general, the atom that carries the largest orbital coefficient in the HOMO acts as the nucleophile, whereas that in the LUMO acts as the electrophile. The most nucleophilic atom is usually, but not always, the most electron-rich atom. In 1,3-dipolar cycloadditions, identity of the dipole-dipolarophile pair determines whether the HOMO or the LUMO character of the 1,3-dipole will dominate.

- **Dipolarophile**

The most commonly used dipolarophiles are alkenes and alkynes. Heteroatom-containing dipolarophiles such as carbonyls and imines can also undergo 1,3-dipolar cycloaddition. Other examples of dipolarophiles include fullerenes and nanotubes, which can undergo 1,3-dipolar cycloaddition with azomethine ylide in the Prato reaction.

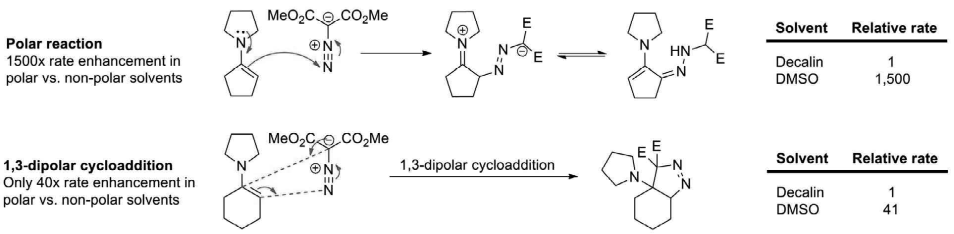
Solvent effects

1,3-dipolar cycloadditions experience very little solvent effect because both the reactants and the transition states are generally non-polar. For example, the rate of reaction between phenyl diazomethane and ethyl acrylate or norbornene changes only slightly upon varying solvents from cyclohexane to methanol.

	Solvent	 relative k_1	 relative k_2
non-polar	cyclohexane	1	1
	dioxane	1.48	0.82
	DMF	3.16	1.06
polar	methanol	5.34	0.98

NOTES

Lack of solvent effects in 1,3-dipolar cycloaddition is clearly demonstrated in the reaction between enamines and dimethyl diazomalonate. The polar reaction, N-cyclopentenyl pyrrolidine nucleophilic addition to the diazo compound, proceeds 1,500 times faster in polar DMSO than in non-polar decalin. On the other hand, a close analog of this reaction, N-cyclohexenyl pyrrolidine 1,3-dipolar cycloaddition to dimethyl diazomalonate, is sped up only 41-fold in DMSO relative to decalin.

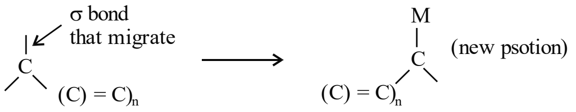


Solvent	Relative rate
Decalin	1
DMSO	1,500

Solvent	Relative rate
Decalin	1
DMSO	41

5.5 SIGMATROPIC REARRANGEMENTS

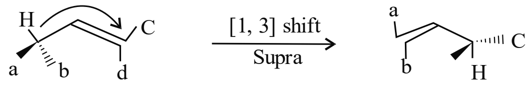
Many thermal and photochemical reactions involves shifting of an atom or group i.e., σ bond, in the same molecule flanked by one or more system leading to relocation of double bond/s. Since there is arrangement of σ bond, these reactions are termed as sigmotropic reaction or rearrangements.



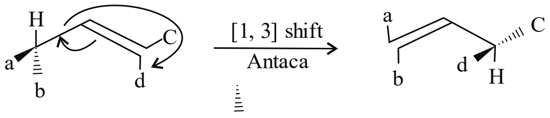
5.5.1 Modes of Migration

There are two geometrical path-ways through which a sigmatropic rearrangement can occur.

(a) **Suprafacial Migration:** In this migration, the migration group migrates across the same path, either along the top or bottom.

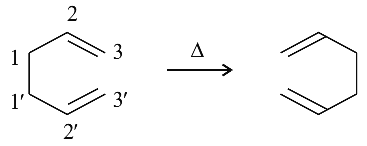


(b) **Antarafacial Migration:** In this migration, the migrating group migrates from top to bottom or vice versa.

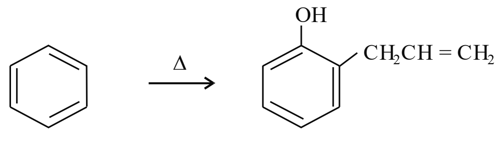


5.5.2 [3, 3] Sigmatropic Rearrangement

Cope rearrangement is a pericyclic reaction involving [3, 3] sigmatropic rearrangement of 1, 5-diene. These arrangements can be performed thermally or phtochemically. The cope rearrangement of diene has found utility in number of regioselectivity and stereoselective syntheses of open ring system.



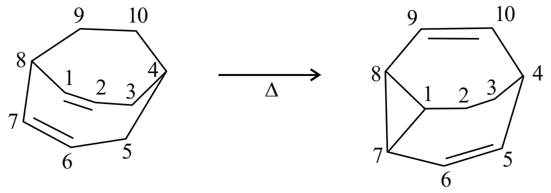
Claisen rearrangement also involves [3, 3] sigmatropic shift with conversion of rings others into carbonyl double bond, shifting the equilibrium completely to the product side.



Allyl phenyl ether   O-allyl pehnol

Degenerate cope rearrangement is shown by bullvalene, degeneracy means a rearrangement in which no gross change in structure has occured. Hence the product of rearrangement is structurally identical to the starting material.

Bullvalene converted to itself with a first order rate constant of 3440 sec^{-1} at 25°C.

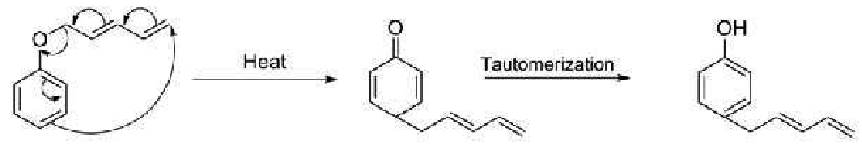


Degenerate Cope Rearrangement in Bullvalene

5.5.3 5, 5- Sigmatropic Rearrangements and Aza-Cope Rearrangements

Similar to [3,3] shifts, the Woodward-Hoffman rules predict that [5,5] sigmatropic shifts would proceed suprafacially, as per the Hückel topology transition state. These reactions are rarer than [3,3] sigmatropic shifts, but this is mainly a function of the fact that molecules that can undergo [5,5] shifts are rarer than molecules that can undergo [3,3] shifts.

[5,5] Shift of Phenyl pentadienylether



Rearrangements, especially those that can participate in cascade reactions, such as the ‘Aza-Cope’ rearrangements, are of high practical as well as conceptual importance in organic chemistry, due to their ability to quickly build structural

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complexity out of simple starting materials. The Aza-Cope rearrangements are examples of heteroatom versions of the Cope rearrangement, which is a [3,3]-sigmatropic rearrangement that shifts single and double bonds between two allylic components. In accordance with the Woodward-Hoffman rules, thermal Aza-Cope rearrangements proceed suprafacially. Aza-Cope rearrangements are generally classified by the position of the nitrogen in the molecule as shown below:

The first example of an Aza-Cope rearrangement was the ubiquitous cationic 2-Aza-Cope rearrangement, which takes place at temperatures 100-200 °C lower than the Cope rearrangement due to the facile nature of the rearrangement. The facile nature of this rearrangement is attributed both to the fact that the cationic 2-Aza-Cope is inherently thermoneutral, meaning there is no bias for the starting material or product, as well as to the presence of the charged heteroatom in the molecule, which lowers the activation barrier. Less common are the 1-Aza-Cope rearrangement and the 3-Aza-Cope rearrangement, which are the microscopic reverse of each other. The 1- and 3-Aza-Cope rearrangements have high activation barriers and limited synthetic applicability, accounting for their relative obscurity.

Check Your Progress

4. What do you understand by cycloaddition?
5. What does disrotatory mean?
6. Give an example of sigmatropic rearrangement.
7. Diels-Alder reaction is an example of which type of reaction?
8. What does HOMO stand for?

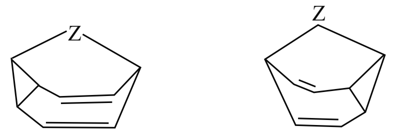
5.6 FLUXIONAL TAUTOMERISM

Bullvalene molecules are called fluxional molecule. Fluxional molecules might undergo dynamics in such a way that some or all of their atoms interchange between symmetry equivalent position.

In fluxional tautomerism compounds maintain the same number of component atoms like in simple tautomerism. At equilibrium these fluxional molecules exhibit several different isomers and fluctuate rapidly among them. Bullvalene molecule contains a three fold axis of symmetry and three symmetrical and equivalent cope systems are thus available to it.

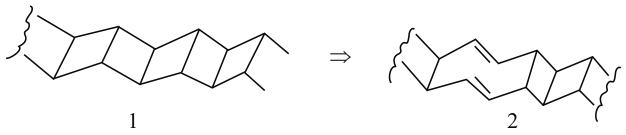
- In general fluxional molecules are a unique class of molecules with no permanent structure. A few common features of fluxional molecules are.

- Fluxional molecules behave differently at different temperature.
- While interchanging between different conformations many intermediates and metastable forms are reached.
- Fluxionality provides diversity in structure of a molecule.
- Several analogue of bullvalene such as semibullvalene and barbaralane also exhibit the phenomenon of fluxional isomers.



Z = bond	semibullvalene	$\Delta H^{*} = 5.2$ Kacl/mole
Z = CH_2	barbaralane	$\Delta H^{*} = 7.2$ Kacl/mole
Z = $CH = CH_2$	bullvalene	$\Delta H^{*} = 13.3$ Kacl/mole
Z = CH_2 CH_2	dhydrobullvalene	$\Delta H^{*} = 8.5$ Kacl/mole

Ladderane are an interesting class of compounds containing two or more fused cyclo butane rings.

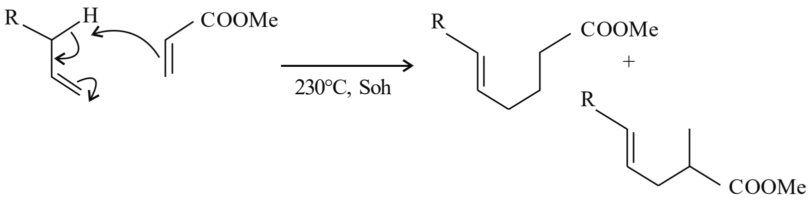


Fluxional Tautomerism

5.6.1 Ene Reaction: (Group Transfer Reaction)

Pericyclic reactions are a unique group of reactions characterized by a cyclic transition state, concerted mechanism and high stereospecificity. Group transfer reactions are a kind of pericyclic reactions, where one or more groups or atoms get transfered from one molecule to another, they follow the conservation of orbital symmetry rules i.e., Woodward-Haffmann rules. Ene reaction is amongst the most studied example of group transfer reaction.

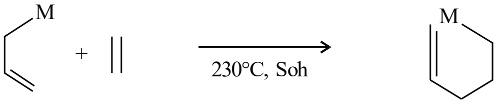
The reaction between the alkene which has an allylic hydrogen (known as the ene) with a compound containing a multiple bond i.e., the enophile is known as Ene reaction (Alder Ene reaction). Reaction is bimolecular and no ring is formed, they are neither signatropic shifts nor cycloaddition reactions.



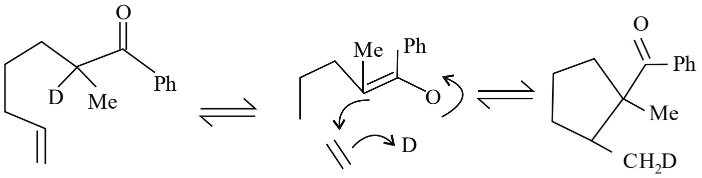
Electron withdrawing groups on the enophile and electron donating groups on Ene favours the reaction. Lewis acid catalyst such as $AlCl_3$ has also been shown to lead to rate enhancement for Ene reactions.

NOTES

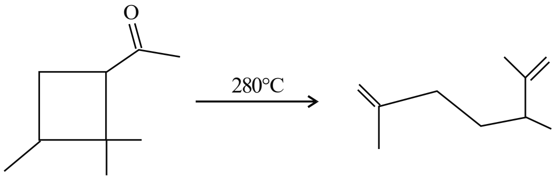
Ene reactions are found to have metal atoms (Mg, Ni, Pd, Li) in place of hydrogen atom such reaction are called a **Metalla-ene reactions.**



The intra molecular Ene reaction of unsaturated ketones, in which the enol-tautomer of the ketone function as the ene partner, is called the **Conia-ene reaction**.



Every step of this reaction is reversible which can be seen in **retro-Conia-ene** reaction of cyclobutanes where the chief product is the open-chain isomer.



Ene reaction with hetero atoms such as oxaene, azaene and thioene reactions are known and follow stereospecificity rules.

Check Your Progress

9. What is a fluxional molecule?
10. Give an example class of compounds containing two or more fused cyclo butane rings.
11. Which reaction are called a metallo-ene reactions?
12. Define Conia-ene reaction.

5.7 ANSWERS TO 'CHECK YOUR PROGRESS'

1. When reactions are highly stereospecific, so much so that initiation of reaction by heat or light gives products with different sterochemical nature.
2. FMO stands for Frontier Molecular Orbital.
3. The basic principle involved in pericyclic reactions is that orbitals of reactants interact to form a transition state which then changes to orbitals of the products. If the transition state is of relatively low energy then the reaction will be favoured.
4. When two or more mulecules containing unsaturated functional groups condense and form cyclic molecules transfering electrons from pi bond to new s bond, the reaction is termed as cyclo as cycloaddition.

5. Disrotatory means opposite directions while conrotatory means the same direction.
6. Claisen rearrangement is an example of sigmatropic rearrangement.
7. Diels-Alder reaction is an example of pericyclic reaction.
8. HOMO stands for Highest Occupied Molecular theory.
9. Bullvalene molecules are called fluxional molecule. Fluxional molecules might undergo dynamics in such a way that some or all of their atoms interchange between symmetry equivalent position.
10. Ladderane is an interesting class of compounds containing two or more fused cyclo butane rings.
11. The intra molecular Ene reaction of unsaturated ketones, in which the enol-tautomer of the ketone function as the ene partner, is called the Conia-ene reaction.

5.8 SUMMARY

- Large number of reactions of olefinic compounds are known which do not involve ionic or free radical intermediates and are initiated by heat or light. Apparently solvents and catalysts do not affect these reactions. Such reactions in which bonds are broken and made in a single concerted step through a cyclic transition state were termed as pericyclic reactions.
- An electrocyclic reaction is a type of pericyclic rearrangement where the net result is one pi bond being converted into one sigma bond or vice versa.
- A cycloaddition is a chemical reaction, in which "two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity." The resulting reaction is a cyclization reaction. Many but not all cycloadditions are concerted and thus pericyclic. Nonconcerted cycloadditions are not pericyclic.
- A sigmatropic reaction in organic chemistry is a pericyclic reaction wherein the net result is one s-bond is changed to another s-bond in an uncatalyzed intramolecular process.
- Woodward and Hofmann (1965) in order to explain pericyclic reactions, suggested that all concerted reactions occur with conservation of molecular orbital symmetry. This is known as conservation of molecular orbital symmetry principle.
- Cheletropic reactions also known as chelotropic reactions are a type of pericyclic reaction.
- A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals.
- The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring.

- The earliest 1,3-dipolar cycloadditions were described in the late 19th century to the early 20th century, following the discovery of 1,3-dipoles.
- Rearrangements involving migration of a s (sigma) bond to a new position within the system on heating (or by photolysis) are known as Sigmatropic rearrangements which proceed in a concerted manner with conservation of orbital symmetry.
- Diels-Alder and other cyloadditions are highly stereospecific.
- The addition of two molecules with p electrons may occur either on the same or opposite side.
- If the new bond formation occurs on the same side of the double bond it is termed as suprafacial addition while if the new bonds are formed on the opposite side of p bonds it is termed as antarafacial addition.
- Ene reactions are found to have metal atoms (Mg, Ni, Pd, Li) in place of hydrogen atom such reaction are called a Metalla-ene reactions.

5.9 KEY TERMS

- **Pericyclic reaction:** A pericyclic reaction is a type of organic reaction wherein the transition state of the molecule has a cyclic geometry, the reaction progresses in a concerted fashion, and the bond orbitals involved in the reaction overlap in a continuous cycle at the transition state.
- **Cycloaddition reaction:** A cycloaddition is a chemical reaction, in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. The resulting reaction is a cyclization reaction.
- **Antarafacial**: The newly formed bonds lie on opposite faces of the p system. This type of orientation is termed as antarafacial addition and subscript “a” is used to denote it.
- **Suprafacial addition:** If the new bond formation occurs on the same side of the double bond it is termed as suprafacial addition.
- **Pericyclic reaction**: A pericyclic reaction is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals. A reorganization of s and p bonds occurs in this cyclic array.
- **Sigmatropic rearrangements**: Rearrangements involving migration of a s (sigma) bond to a new position within the system on heating (or by photolysis) are known as Sigmatropic rearrangements which proceed in a concerted manner with conservation of orbital symmetry.
- **Fluxional molecule**: Bullvalene molecules are called fluxional molecule. Fluxional molecules might undergo dynamics in such a way that some or all of their atoms interchange between symmetry equivalent position.

- **Fluxional Tautomerism**: In fluxional tautomerism compounds maintain the same number of component atoms like in simple tautomerism. At equilibrium these fluxional molecules exhibit several different isomers and fluctuate rapidly among them.
- **Conia-ene reaction**: The intra molecular Ene reaction of unsaturated ketones, in which the enol-tautomer of the ketone function as the ene partner, is called the Conia-ene reaction.

5.10 SELF ASSESSMENT QUESTIONS AND EXERCISES

Short-Answer Questions

1. What are electrocyclic reactions? Give an example.
2. What are cycloaddition reactions?
3. Write the application of cycloaddition reaction.
4. Give one example each of cope reaction, claisen reaction and chelotropic reaction.
5. What is cope's rearrangement?
6. Write the mechanism of claisen rearrangement.
7. State the mechanism of 1,3 dipolar addition.
8. What are the solvent effects of 1,3 dipolar addition?
9. Write few common features of fluxional molecules
10. What is fluxional tautomerism?
11. Write an example of ene reaction.

Long-Answer Questions

1. Discuss the mechanism of pericyclic reaction.
2. Explain the reactions of the major classes of pericyclic reaction.
3. Describe the conservation of molecular orbital symmetry principle.
4. Explain the difference between electrocyclic reaction and cycloaddition reaction.
5. Analyze cycloaddition reaction by correlation diagram method.
6. Discuss chelotropic reactions in detail.
7. Explain the general reaction of sigmatropic rearrangement.
8. Discuss the mechanism of Diels-Alder reaction.

5.11 FURTHER READING

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