

9

Dr. RAJIV Kaur
(Chemistry)

ORGANIC REACTIONS AND SYNTHESIS OF A DRUG MOLECULE

SYLLABUS

(6 Lecturers)

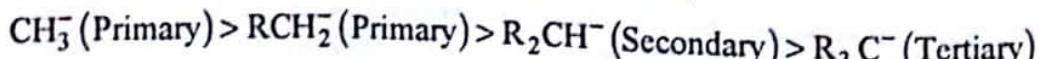
Introduction to reactions involving substitution, addition, elimination, oxidation, reduction, cyclization and ring openings. Synthesis of a commonly used drug molecule.

9.1 INTRODUCTION

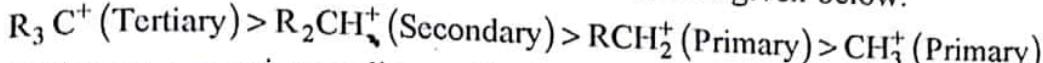
All chemical reactions involve the breaking of existing bond in the reactant molecules and formation of new bonds in the product of the molecules. An intermediate transition complex is first formed during the reaction, which is immediately change to final products. In the covalent bond, the shared electrons are held together by mutual attraction of the two atomic nuclei of the concerned atoms. So, it is important to know in what ways the bonds are broken and transition state is formed. When a bond between the two atoms breaks in such a way that one electron of the shared pairs remains with each of the two atoms, we call it *homolytic fission* and it results into the formation of *free radicals*. The free radicals are highly reactive due to the presence of *unpaired electrons* with them. Alternatively, when the two shared electrons remains associated with only one of two atoms, the type of fission is heterolytic fission. It results into the formation of a cation and an anion which type of fission will take place depends upon the nature of bond and the prevailing conditions. Mostly, it depends upon the electronegativity of the two concerned atoms. Homolytic fission will appear when the electronegativities are equal or almost equal. For example, molecules like Cl_2 , Br_2 , CCl_4 etc. undergo homolytic fission. but when the electronegativity differs, heterolytic fission results, e.g. in HCl , HBr , H_2O , HN_3 etc.

The carbon atoms carrying a negative charge due to the presence of electron pair with it, is called *carbanion* and other carbon atoms carrying a positive charge is called *carbonium ion (or carbocation)*.

The stability of carbanions follow the order given below:



The stability of carbocations follows the reverse order as given below:



In this chapter, we are going to discuss the details of the above noted types of organic reactions particular regarding the mechanism of these reactions. In studying the mechanisms of any organic reactions, it is essential to know about the different types of attaching agents also because the mechanism of the reaction is named on the attacking agent. The following are some important types of attaching reagents.

9.2 TYPES OF ATTACHING REAGENTS

1. Electrophilic reagents (Electrophiles)

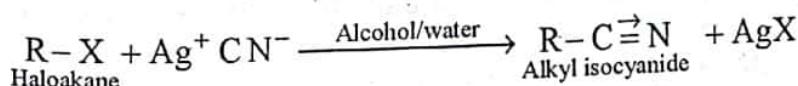
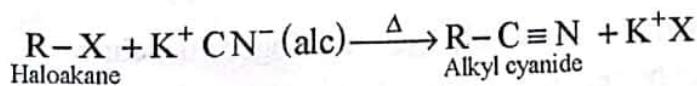
It is an electron-deficient (or electron-loving) chemical species. Due to the electron-efficency, it always attacks at the centre of high electron-density. Electrophiles are further classified as:

- (i) *Positive electrophiles*, e.g. H^+ , H_3O^+ , Cl^+ , Br^+ , I^+ , N^+O_2 , R^+ (carbocation) etc.
- (ii) *Neutral electrophiles*, e.g. $\cdot R$ (free radical), BF_3 , $AlCl_3$, $SnCl_4$, $RCOCl$, SO_3 , $:CR_2$ (carbene), $:NR$ (nitrone), etc.

2. Nucleophilic reagent (Nucleophiles)

It is an electron-rich (or nucleus loving) chemical species. Due to the presence of a pair of free electrons, it always attacks at the centre of low electron density. Nucleophiles are:

- (i) *Negative nucleophiles*, e.g. F^- , Cl^- , Br^- , I^- , $.OH^-$, CN^- , OR^- , NH_2^- , $RCOO^-$, R^- (carbonion) etc.
- (ii) *Neutral nucleophiles*, e.g. H_2O , ROH , NH_3 , KOH , $R.NH_2$, ROR etc.
- (iii) *Ambident nucleophiles*: When an electron rich species H_2 can react from both sides it is known as *ambident nucleophiles*, such as CN^- and NO_2^- . For example, cyanide ion (CN^-) can react from carbon side as well as nitrogen side. Likewise, NO_2^- can react from oxygen side as well as nitrogen side.



9.3

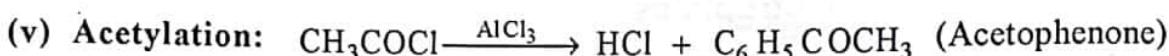
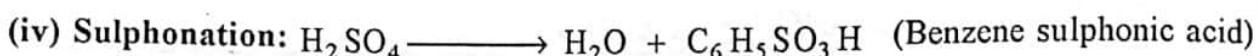
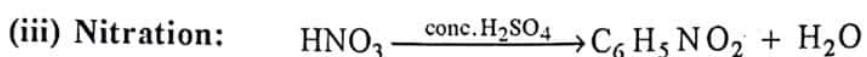
SUBSTITUTION REACTIONS

On the basis of mechanism of the reaction, the substitution reactions of the following two types:

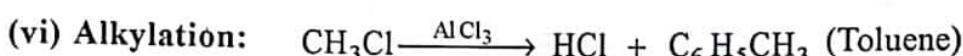
1. Electrophilic substitution reaction
2. Nucleophilic substitution reaction

1. Electrophilic substitution reactions

Substitution reaction of benzene are summarised as below:



This reaction is called *Friedel-Craft acylation*.



This reaction is called *Friedel-Craft alkylation*.

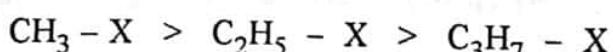
2. Nucleophilic substitution reaction

Alkyl halides are highly reactive in nature. This is due to the fact that halogen atom is held rather loosely in the carbon atom and hence can be easily removed.

(i) For a given alkyl group, the order of reactivity is:

iodides > bromides > chlorides.

(ii) Among the primary alkyl halides the order to reactivity is:

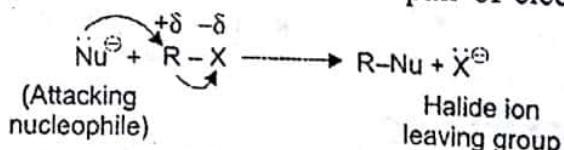


Explanation for reactivity of alkyl halides:

The C-X bond in R-X is polar, i.e. $\delta+$ $\delta-$



Due to the presence of partial negative charge on halogen, it behaves as a Lewis base. This weak basic halogen atom can be readily displaced by stronger bases (nucleophile), which are also electron-rich and possess at least one lone pair of electrons as shown below:



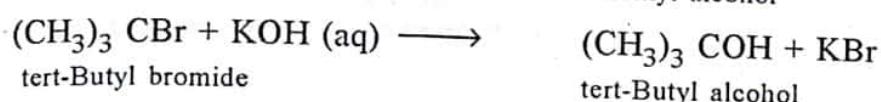
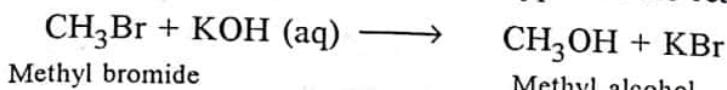
9.3.1 Types of Nucleophilic Substitution Reactions

There are mainly two types of nucleophilic substitution reactions. They are:

- (i) SN_2 (nucleophilic substitution, bimolecular) reactions.
- (ii) SN_1 (nucleophilic substitution, unimolecular) reactions

Kinetics of nucleophilic substitution reactions

It seems probable that the two mechanisms involved in alkyl halides with hydroxyl ions are the same with other nucleophiles. The two types of the reactions are as follows:



These two reactions appear to be similar and are expected to follow similar mechanistic path. However, both the reactions follow different kinetic order as illustrated below:

The rate of the first reaction is:

$$\text{Rate} = k [\text{CH}_3\text{Br}] [\text{KOH}]$$

It means that the reaction results from the collision between methyl bromide and hydroxyl ion. This is found to be so.

In second reaction, the rate is dependent on the concentration of alkyl halide only and is independent of base concentration, i.e.

$$\text{Rate} = k [\text{C}_4\text{H}_9\text{Br}]$$

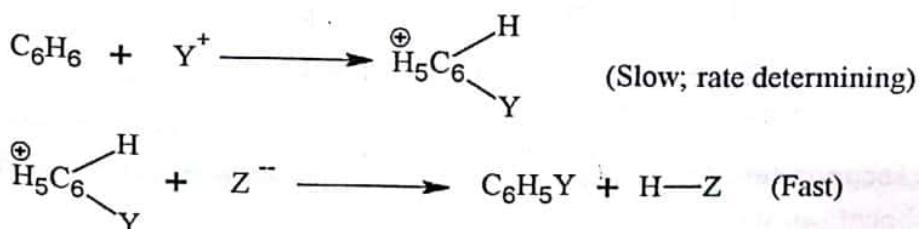
Hence, first reaction follows second-order kinetics and second reaction follows first-order kinetics. To account for this difference, two different mechanisms are proposed for these reactions:

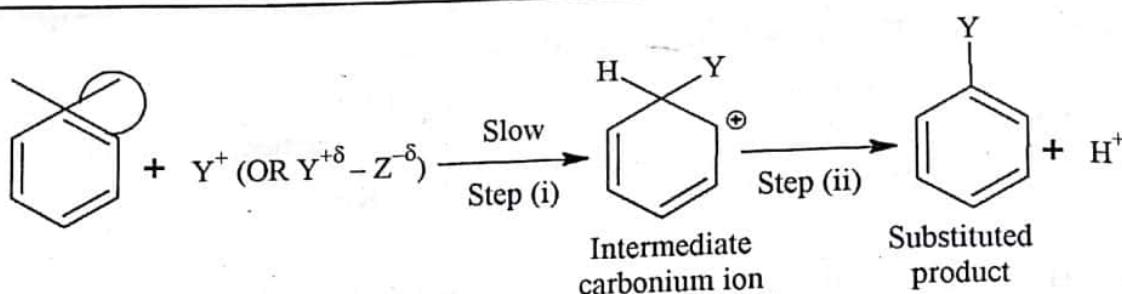
- (i) **$\text{S}_{\text{N}}1$ Reactions:** Tertiary alkyl halides undergo nucleophilic substitution reactions by a first-order mechanism.
- (ii) **$\text{S}_{\text{N}}2$ Reactions:** Primary alkyl halides undergo nucleophilic substitution reactions by a second-order mechanism. The details of $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions are explained at a later stage in this chapter.

9.4 MECHANISMS OF ELECTROPHILIC MONO-SUBSTITUTION IN BENZENE RING

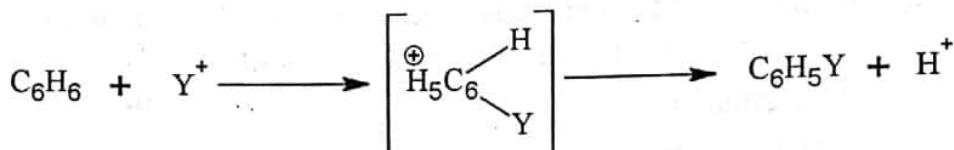
In monosubstitution, two steps are involved:

The key step is considered to be the attack of an electrophile at carbon of the ring to form a cationic intermediate. This step may be represented by the following general equation in which the attacking reagent is represented either as a electrophile (Y^+) or as a neutral but polarized ($\text{Y}^{+\delta} - \text{Z}^{-\delta}$) molecule.





The overall mechanism is as follows:



This is based upon the fact that when aromatic compounds labelled with deuterium or tritium were subjected to nitration, bromination and Friedel-Crafts alkylation, deuterium and tritium are replaced at the same rate as protium H.

This conclusively proves that the above reactions whose rate we are comparing do not involve the breaking of the carbon-hydrogen bond.

The rate of the overall substitution is determined by the slow attachment of the electrophile, Y^+ , to the aromatic ring to form the carbonium ion. Once formed, the carbonium ion rapidly loses hydrogen ion to form the products. Step (i) is thus the *rate-determining step*. Since it does not involve the breaking off carbon-hydrogen bond, its rate is independent of the particular hydrogen isotope which is present.

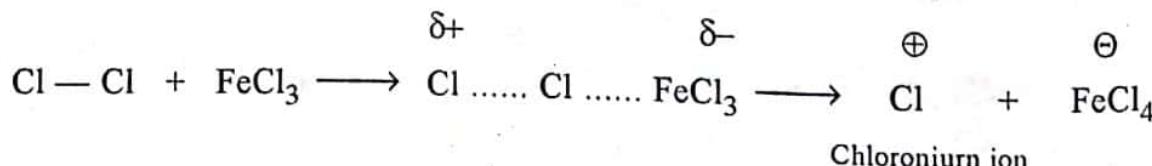
Thus the absence of isotopic effect establishes not only the two-step nature of electrophilic aromatic substitution but also the relative speeds of the steps.

Mechanisms of Some Electrophilic Substitution Reactions of Benzene

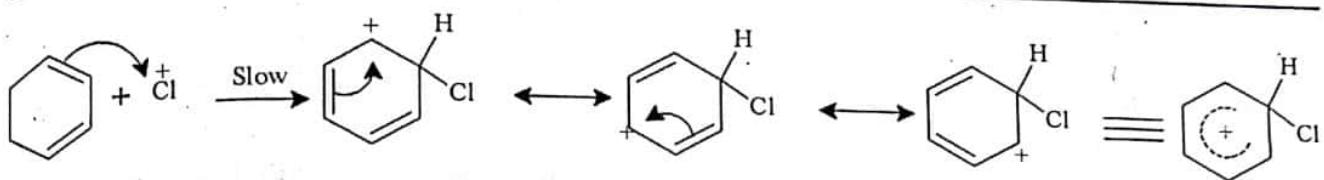
1. Mechanism of halogenation

The commonly accepted mechanism for aromatic halogenation, illustrated for chlorination, involves the following steps:

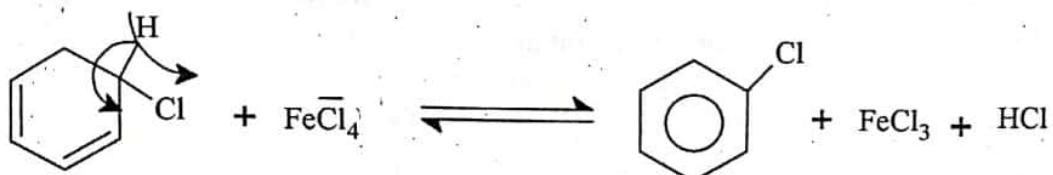
The first step generates the attacking electrophile Cl^+ by an acid-base equilibrium (Lewis acid). Metallic iron, which is added as a catalyst, is converted into ferric chloride by chlorine. The ferric chloride, in turn, polarizes the chlorine molecule yielding an electrophile which brings about the further reaction, e.g., generation of the electrophile



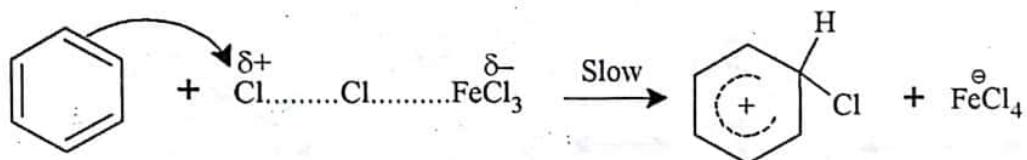
In the second step, chloronium (Cl^+) ion attacks the π -electron cloud of benzene ring forming a carbocation, which is stabilized by resonance.



Abstraction of proton from the carbocation: In the third step, the proton is then abstracted from the carbocation intermediate by the base FeCl_4^- to form the final product, chlorobenzene.



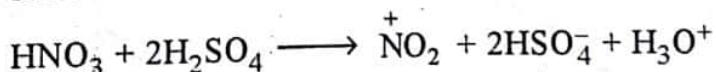
It may be pointed out here that in actual practice, the free chloronium ion may not be formed at all. Rather, the true electrophile is the complex between the Lewis acid and the chlorine molecule, whose positive end attacks the π -electrons of the benzene ring, i.e.



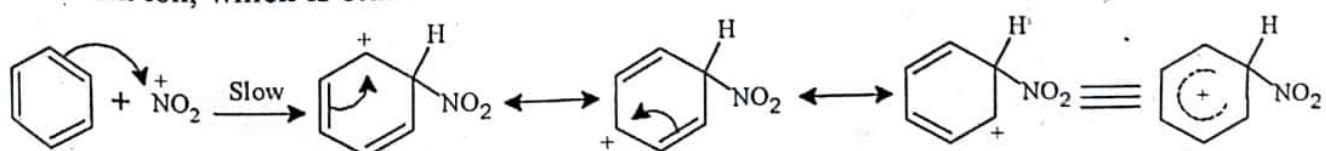
2. Mechanism of nitration

The following steps were involved.

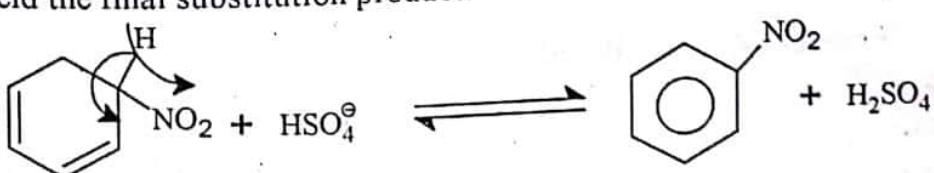
In the **first step**, nitronium ion NO_2^+ which is electrophilic reagent that attacks the benzene ring is obtained. The reaction is simply acid—base equilibrium in which H_2SO_4 serves as the acid and HNO_3 serves as a base.



In the **second step**, the nitronium ion reacts with benzene to form an intermediate carbonium ion, which is stabilized due to resonance.



In the **third step**, the hydrogen ion is removed from the carbonium ion by the basic ion (HSO_4^-) to yield the final substitution product.



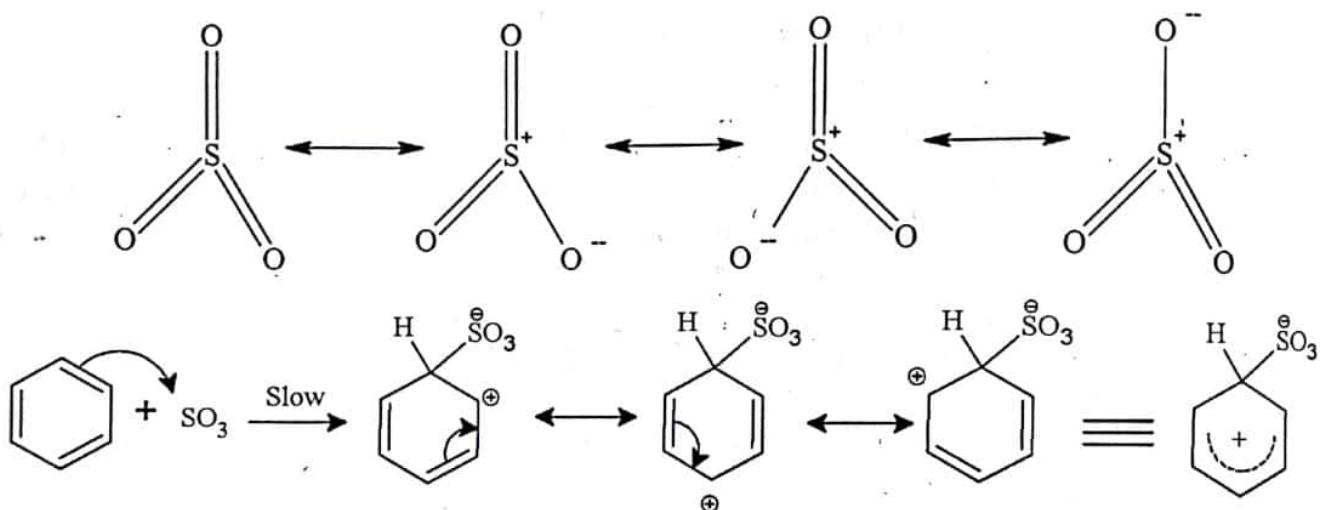
3. Mechanism of sulphonation

The commonly accepted mechanism for sulphonation of aromatic compounds involves the following steps:

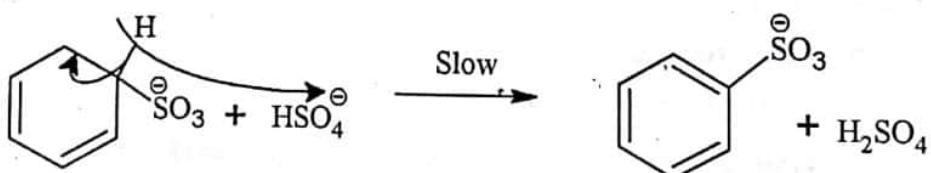
In the first step, electrophilic sulphur trioxide is produced by an acid—base equilibrium between two molecules of sulphuric acid.



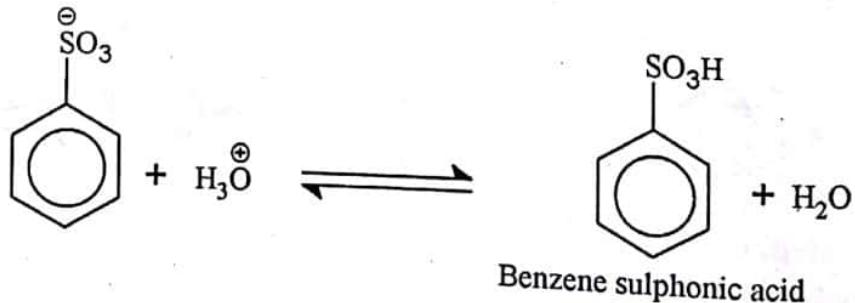
In the second step, SO_3 molecule is a neutral molecule but it has a powerful electron-deficient sulphur atom. It is clear from its resonance hybrid structures shown below:



In the third step, there is a loss of hydrogen ion to form the resonance-stabilized anion of benzene sulphonic acid.



In the fourth step, the benzene sulphonic acid anion reacts with H_3O^+ to form benzene sulphonic acid.

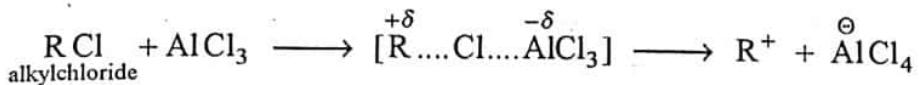


4. Mechanism of Friedel—Crafts alkylation reaction

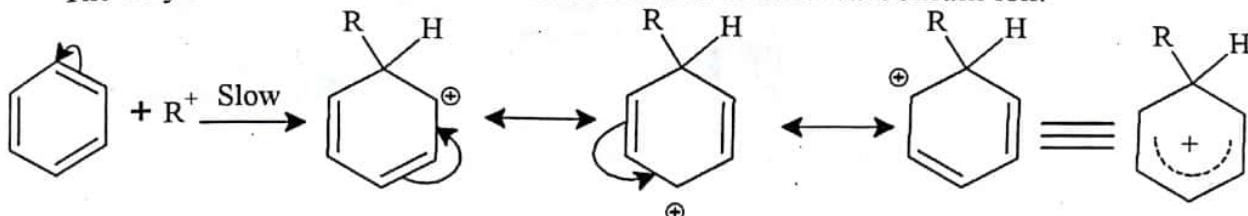
Benzene on treatment with an alkyl halide in the presence of a Lewis acid like AlCl_3 yields an alkyl benzene. In this reaction, a nuclear hydrogen is replaced by an alkyl. This reaction is known as *Friedel—Crafts alkylation reaction*.

Until recently the commonly accepted mechanism of Friedel—Crafts alkylation is shown in the following equations:

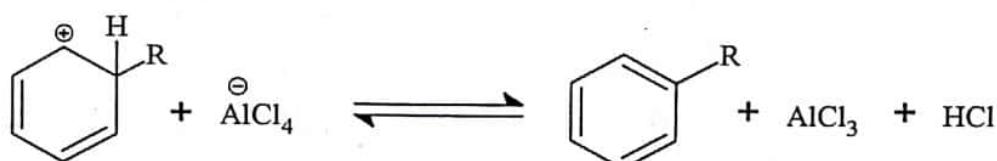
In the first step, the Lewis acid AlCl_3 converts the alkyl chloride into an alkyl carbonium ion.



The alkyl carbonium ion attacks benzene to form a carbonium ion.



The hydrogen ion from the carbonium ion is removed by the basic AlCl_4^- to produce the final substitution alkyl product.

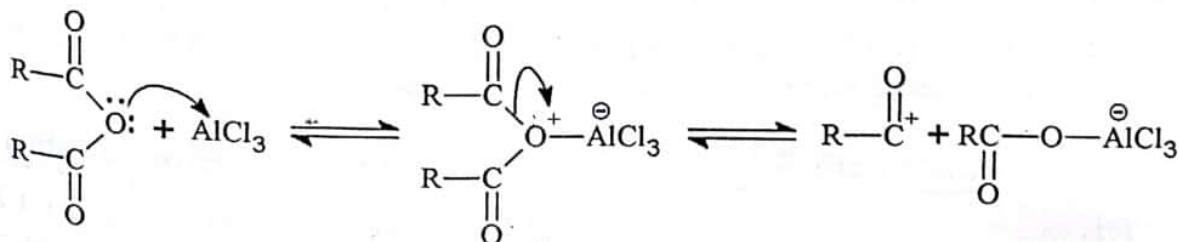
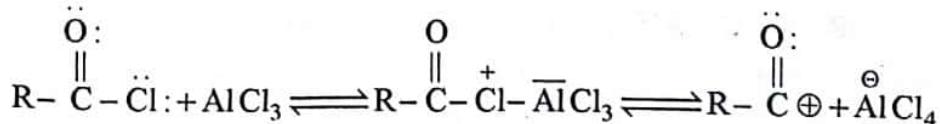


As shown above, Friedel—Crafts alkylations are reversible. Again the rate determining step is (b).

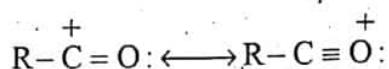
5. Friedel—Crafts acylation



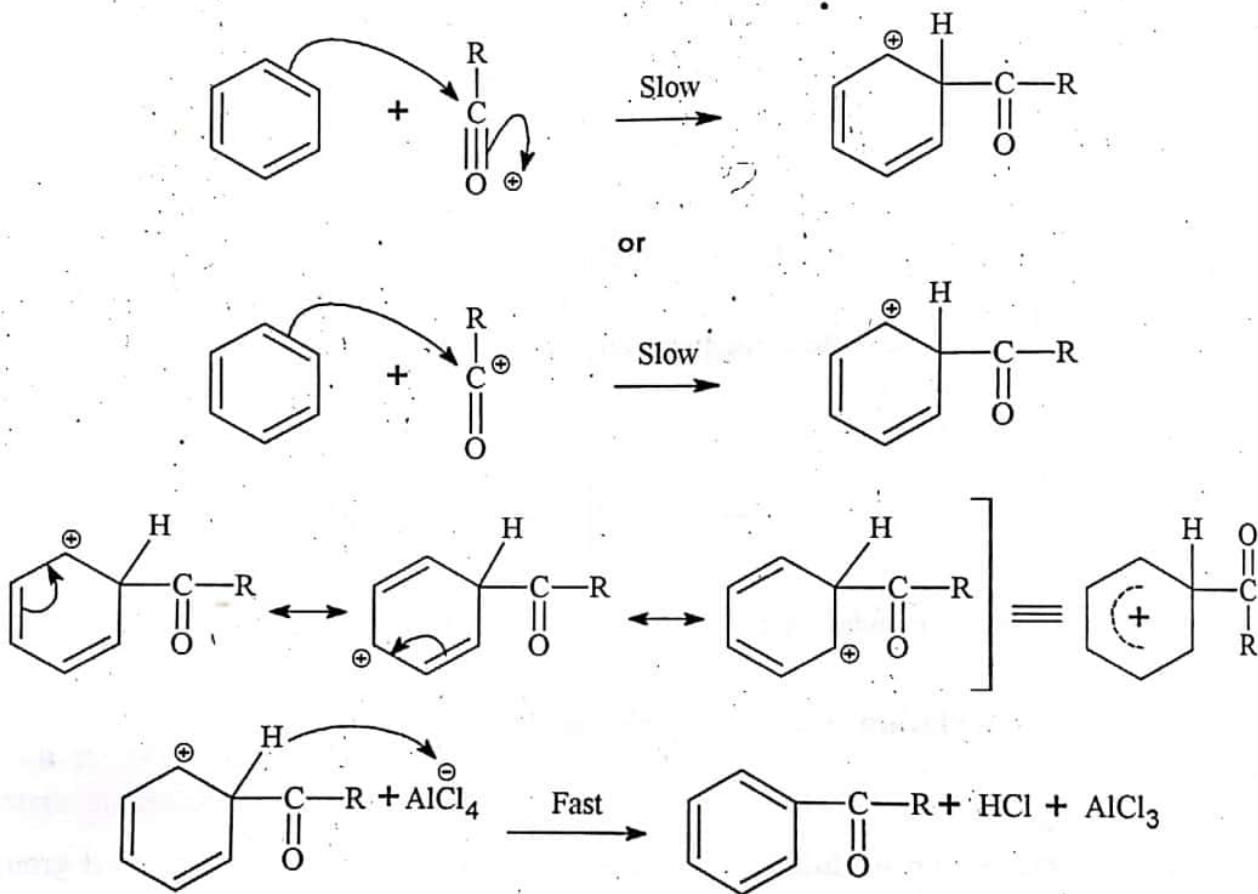
The $\text{R}-\text{C}-$ group is called an *acyl group*, and a reaction whereby an acyl group is introduced into a compound is called an *acylating agent*. Two common acylating agents are acid chlorides and carboxylic acid anhydrides. In most Friedel—Crafts acylations, the electrophile appears to be acylium ion formed from acyl chloride or acid anhydride with the help of Lewis acids in the following ways:



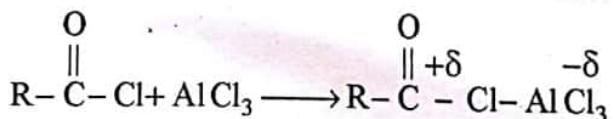
An acylium ion is the resonance hybrid of the following two resonating structures:



The remaining steps in the Friedel-Crafts acylation of benzene are as follows:



Alternatively, it has been suggested that the true tiectrophile in acylation reactions is actually the positive end of the complex between the acid chloride (or anhydride) and the Lewis acid.

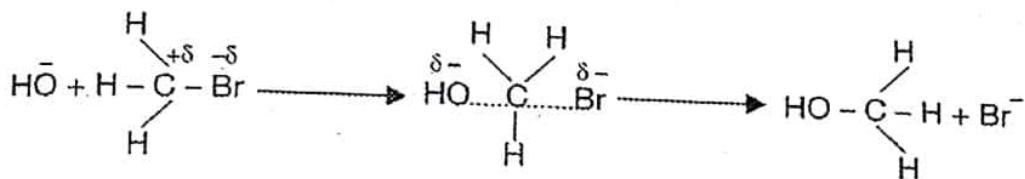


It may be pointed out here that since the aromatic ring is deactivated by the introduction of an electron withdrawing acyl group, unlike alkylation, there is no chance of polysubstitution in acylation reactions. Besides, the acylium ion does not undergo any rearrangement. It is on this account that this reaction is often employed for the preparation of alkylbenzenes by reduction of acylbenzenes (aliphatic aromatic ketones) by Clemensen reduction.

9.5 MECHANISMS OF $\text{S}_{\text{N}}2$ (Substitution Nucleophilic Bimolecular)

It is clear that in such reactions the nucleophile (OH^-) collides with the reactant (CH_3Br) molecule by the back side attack from the halogen atom (Br) and possesses sufficient energy

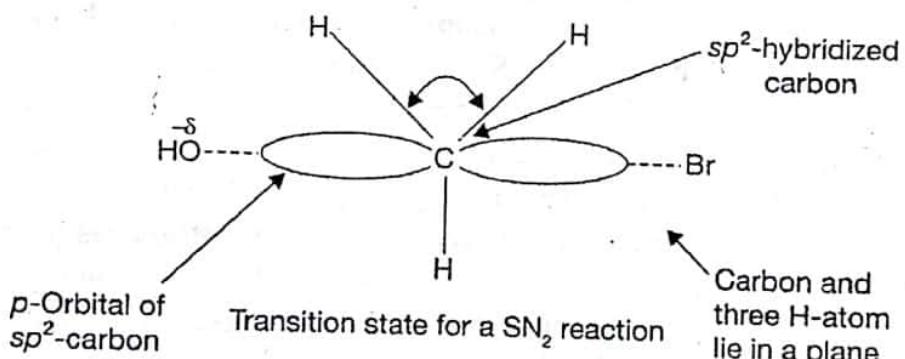
to break the C—Br bond and form C—OH bond. Hence the reaction (SN_2) proceeds through a transition state involving two reactant molecules. Thus a complete inversion of configuration takes place.



Backside attack of methyl bromide

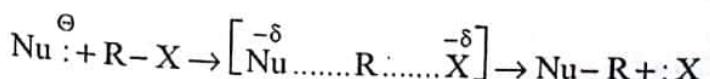
Transition state of a SN_2 reaction

In the transition state, the central carbon atom is sp^2 -hybridized and the three hydrogen atoms attached to it lie in a plane at bond angles of 120° . The OH group and the Br atom are partially bonded to each lobe of the p-orbital, which is perpendicular to the plane of three H atoms. The C—OH bond is partly formed and the C—Br bond is partly broken.



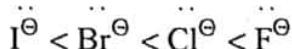
9.5.1 . Factors which influence SN_2 reactions

1. **Reactivity of alkyl halides:** The basic requirement of mechanism is the backside attack of the incoming nucleophile on the carbon atom carrying the halogen atom. This type of attack is quite easy in the case of primary halides as the small size of hydrogen atom does not hinder the attack. However, in case of tertiary alkyl halides, there are three bulky groups attached to carbon atom carrying a halogen atom. These alkyl groups cause overcrowding and hinder the incoming nucleophile. This type of hindrance is called *steric hindrance*. So the rate of SN_2 reaction decreases as the bulk of the substituents increases.
 $\text{CH}_3\text{X} > \text{Primary alkyl halide} > \text{Secondary alkyl halide} > \text{Tertiary alkyl halides} > \text{Neopentyl halides}$
2. **Nature of the halogen atom:** In the transition state for SN_2 reactions, the negative charge is normally distributed over the nucleophile and the leaving group. The better the leaving group, more stable is the transition state due to greater stabilization of the negative charge by the leaving group and hence more rapid is the reaction.

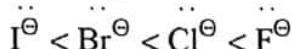


The stability of an anion is inversely proportional to its basicity. Therefore, best leaving groups are of weak-bases.

The order of increasing basic strength of halide ions is:



Therefore, the order of ease of elimination of leaving groups would be:



The bond dissociation energies of C-X bond are: 452 ($\text{CH}_3 - \text{F}$), 351 ($\text{CH}_3 - \text{Cl}$), 293 ($\text{CH}_3 - \text{Br}$) and 234 ($\text{CH}_3 - \text{I}$) kJ mol^{-1} . Therefore, C-I bond is the easiest to break while C-F bond is the most difficult.

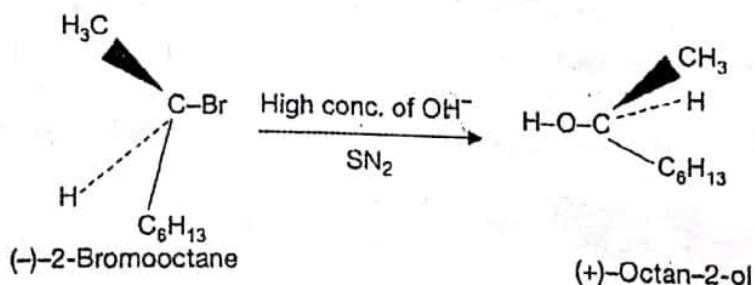
Hence the order or reactivity of alkyl halides having same alkyl group but different halogens is as $\text{R}-\text{I} > \text{R}-\text{Br} > \text{R}-\text{Cl} > \text{R}-\text{F}$

Nucleophilicity or strength of the nucleophile: Since the transition state in a $\text{S}_{\text{N}}2$ reaction is formed by the attack of the nucleophilic reagent on alkyl halide, stronger the nucleophilic reagent, more rapid would be $\text{S}_{\text{N}}2$ reaction. *The nucleophilicity of a reagent may be defined as its ability to donate a pair of electrons to the carbon atom.* Thus, greater is the nucleophilicity of a nucleophile, the more rapid should be its $\text{S}_{\text{N}}2$ reaction. As the nucleophiles have complete octet and a lone pair of electrons, therefore, all the nucleophiles should be basic in nature. However, their nucleophilicity does not always parallel their base strength. For instance, the hydroxide ion is a strong base and is also a good nucleophile but iodide ion is a very good nucleophile though it is very weak base. In a series of nucleophiles belonging to the same family, the nucleophilicity increases with the increase in the size of the atom bearing the unshared pair (lone pair) of electrons. Therefore, the nucleophilicity of halide ions in the decreasing order is: $\text{I}^\ominus > \text{Br}^\ominus > \text{Cl}^\ominus > \text{F}^\ominus$

9.5.2 Effect of solvent on $\text{S}_{\text{N}}2$ reaction

As the transition state in $\text{S}_{\text{N}}2$ reaction is non-polar, therefore, non-polar solvent will stabilize it and will lower the activation energy of the $\text{S}_{\text{N}}2$ reaction. Hence non-polar solvent will favour $\text{S}_{\text{N}}2$ reaction.

Stereochemistry of $\text{S}_{\text{N}}2$ Reaction: Due to the attack of incoming nucleophile on the alkyl halide from the backside, the configuration of the molecule is inverted. This is proved when (-)-2-bromo-octane is hydrolysed under $\text{S}_{\text{N}}2$ conditions (high concentration of hydroxide ion), it gives exclusively, (+)-octan-2-ol as shown below:



Thus if the alkyl halide is optically active and laevorotatory, the substitution product is also optically active and dextrorotatory. This inversion of configuration is known as *Walden inversion*.

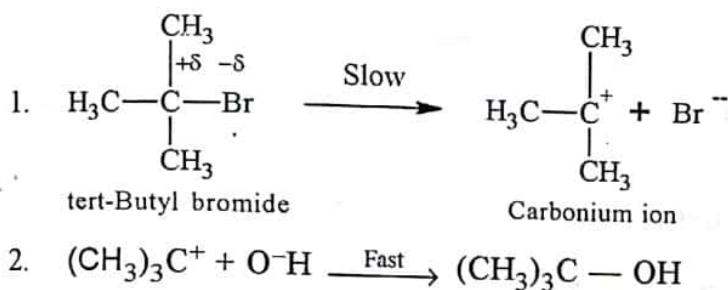
9.6 SN_1 REACTION

A nucleophilic substitution reaction in which the rate of kinetics depends upon the concentration of only one reactant is called an SN_1 reaction.

$$\text{Rate} = k [\text{RX}]$$

Mechanism of SN_1 (substitution nucleophilic unimolecular) reaction

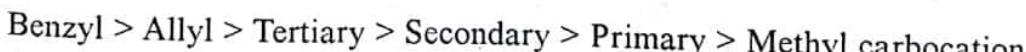
The mechanism suggested for the reaction between tert-butyl bromide and hydroxide ion is as under:



As the rate-determining step is only the slowest one, it means that the rate of reaction depends upon the concentration of tert-butyl bromide only, Rate = $k (\text{CH}_3)_3\text{CBr}$.

9.6.1 Factors which influence SN_1 reactions

- (i) **Effect of solvent:** As the transition state of SN_1 reaction is polar, therefore polar solvents will stabilize it and lower its activation energy. Hence polar solvents favour SN_1 reaction.
- (ii) **Nature of nucleophiles:** As the nucleophiles do not take part in the rate-determining step of SN_1 reaction, the strength of the nucleophile has no effect the rate o reaction.
- (iii) **Effect on structure of alkyl halides:** We have discussed above that the carbocations are be intermediates in SN_1 reactions. Therefore, the more stable the carbocation formed, the more rapid should be the SN_1 reaction. As the order of the stability of various carbocations follows be order:



Therefore, the order of reactivity of alkyl halides in SN_1 reactions follows the same sequences: Benzyl > Allyl > Tertiary > Secondary > Primary » Methyl halides

However, it may be noted here that this order of reactivity of alkyl halides is opposite to that of the SN_2 reactions.

- (iv) **Effect of nature of the leaving group:** Evidently, better the leaving group, lesser is the E_{act} for the zansition state leading to the formation of the carbocation and hence more should be the reactivity of the alkyl halide in SN_1 reactions. Thus the order of reactivity of the different leaving groups follows the sequence: $\text{I}^\ominus > \text{Br}^\ominus > \text{Cl}^\ominus > \text{F}^\ominus$

Stereochemistry of SN_1

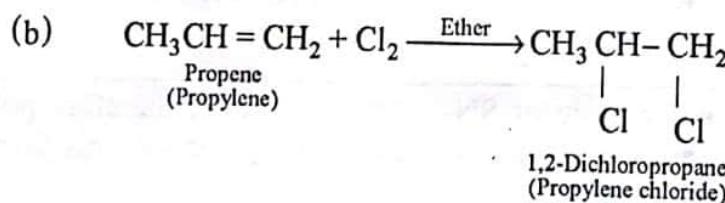
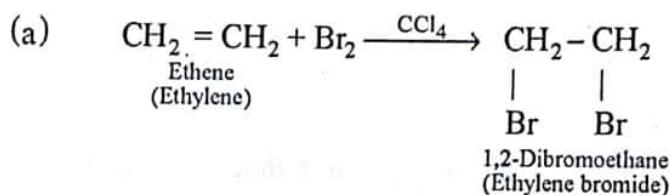
As the carbonium ion has a flat structure, therefore nucleophile can attack the carbocation carbon from either of the two directions. But the side of the leaving group is to some extent hindered because of the presence of halides ion, so attack from this side is less. Thus, the major attack from this side which is just opposite to the halide ion. Hence, partial racemization takes place in which inverted product is major and retention product is minor.

9.7 ADDITION REACTIONS

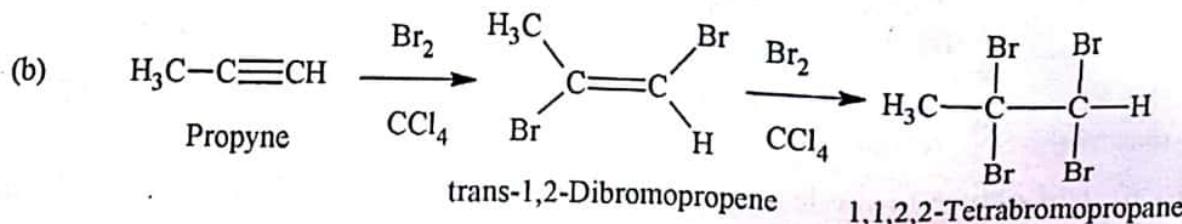
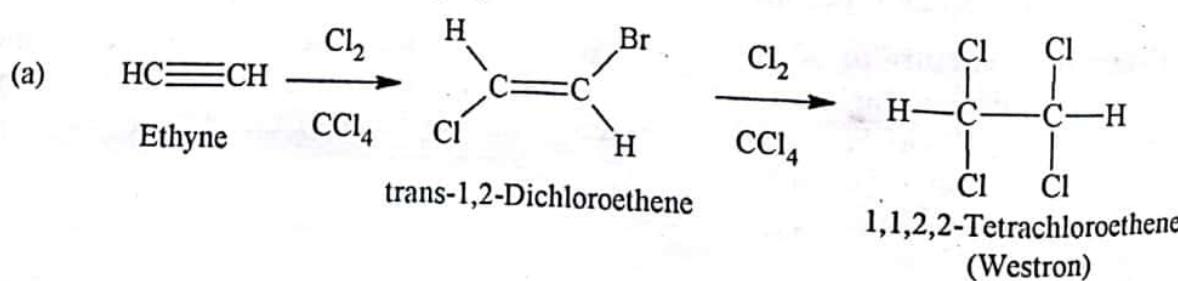
Unsaturated compounds containing double and triple bond between the two C atoms i.e. alkenes and alkynes give addition reactions. Their addition reactions with halogens and halogen acids are given below:

Addition of halogens

Halogens such as chlorine and bromine readily add to alkenes to form 1, 2-dihaloalkanes. For example,



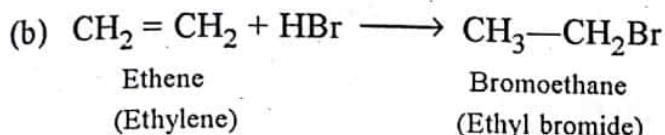
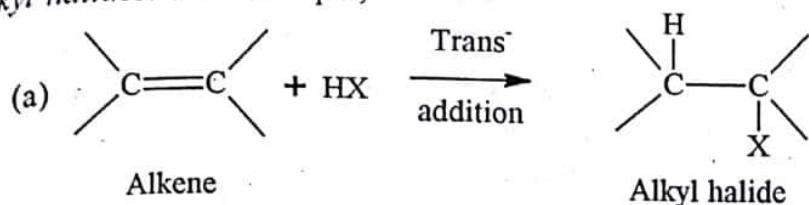
Chlorine and bromine readily add to alkynes first forming 1,2-dihaloalkenes and then 1, 2, 2-tetrahaloalkanes. For example,



During this reaction, the reddish brown colour of Br_2 is decolourised and hence this reaction is used as a test for unsaturation, i.e. for double bond and triple bond.

Addition of halogen halides.

Alkenes react with halogen halides (HCl , HBr , HI) to form monohaloalkanes called *alkyl halides*. For example,



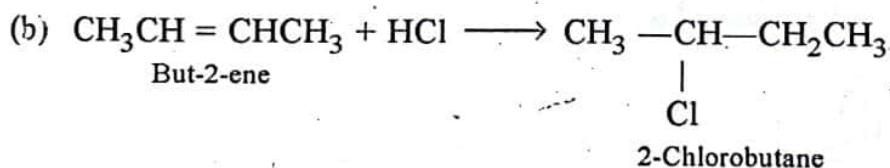
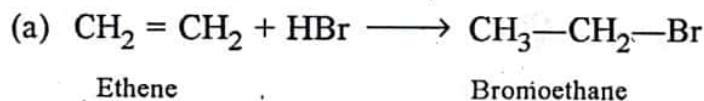
The order of reactivity of halogen halides in this reaction is : $\text{HI} > \text{HBr} > \text{HCl}$. This order of reactivity can be explained on the basis of bond dissociation energies of the halogen halides; lower the bond dissociation energy, more reactive is the halogen halide.



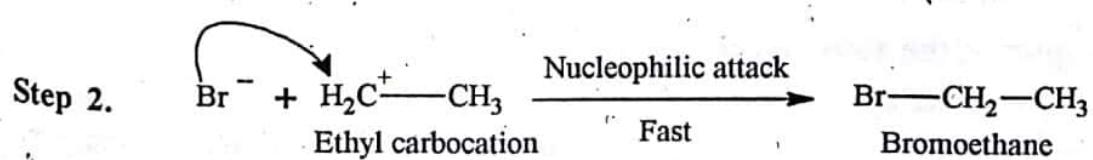
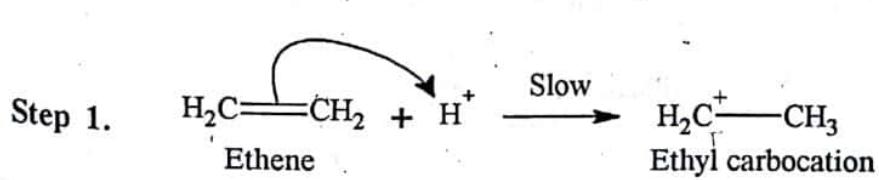
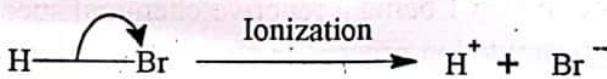
The actual product formed, however, depends upon whether the alkene is symmetrical or unsymmetrical as discussed below :

Addition to symmetrical alkenes.

When the alkene is symmetrical only one product is theoretically possible. For example,



Mechanism: Like the addition of halogens, addition of halogen halides to alkenes is also an *electrophilic addition reaction* and occurs by the following steps:



9.7.1 Electrophilic Addition Reactions

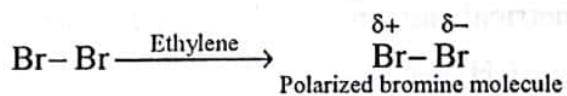
Alkenes are characterized by the presence of a double bond which consists of a strong C—C, σ -bond and a weak C—C, π -bond. The π -electrons form an electron cloud which lies above and below the plane of σ -bonded carbon atoms. These, π -electrons are, therefore, more exposed and hence are less tightly held between the two carbon atoms. Since the electrons are negatively charged particles, therefore, the electrons attract the *electrophiles* and repel *nucleophiles*. In other words, alkenes undergo *electrophilic reactions*.

Thus, the typical reactions of alkenes are *electrophilic addition reactions* and not the *electrophilic substitution reactions*.

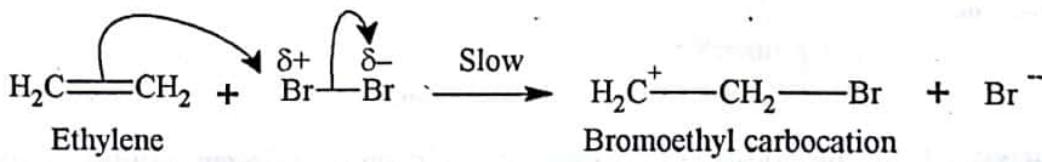
Mechanism of Electrophilic Addition Reactions

Let us illustrate the mechanism of electrophilic addition reactions by taking the example of addition of Br_2 to ethylene. The reaction occurs by a *two-step ionic mechanism* as discussed below:

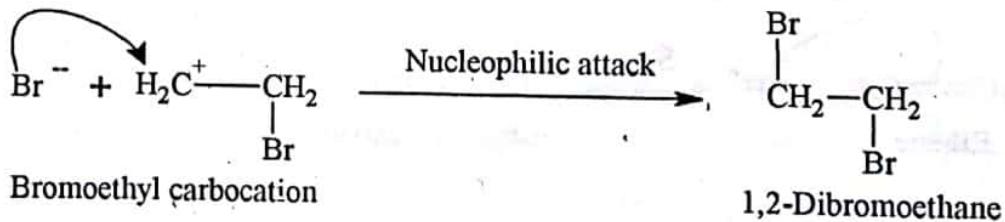
Step 1. Bromine molecule itself is *non polar* but when it comes close to an ethylene molecule, the π -electrons of the double bond begin to repel the electron pair holding the two bromine atoms together in the bromine molecule. As a result, bromine molecule gets *polarized*. The positive end of this bromine dipole behaves as an *electrophile* and is attracted by the π -electrons of the ethylene molecule to form a π -complex which subsequently gives the carbocation and the bromide ion. *This step is slow and hence is the rate-determining step of the reaction.*



This step can simply be represented as



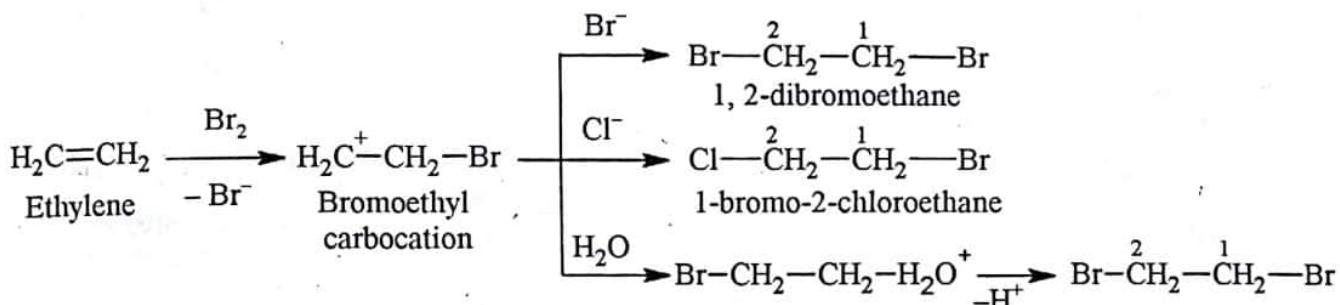
Step 2. The carbocation formed in step 1 being a reactive chemical species immediately undergoes *nucleophilic attack* by the bromide ion present in the solution forming the addition product. *This step is fast and hence does not affect the rate of the reaction.*



Evidence in support of the above mechanism.

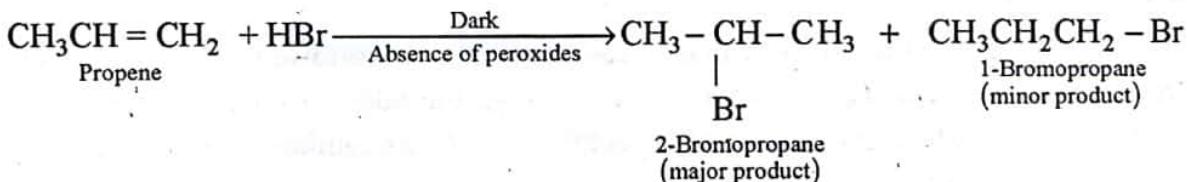
If the carbocations are really the intermediates in the above mechanism, then they should also react with other nucleophiles when added to the reaction mixture and hence a

mixture of products should be formed. This has indeed been found to be so. For example, when ethylene is bubbled into an aqueous solution of bromine containing sodium chloride, besides 1, 2-dibromoethane, 1-bromo- 2-chloroethane and 2-bromoethanol are also formed.



Addition to unsymmetrical alkenes.

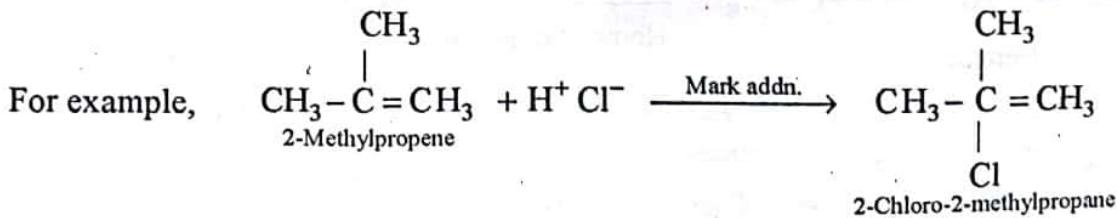
When the alkene is unsymmetrical, two products are theoretically possible. For example, the addition of HBr to propene *in the dark and in the absence of peroxides* can, in principle, give two products. But experimentally, it has been found that under these conditions, the major product is 2-bromopropane and the minor product is 1-bromopropane.



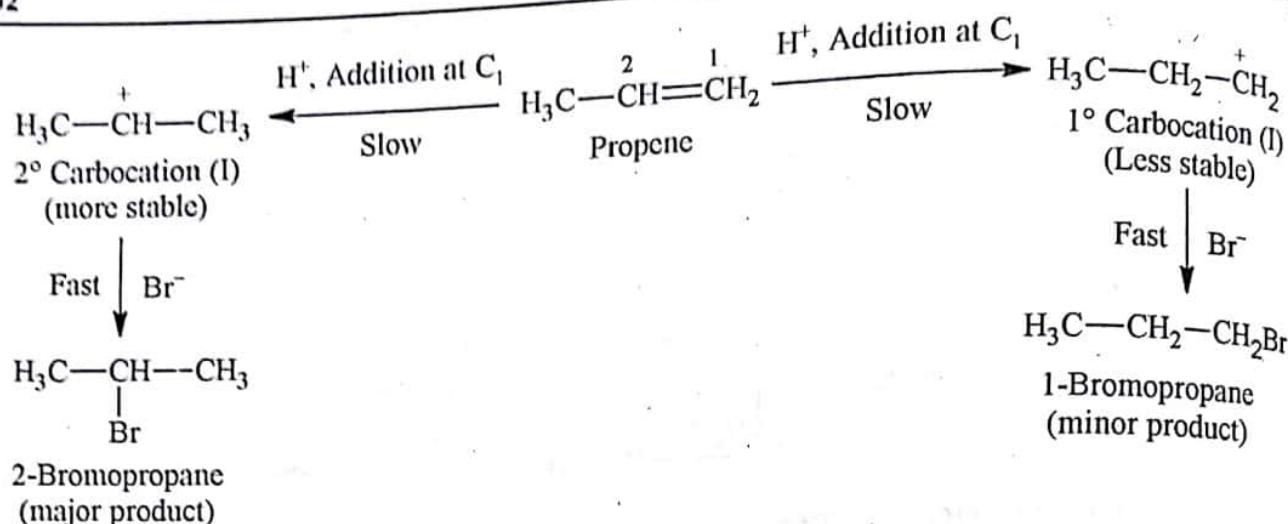
Markovnikov's rule.

Markovnikov, a Russian chemist, studied a large number of such addition reactions and postulated an empirical rule in 1869 which is known after his name as Markovnikov's rule. The rule states that,

The addition of unsymmetrical reagents such as HX , H_2O , HOX , etc. to unsymmetrical alkenes occurs in such a way that the negative part of the addendum (i.e., adding molecule) goes to that carbon atom of the double bond which carries lesser number of hydrogen atoms.



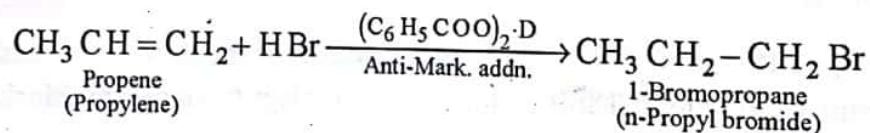
Explanation of Markovnikov's rule. The addition of halogen halides to alkenes is an *electrophilic addition reaction*. Thus, during the addition of HBr to propene, the first step involves the addition of a proton. This addition, in principle, can occur in two ways. If the proton adds on the terminal carbon atom of the double bond, a 2° carbocation (I) is formed and if the addition occurs on the middle carbon atom, a 1° carbocation (II) is produced.



Since, a 2° carbocation (I) is more stable than 1° carbocation (II), therefore, carbocation (I) is predominantly formed. This carbocation then rapidly undergoes nucleophilic attack by the Br^- ion forming 2-bromopropane as the major product. *Thus, Markovnikov's addition occurs through the more stable carbocation intermediate.*

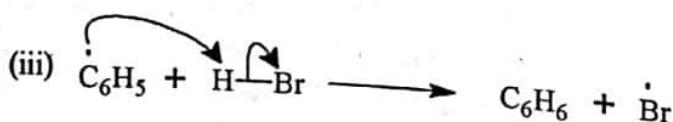
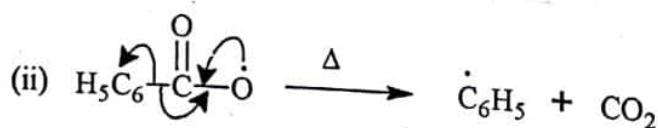
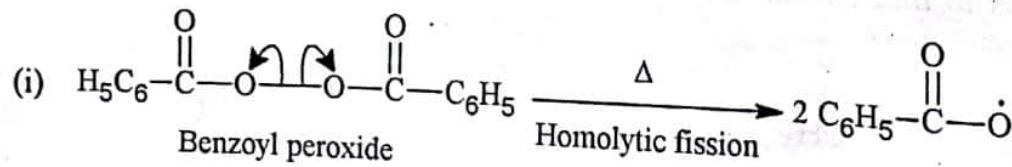
Peroxide effect.

It may be noted that Markovnikov's rule is not always followed. In presence of peroxides such as benzoyl peroxide ($\text{C}_6\text{H}_5\text{CO-O-O-CO-C}_6\text{H}_5$), the addition of HBr (but not of HCl or HI) to unsymmetrical alkenes takes place contrary to Markovnikov's rule. This is known as *Peroxide effect or Kharasch effect*. Thus,



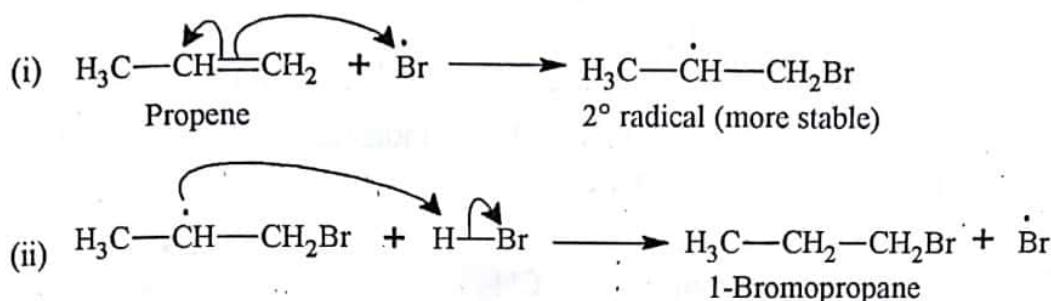
Mechanism. The addition of HBr to alkenes in presence of peroxides occurs by a *free radical mechanism*. It consists of the following three steps:

(a) Initiation.

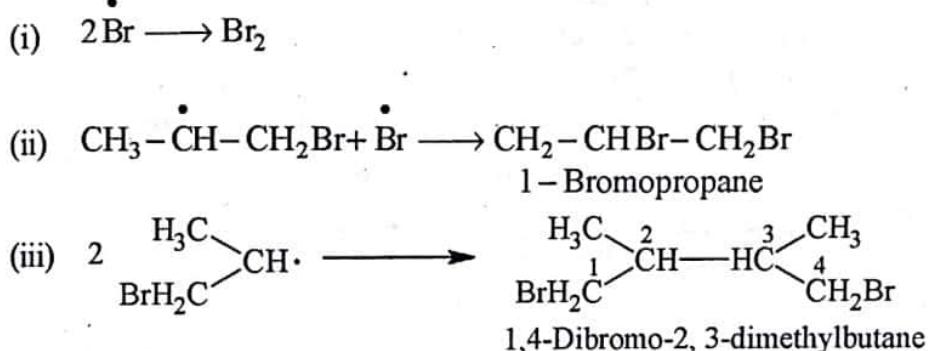


(b) Propagation. It consists of two steps.

During the first step, a Br adds to the double bond in such a way so as to give the more stable free radical. In the second step, the free radical thus produced abstracts a H from HBr to complete the addition.



(c) Termination.



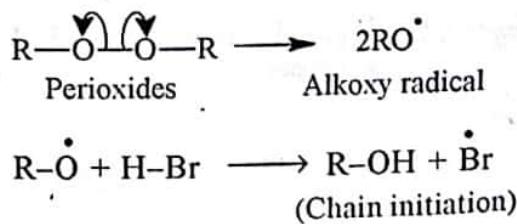
Exceptional behaviour of HBr. To understand why peroxide effect is observed only with HBr and not with HF, HCl or HI, let us consider the ΔH of the two propagation steps.

From the ΔH , it is clear that only with HBr, both the steps are *exothermic* and hence the peroxide effect is observed. With HCl or HF, the peroxide effect is not observed because the second step involving the reaction of carbon radical with HCl or HF is *endothermic*. Further, the peroxide effect is also not observed with HI because the first step involving the addition of iodine radical to alkenes is *endothermic*.

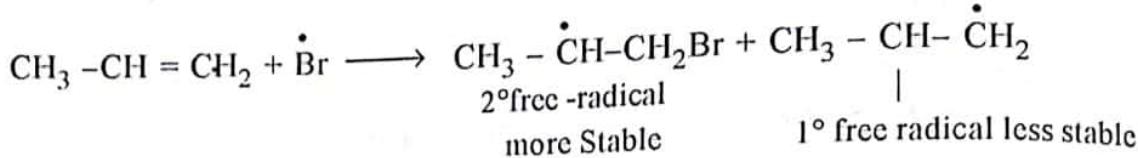
9.7.2 Free-radical addition

An example of free radical addition mechanism is addition of H—Br to an unsymmetrical alkene in the presence of peroxide. This is an anti-Markonikoff addition. It involves the following steps:

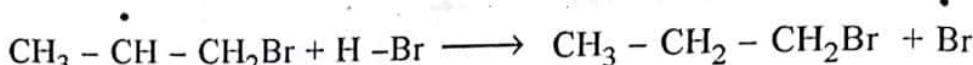
- (i) **Chain initiation step:** The reaction is initiated by the alkoxy radicals produced by the homolytic fission of peroxides, which abstracts an atom of hydrogen from HBr generating bromine free radicals (Br^\bullet).



(ii) **Chain Propagation Step:** The Br^{\cdot} then attacks the propylene molecule to give (by analogy with carbonium ions), a more stable secondary (as opposed to 1°) free radical;

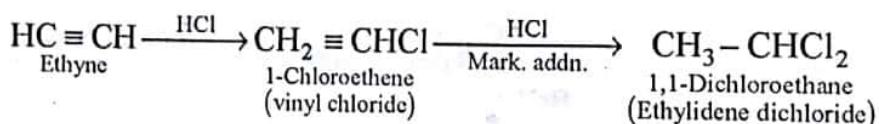


The secondary radical then reacts with another H–Br molecule to yield the product at another Br which can further propagate the reaction.

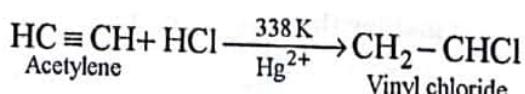


9.7.3 Addition of Halogen acids to alkynes

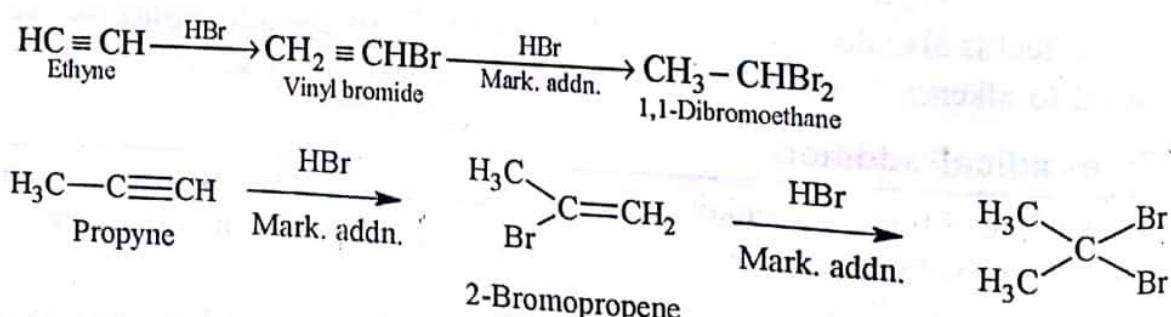
Halogen halides add to alkynes, their order of reactivity being $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$; HF adds only one under pressure. The addition of halogen acids can take place in the dark but is catalysed by light or metallic halides. *These additions occur in accordance with Markovnikov's rule to form first vinyl halides and then alkylidene halides.*



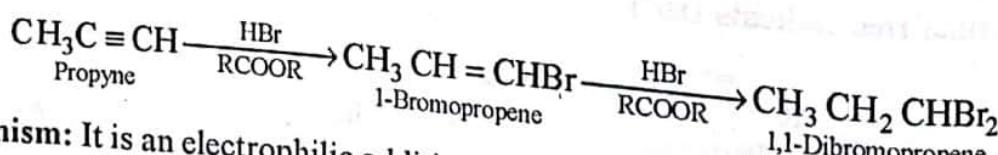
However, when acetylene is passed through dil. HCl at 338 K in presence of Hg^{2+} ions as catalyst, only vinyl chloride is formed.



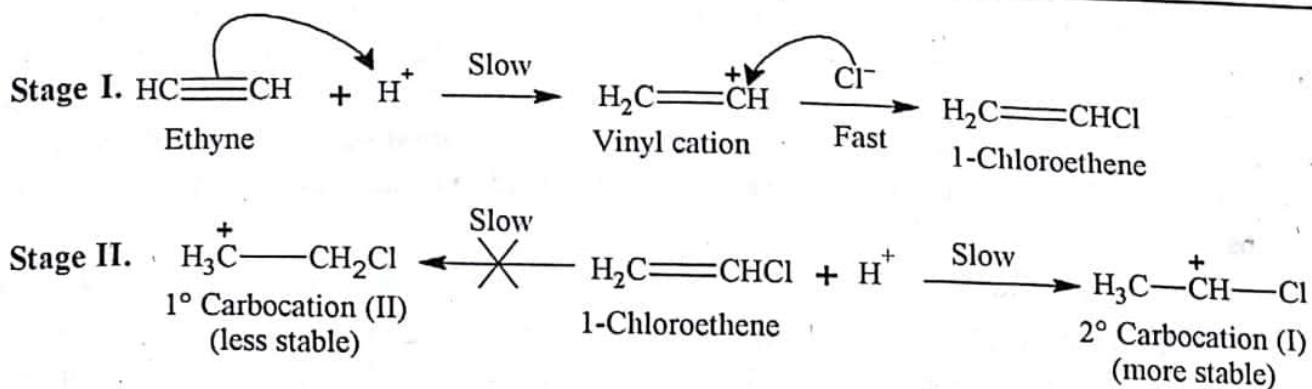
With hydrogen bromide, first a vinyl bromide and then an alkylidene dibromide is formed. For example,



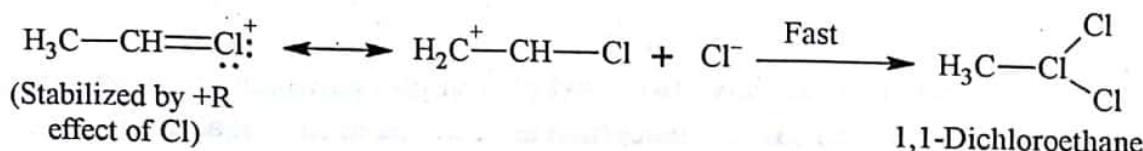
However, in presence of peroxides, anti-Markovnikov's addition of HBr occurs. For example,



Mechanism: It is an electrophilic addition reaction and occurs in two stages as discussed below:



Since carbocation (I) is stabilized by $+R$ -effect of the Cl atom while carbocation (II) is destabilized by $-I$ -effect of Cl, therefore, reaction occurs through the more stable carbocation (I) forming 1,2-dichloroethane.



9.7.4 Nucleophilic addition reaction

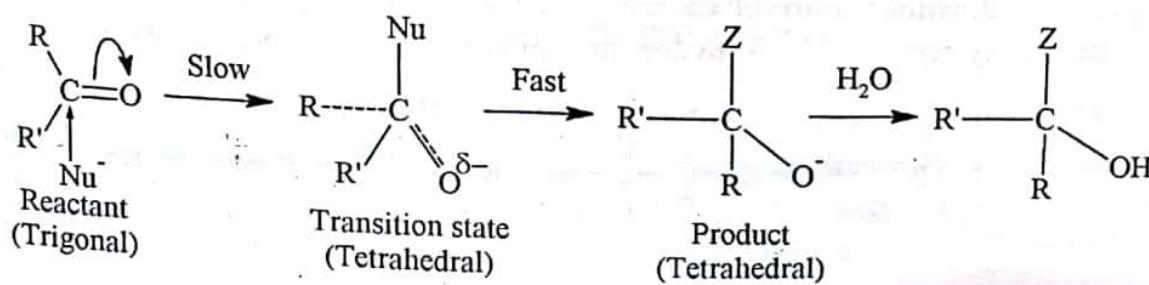
Aldehydes and ketones have a carbonyl group ($>\text{C}=\text{O}$) which is polar C^+-O^- , so as that the carbon atom is electron-deficient and the oxygen atom is relatively electron rich. In many reactions of carbonyl compounds, a new bond is set up between the carbonyl carbon and electron-rich species (nucleophile). Such reactions are called *nucleophilic additions*.

An example of this types of reactions is illustrated by the base -catalysed addition of HCN to acetaldehyde giving acetaldehyde cyanohydrin.

Mechanism of Nucleophilic Addition: Chemical reactions of carbonyl compounds are due to the presence of carbonylic group. This group:

- (i) provides site for nucleophilic addition and
- (ii) increases the acidity of α -hydrogen.

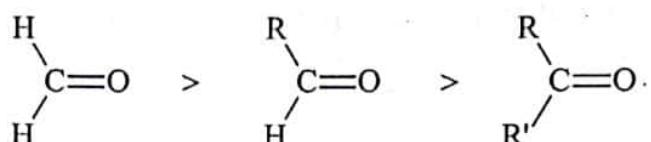
Both these effects are due to the ability of oxygen to accommodate a negative charge because there carbond–oxygen double bond and mobile π -electrons are pulled strongly towards oxygen. So carbonylic oxygen is electron rich and carbonylic carbon is electron deficient. A nucleophile can attack on carbonylic carbon and aldehydes or ketones undergo nucleophilic addition reactions.



In this reaction, rate-determining step is the attack of nucleophile on carbonylic carbon. So greater the electron deficiency on carbonylic carbon, more easy will be the attack of nucleophile. Moreover, in reactant carbon is sp^2 hybridized, i.e. trigonal in nature, but in transition state and in product carbon is tetrahedral in nature. So transition state is crowded, and there is steric hindrance in this reaction, i.e. larger group will tend to resist crowding more than smaller groups.

Therefore, order of reactivity of carbonyl compounds depends upon the following factors:

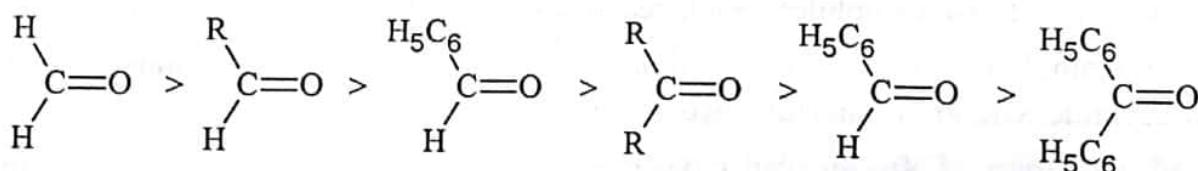
1. Electronic effect: Alkyl groups have +I effect and being electron releasing they tend to destabilize the transition state. So greater the number of alkyl groups lesser will be the reactivity and order of reactivity is



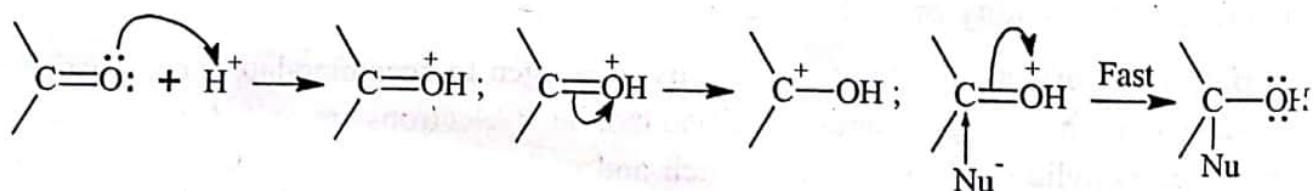
2. Steric effect: Ketones have two alkyl or aryl groups which are bulky and therefore nucleophile could approach to carbonylic carbon as easily as in case of aldehydes that have one alkyl or aryl groups.

Ketones resist more strongly the crowding together in the transition state to make the formation of tetragonal transition state difficult. So ketones are less reactive than aldehydes.

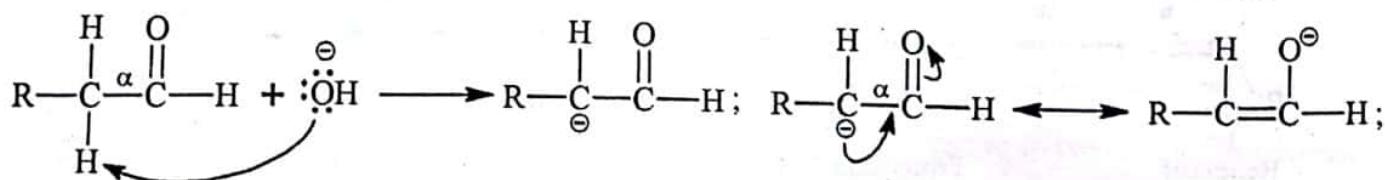
On the basis of these two factors order of reactivity of different carbonyl compounds can be written as



Nucleophilic addition reactions of carbonyl compounds can be catalysed by the addition of acids. Acids protonates carbonylic oxygen forming a conjugated acid of carbonyl compound. This acid is more prone to the attack by the nucleophile.



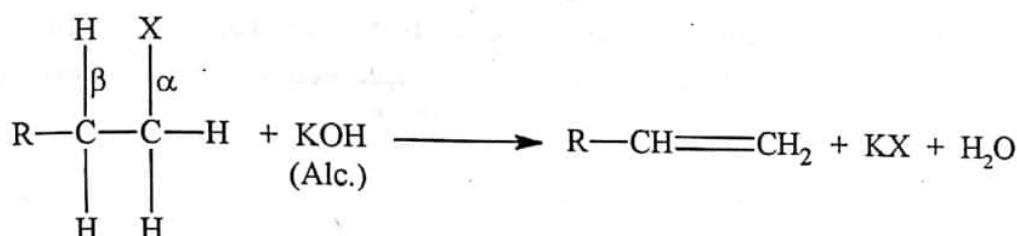
Some of the properties of carbonyl compounds are due to acidity of α -hydrogen. Due to electron withdrawing nature of carbonylic group, α -hydrogen is acidic in nature. Basic reagents can easily remove this α -hydrogen. Anion formed is resonance stabilized.



9.8 ELIMINATION REACTIONS

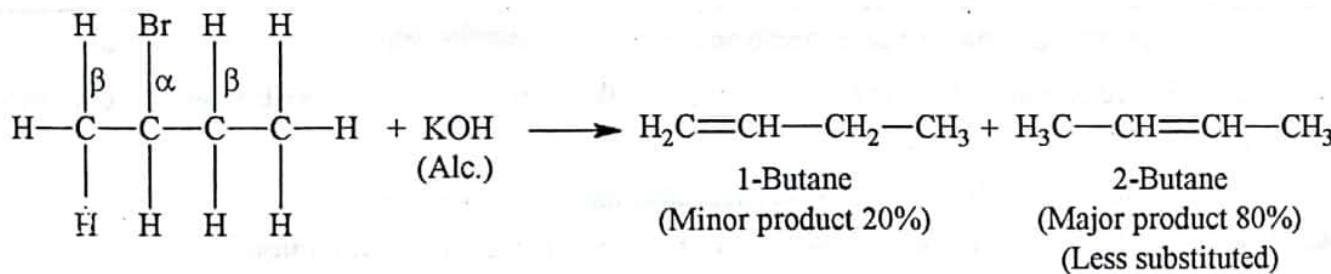
Reaction with alcoholic potash—Dehydrohalogenation (formation of alkenes)

When heated with concentrated alcoholic potassium hydroxide, alkyl halides eliminate halogen acid to form alkenes. This reaction known as dehydrohalogenation involves the loss of halogen and the hydrogen atom from a carbon adjacent to the one losing the halogen (β -elimination).



Saytzeff's rule: If the structure of an alkyl halide is such that it can undergo dehydrohalogenation in two different ways, the preferred product is the alkene that contains least number of hydrogen atoms on doubly bonded carbon atoms. The highly substituted alkene is the major product.

This generalization is known as *Saytzeff's rule*, e.g. when heated with alcoholic potash, 2-bromobutane forms 2-butene as a major product.



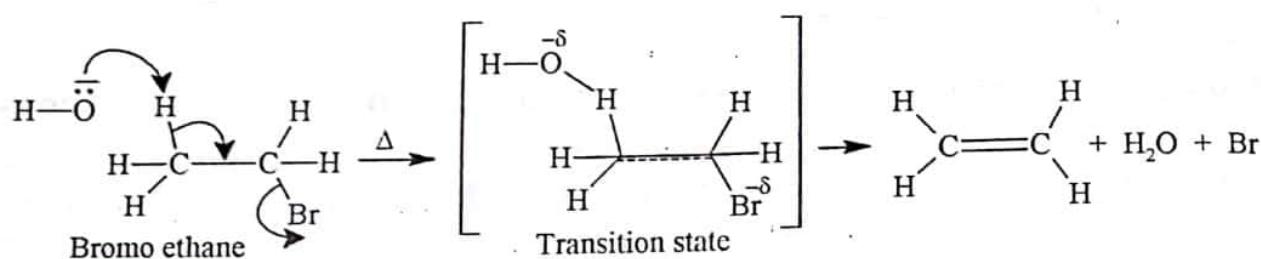
Order of dehydrohalogenation of alkyl halides is $3^\circ > 2^\circ > 1^\circ$.

9.8.1 Mechanism of E_2 (Elimination bimolecular) Reactions

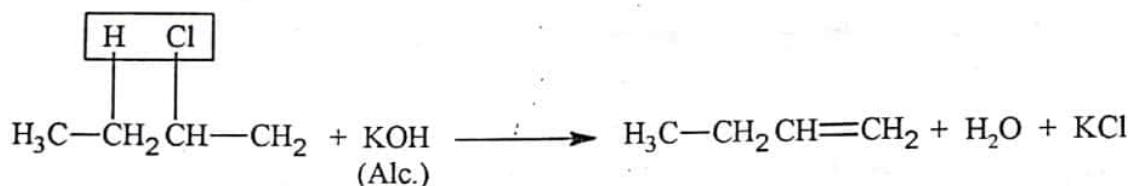
The dehydrohalogenation of a majority of primary alkyl halides occurs by E_2 mechanism. Kinetic studies of this reaction reveal so that the reaction follows second-order kinetics, i.e. rate of dehydrogenation reaction ther is proportional to the concentration of both the alkyl halide and the base. Thus,

$$\text{Rate} \propto [\text{Alkyl halide}] [\text{Base}]$$

This means that E_2 reaction should be a one-step process and occurs through a transition state. As the hydroxide ion (hydrogen attached to carbon atom which is next to the carbon atom carrying the halogen atom), the carbon hydrogen bond begins to break. The carbon-carbon π bond starts forming and the leaving group (i.e. the halogen atom) starts leaving the α -carbon atom taking with it electron pair, breaking the carbon halogen bond. This is explained below with the help of dehydrohalogenation of bromoethane.



As elimination of a proton by a base and simultaneous expulsion of halide ion takes place in one step, there is no opportunity of rearrangement. It is clear from the reaction that the transition state has acquired some alkene character. This is explained by the following reaction:



In case of an alkyl halide having two different types of hydrogens, two alkenes can be obtained. It is thus, clear that more substituted the alkene the more stable the transition state and hence more of this alkene would be formed. This explains the formation of 2-butene as the major product in the dehydrohalogenation of 2-bromobutane.

9.8.2 Mechanism of E_1 (Elimination unimolecular) Reactions

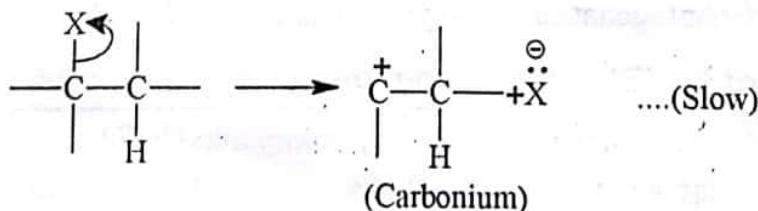
The rate of reaction in these reactions depends only on one reactant molecule.

The E_1 reactions are shown by tertiary alkyl halides and in solution of low base concentration.

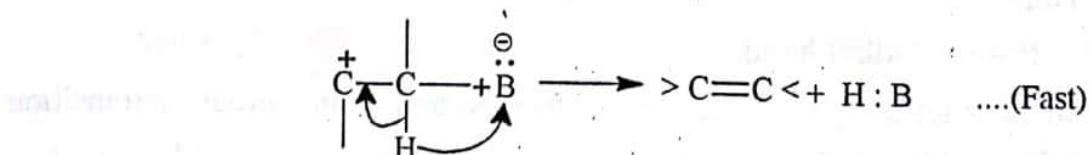
The complete mechanism may be depicted as shown below.

Step I. Dissociation of halide to a carbonium ion by splitting a halogen anion.

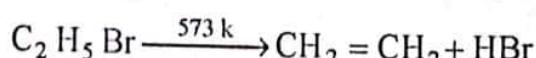
E_1 (Unimolecular elimination)



Step II. Splitting a proton in presence of a base forming an alkene.



Action of heat: Alkyl halides when heated above 573 K tend to lose a molecule of hydrogen halide to alkenes.

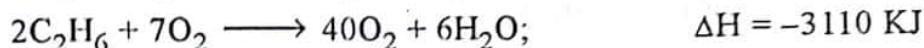
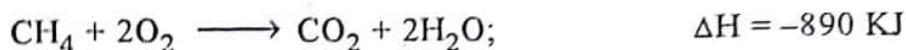


9.9 OXIDATION REACTION

Most of the organic compounds undergo oxidation reactions as exemplified below:

1. Oxidation of alkanes

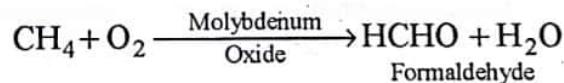
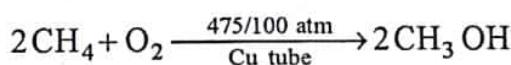
- (i) **Combustion:** When burnt in excess of air or oxygen, alkanes undergo complete oxidation to produce carbon dioxide, water and large quantities of heat. For example,



Due to the large quantities of heat produced during combustion of alkanes, this reaction has tremendous practical importance. Vast quantities of hydrocarbons obtained from petroleum are used as fuels for the production of heat and power by combustion.

- (ii) **Incomplete combustion** of alkanes due to insufficient supply of air or oxygen results in the formation of soot or carbon black. This is used in the manufacture of Indian ink, printer's ink, black varnish and as a filler for rubbers.

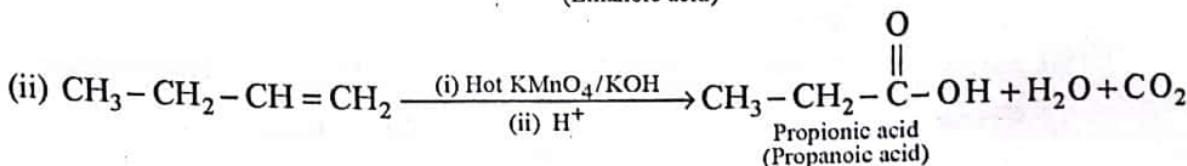
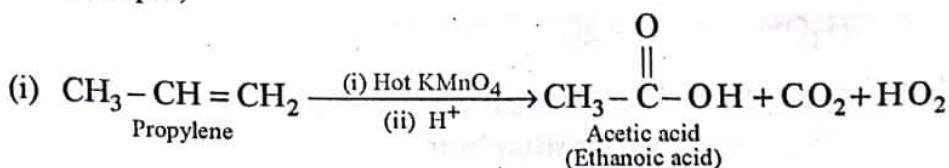
Catalytic oxidation: When heated in a regulated supply of air or oxygen at high pressure and in the presence of suitable metallic catalysts, lower alkanes are oxidized to alcohols and aldehydes while higher homologues yield long-chain fatty acids. For example, when a mixture of methane and oxygen, in suitable proportions compressed to 100 atm and passed through copper tubes at 475 K, methane is oxidized to methanol.

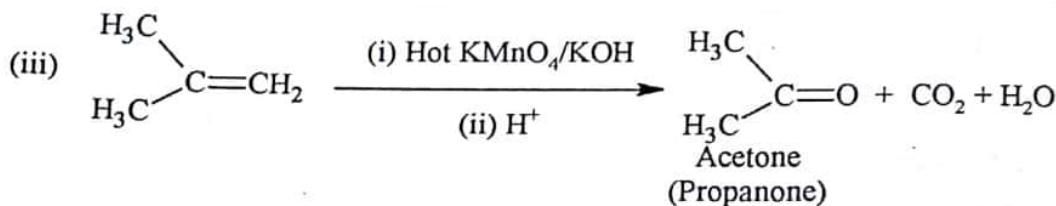


2. Oxidation with Hot Alkaline KMnO_4 (Oxidative Cleavage of Alkenes)

If an alkene is heated with concentrated solution of alkaline KMnO_4 at 373–383 K, cleavage of the C–bond takes place resulting in the formation of ketones and/or carboxylic acids and CO_2 depending upon nature of the alkene as shown below:

- (a) Terminal $=\text{CH}_2$ is oxidized to CO_2 .
- (b) If there is any hydrogen attached to the double-bonded carbon atom, it is oxidized to COOH .
- (c) If there is no hydrogen attached to the doubly bonded carbon, it is oxidized to ketone.
For example,

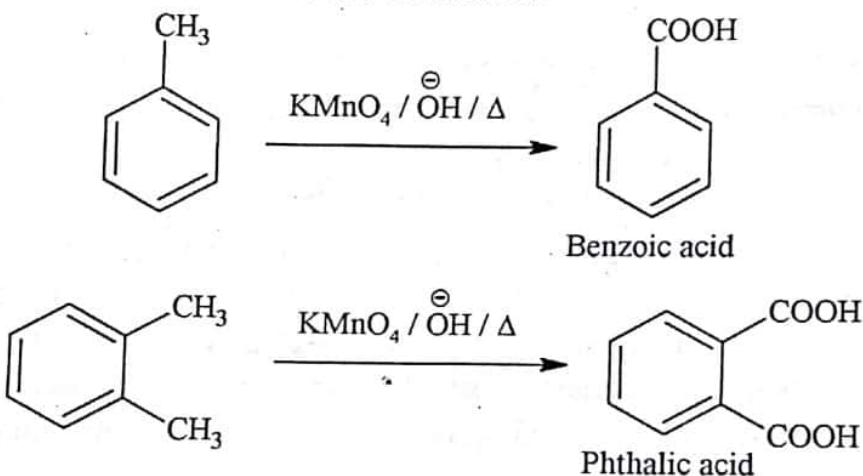




Thus, by identifying the products formed on oxidation with alkaline KMnO_4 , it is possible to locate the position of double bond in an unknown alkene molecule.

3. Oxidation of aromatic compounds

Oxidation with hot alkaline KMnO_4 oxidizes side chain into acidic functional group. Benzene ring is not oxidized under these conditions.

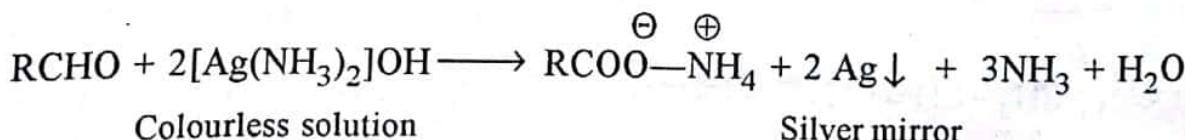
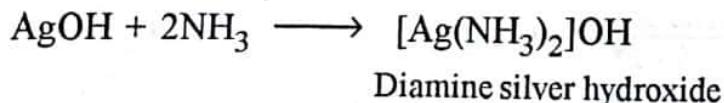


4. Oxidation of Aldehydes

Aldehydes can be easily oxidized to carboxylic acids having same number of carbon atoms. Ketones cannot be easily oxidized, as their oxidation involves the cleavage of C-C bond. Ketones are oxidized by strong oxidizing agents like acidified KMnO_4 , or conc. HNO_3 , or conc. $\text{H}_2\text{SO}_4 + \text{K}_2\text{Cr}_2\text{O}_7$, under strong conditions to carboxylic acids with less number of carbon atoms.

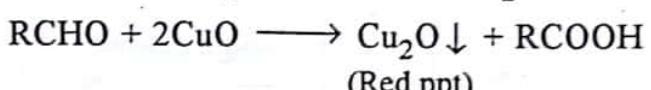
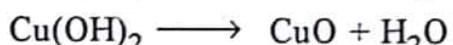
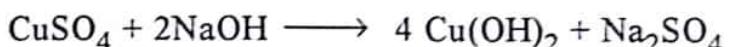
Aldehydes can be oxidized by mild oxidizing agent like Br_2 water, Tollen's reagent, Fehling's and Benedict's solution.

- (i) **Tollen's reagent is ammonical AgNO_3 .** When aldehydes are warmed with Tollen's reagent, a silver mirror is formed on the walls of container, i.e. Tollen's reagent is reduced to metallic silver and aldehydes are oxidized to carboxylic acids. This test is also known as *silver mirror test*.



(ii) **Fehling's solution:** Fehling's solution is prepared by mixing equal volumes of Fehling's solution 'A', which is copper sulphate solution containing few drops of conc. H_2SO_4 and Fehling's solution 'B', which is alkaline solution of Rochelle salt. Rochelle salt is sodium potassium tartarate.

Aldehydes form complex with Cu^{2+} (from Fehling's solution) and are oxidized to carboxylic acid and is reduced to red coloured Cup.



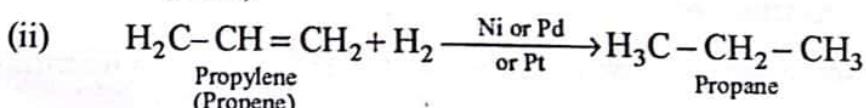
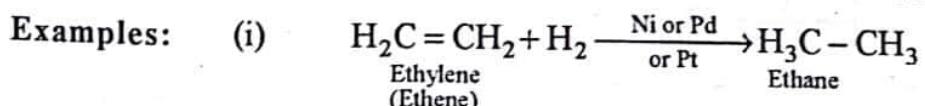
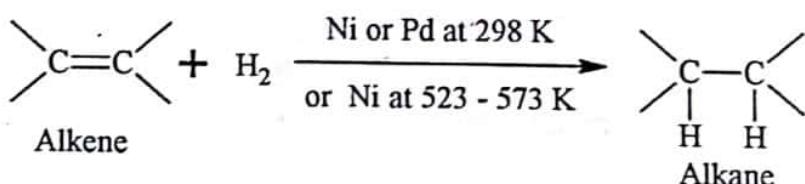
Note: Aromatic aldehydes, however, do not reduce Fehling's solution.

9.10 REDUCTION REACTIONS

Most of the organic compounds undergo reduction to give different products under varying reactions condition as illustrated by the following examples.

1. Reduction (Hydrogenation) of Alkenes

Alkenes react with hydrogen in the presence of certain finely divided metal, such as nickel at 523-573 K (Sabatier—Senderen's reaction) or palladium or platinum at room temperature (298 K) to form alkanes.

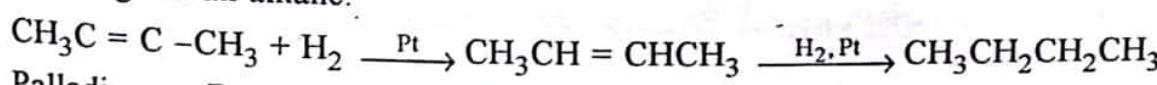


Hydrogenation of alkenes is an exothermic reaction. The heat evolved when 1 mole of unsaturated compound is hydrogenated, which is known as *heat of hydrogenation*.

2. Hydrogenation of Alkynes

Depending on the conditions and the catalyst employed, one or two molar equivalents of hydrogen will, to a carbon–carbon triple bond.

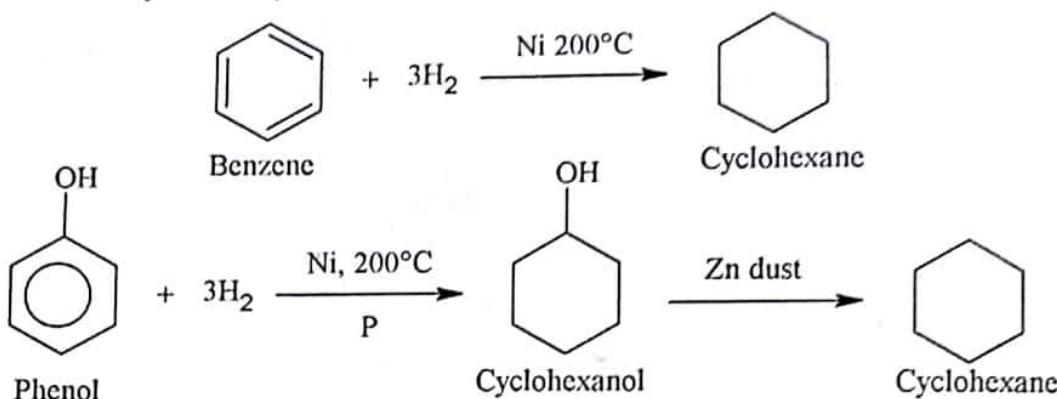
When a platinum catalyst is used, the alkyne generally reacts with two molar equivalents of hydrogen to given an alkane:



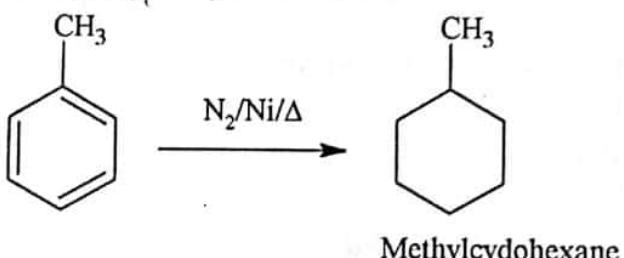
Palladium or Raney nickel can also be used as catalyst.

3. Reduction of Aromatic Compound

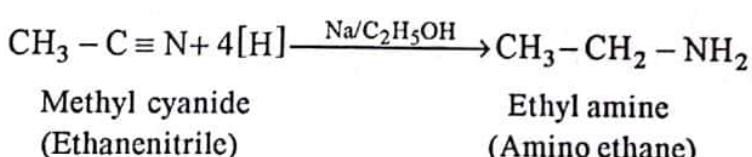
- (a) By the catalytic reduction of benzene and its derivatives, we can easily obtain six-membered cyclo compounds.



- (b) On reduction with hydroiodic acid at 520 K or hydrogen under pressure in the presence of finely divide nickel at 470 K, arenes form cycloalkanes. For example, toluene on reduction gives methylcyclohexane.



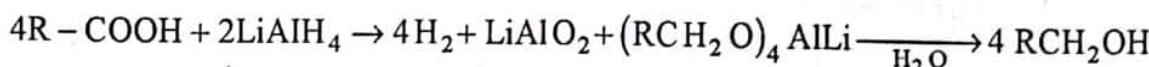
- (c) On reduction with nascent hydrogen obtained by the activity of sodium and ethanol, alkyl cyanides from primary amines. This reaction is known as *Metallic reaction*. Thus,



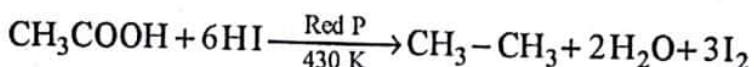
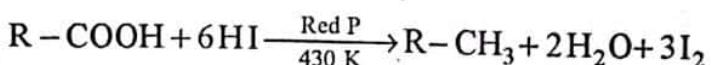
Reduction can also be achieved with H_2/Ni or lithium-aluminium hydride (LiAlH_4).

4. Reduction of Carboxylic Acids

- (i) **Reduction to alcohol:** Carboxylic acids can be reduced to alcohol by LiAlH_4 . The initial products are alkoxide from which alcohol is liberated by hydrolysis.

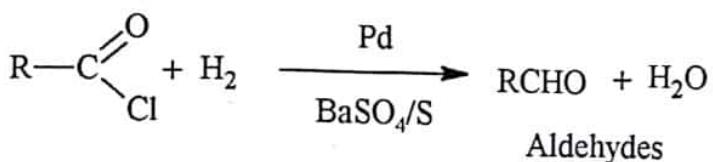


- (ii) **Reduction to alkanes:** Carboxylic acids can be reduced to alkane with HI in presence of red phosphorous at 430 K.



5. Reduction of Acid Chloride

(i) **Reduction to aldehydes (Rosenmund's reduction):** Acid chlorides can be reduced with H_2 in the presence of finely divided palladium precipitated on $BaSO_4$ and S, to aldehydes. Sulphur is used to partially poison the catalyst to prevent further reduction to alcohol or alkane.

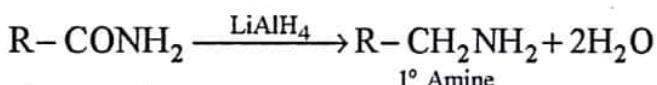


(ii) **Reduction to alcohols:** Alcohols are formed from acid chlorides with sodium and alcohols or LiAlH_4 .



6. Reduction of Acid Amide

Acid amides on reduction with LiAlH_4 give primary amines with the same number of carbon atoms.

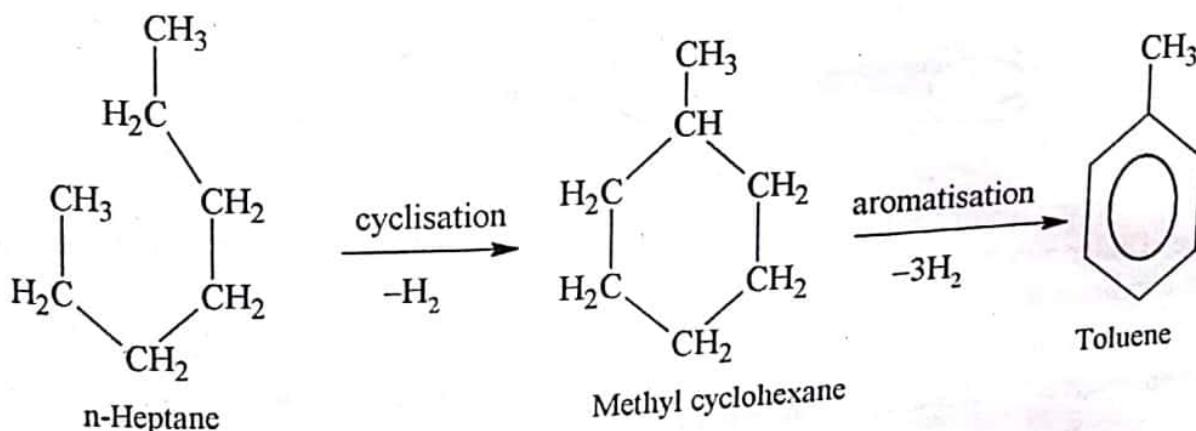


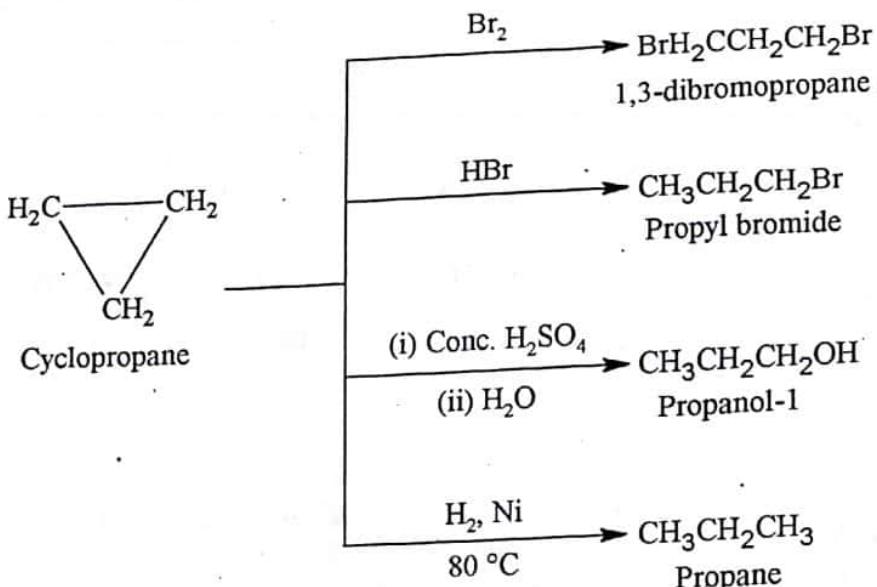
9.11 CYCLISATION

Cyclisation can be carried out by catalytic reforming. It involves reforming the petroleum hydrocarbon molecules to enhance their octane number for gasoline blending. In this process, normally paraffin and naphthene (alicyclic hydrocarbon) molecules are reshaped into aromatics. For instance, n-heptane (C_7H_{16}) is changed to toluene (C_7H_8), n-octane (C_8H_{18}) to ortho-xylene (C_8H_{10}), cyclooctane (C_8H_{16}) to p- and m-xyles. The process is carried out for the manufacture of benzene, toluene and xylene etc.

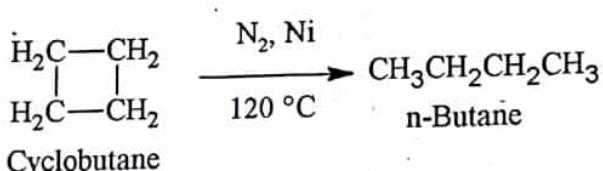
The process is carried out at a temperature range of $250\text{--}550^\circ\text{C}$ in an adiabatic reactor at a pressure of 10 kg/cm^2 in the presence of bimetallic catalysts platinum and rhenium, tin or germanium on a silica-alumina support.

1. Cyclisation and Aromatisation (n-heptane is converted to toluene)

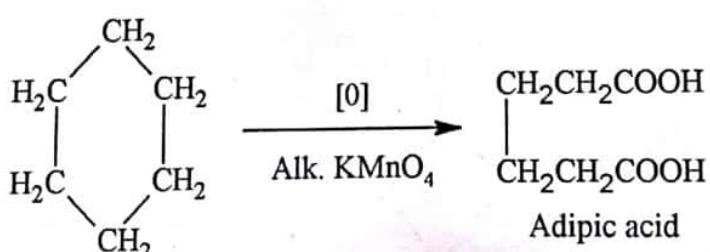




- (ii) Cyclobutane (bond angle 90°) is generally less reactive because of less ring strain and therefore, does not undergo addition reaction under normal conditions.



- (iii) Dicarboxylic acid formed when cycloalkanes are oxidized by alkaline potassium permanganate.



9.13 SYNTHESIS OF A COMMONLY USED DRUG MOLECULE

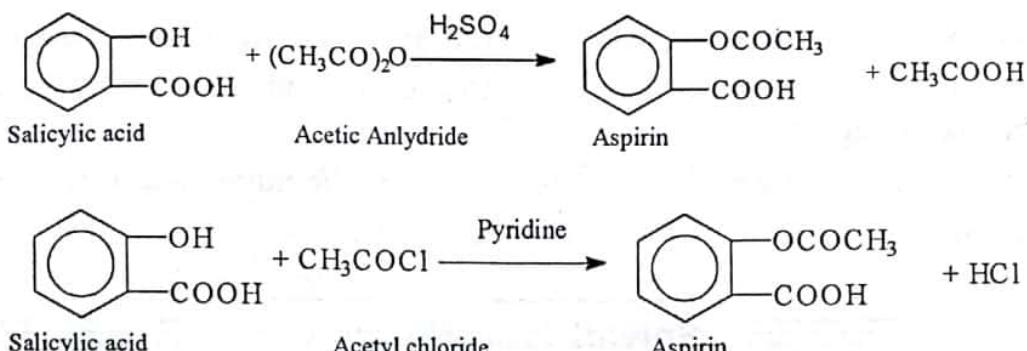
Chemical substance used for the treatment of diseases and for reducing the suffering from pain are called *medicines or drugs*. These chemicals are mainly classified as:

- | | |
|-------------------------------------|--------------------------|
| (i) Antipyretics | (ii) Analgesics |
| (iii) Antiseptics and disinfectants | (iv) Tranquillisers, and |
| (v) Antibiotics | |

We will not go into the details of the above noted types of drugs.

The most commonly used drug is **Aspirin** whose synthesis is discussed below.

Aspirin is obtained by the acetylation of Salicylic acid (o-hydroxy benzoic acid) with acetic anhydride or acetyl chloride in the presence of little concentrated sulphuric acid or pyridine respectively.



Requirements:

Acetylation with acetic anhydride

- a) Salicylic acid = 5 gm
- b) Acetic anhydride = 8 ml.
- c) Conc. H_2SO_4 = 2-3 drops

Acetylation with acetyl chloride

- a) Salicylic acid = 5 gm
- b) Pyridine = 4 ml
- c) Acetyl chloride = 4 ml

Procedure:

Step I. Acetylation with acetic anhydride

- i) Place 5gm of salicylic acid and 7 ml of acetic anhydride in a small absolutely dry conical flask.
- ii) Add 2-3 drops of conc. H_2SO_4 and rotate the flask for thorough mixing.
- iii) Warm the conical flask on a water bath to about $50-60^\circ\text{C}$, while shaking, for about 15 minutes.
- iv) Allow the mixture to cool and stir occasionally.
- v) Add about 80 ml of water, stir well and filter at the pump.
- vi) Recrystallize the crude product from a mixture of equal volume of water and acetic acid.

Step II. Acetylation with acetyl chloride

- i) Dissolve 5gm of salicylic acid in 4ml of dry pyridine contained in a small conical flask.
- ii) Then without delay run in 5ml. of acetyl chloride, adding about 1ml of chloride at a time.
- iii) Shake the content continuously during the addition.
- iv) Since the reaction is exothermic, maintain the temperature between 50°C and 60°C throughout the addition, cooling the flask occasionally in cold water, if necessary.
- v) Finally heat the mixture on a boiling water bath for 5 minutes.
- vi) Then cool in cold water and pour in a thin stream into about 200 ml of cold water, stirring the mixture vigorously.
- vii) The crude aspirin solidifies.

- viii) Filter the solid at pump and wash thoroughly with water.
 ix) Recrystallize from a mixture of equal volumes of water and acetic acid.

Precautions:

- The conical flask must be absolutely dry. Rinse it with alcohol and dry it in an electric oven.
- Coal the contents of the flask in water after addition of each small instalment of acetylating agent.
- Use an air condenser while heating the reaction mixture on a water bath.
- Use minimum quantity of the solvent for recrystallisation.

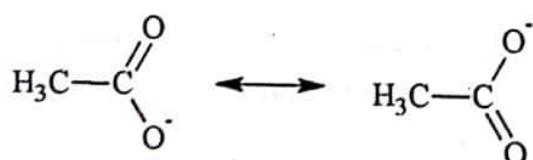
Solved Typical Problems

Problem 1. Free radicals are paramagnetic, but carbonium ions and carbanions are diamagnetic. Why.

Solution. Free radicals possess odd electrons in them and are, therefore, paramagnetic in nature. While carbonium ion and carbanions have no unpaired electron in them and are, therefore, diamagnetic.

Problem 2. What is the effect of increasing the number of carbon atoms on the acidic strength of carboxylic acid?

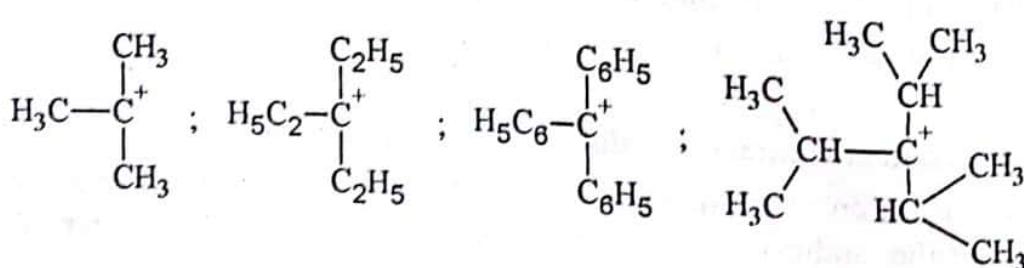
Solution. Acidic strength of carboxylic acid decreases as the number of carbon atoms increases because of +I effect. The carboxylate Ion show resonance as shown.



The electron releasing group (+I effect) will intensify the negative charge on the oxygen and destabilise the carboxylate ion. Greater the +I effect of the group attached to the carboxyl group, weaker in the acid.



Problem 3. Arrange the following in increasing order of stability.



Solution. In organic reactions the starting substance seldom change into products directly in one step. On the other hand, the reactants first change into the intermediate species, which ultimately yield the products. The reaction intermediates are generally short lived, and stable and reactive substance which cannot be even isolated. They are formed during the reaction